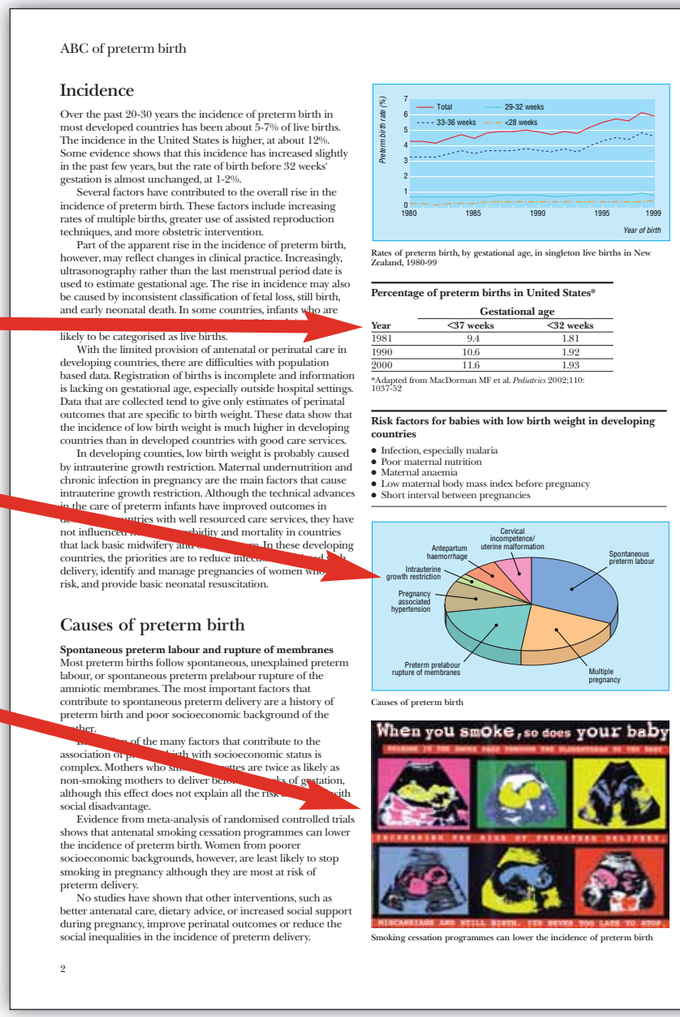
ABC SERIES

Features of the ABC Series

- The ABC titles are serialised and peer reviewed in the **BMJ** before being published in this great series of books
- The pages are always laid out in two columns with the highly illustrated ‘slide show’ of relevant visual aids alongside the text, pulling out key points from the text
- Each book is easy to read and contains a consistent style and the following key features which help to show the important aspects of the text



ABC of preterm birth

Incidence

Over the past 20-30 years the incidence of preterm birth in most developed countries has been about 5-7% of live births. The incidence in the United States is higher, at about 12%. Some evidence shows that this incidence has increased slightly in the past few years, but the rate of births before 32 weeks' gestation is almost unchanged, at 1-2%.

Several factors have contributed to the overall rise in the incidence of preterm birth. These factors include increasing rates of multiple births, greater use of assisted reproduction techniques, and more obstetric intervention.

Part of the apparent rise in the incidence of preterm birth, however, may reflect changes in clinical practice. Increasingly, ultrasonography rather than the last menstrual period date is used to estimate gestational age. The rise in incidence may also be caused by inconsistent classification of fetal loss, still birth, and early neonatal death. In some countries, infants who are likely to be categorised as live births.

With the limited provision of antenatal or perinatal care in developing countries, there are difficulties with population based data. Registration of births is incomplete and information is lacking on gestational age, especially outside hospital settings. Data that are collected tend to give only estimates of perinatal outcomes that are specific to birth weight. These data show that the incidence of low birth weight is much higher in developing countries than in developed countries with good care services.

In developing counties, low birth weight is probably caused by intrauterine growth restriction. Maternal undernutrition and chronic infection in pregnancy are the main factors that cause intrauterine growth restriction. Although the technical advances in the care of preterm infants have improved outcomes in [illegible] countries with well resourced care services, they have not influenced [illegible] bility and mortality in countries that lack basic midwifery and [illegible]. In these developing countries, the priorities are to reduce infec[illegible] delivery, identify and manage pregnancies of women who risk, and provide basic neonatal resuscitation.

Rates of preterm birth, by gestational age, in singleton live births in New Zealand, 1980-99

Percentage of preterm births in United States*

	Gestational age	
Year	<37 weeks	<32 weeks
1981	9.4	1.81
1990	10.6	1.92
2000	11.6	1.93

*Adapted from MacDorman MF et al. *Pediatrics* 2002;110: 1037-52

Risk factors for babies with low birth weight in developing countries

- Infection, especially malaria
- Poor maternal nutrition
- Maternal anaemia
- Low maternal body mass index before pregnancy
- Short interval between pregnancies

Causes of preterm birth

Smoking cessation programmes can lower the incidence of preterm birth

Causes of preterm birth

Spontaneous preterm labour and rupture of membranes
Most preterm births follow spontaneous, unexplained preterm labour, or spontaneous preterm prelabour rupture of the amniotic membranes. The most important factors that contribute to spontaneous preterm delivery are a history of preterm birth and poor socioeconomic background of the [illegible]ber.

[illegible] of the many factors that contribute to the association of p[illegible]th with socioeconomic status is complex. Mothers who sm[illegible]ttes are twice as likely as non-smoking mothers to deliver be[illegible]ks of gestation, although this effect does not explain all the risk [illegible]with social disadvantage.

Evidence from meta-analysis of randomised controlled trials shows that antenatal smoking cessation programmes can lower the incidence of preterm birth. Women from poorer socioeconomic backgrounds, however, are least likely to stop smoking in pregnancy although they are most at risk of preterm delivery.

No studies have shown that other interventions, such as better antenatal care, dietary advice, or increased social support during pregnancy, improve perinatal outcomes or reduce the social inequalities in the incidence of preterm delivery.

The rate of preterm birth varies between ethnic groups. In the United Kingdom, and even more markedly in the United States, the incidence of preterm birth in black women is higher than that in white women of similar age. The reason for this variation is unclear because differences remain after taking into account socioeconomic risk factors.

Preterm births by ethnic group in United States 2000*

- Black—17.3%
- Hispanic—11.2%
- Non-Hispanic white—10.4%

*Adapted from MacDorman MF et al. *Pediatrics* 2002;110:1037-52

Multiple pregnancy and assisted reproduction
Multifetal pregnancy increases the risk of preterm delivery. About one quarter of preterm births occur in multiple pregnancies. Half of all twins and most triplets are born preterm. Multiple pregnancy is more likely than singleton pregnancy to be associated with spontaneous preterm labour and with preterm obstetric interventions, such as induction of labour or delivery by caesarean section.

The incidence of multiple pregnancies in developed countries has increased over the past 20-30 years. This rise is mainly because of the increased use of assisted reproduction techniques, such as drugs that induce ovulation and in vitro fertilisation. For example, the birth rate of twins in the United States has increased by 55% since 1980. The rate of higher order multiple births increased fourfold between 1980 and 1998, although this rate has decreased slightly over the past five years. In some countries two embryos only are allowed to be placed in the uterus after in vitro fertilisation to limit the incidence of higher order pregnancy.

Singleton pregnancies that follow assisted reproduction are at a considerable increased risk of preterm delivery, probably because of factors such as cervical trauma, the higher incidence of uterine problems, and possibly because of the increased risk of infection.

Twin pregnancy increases the risk of preterm birth

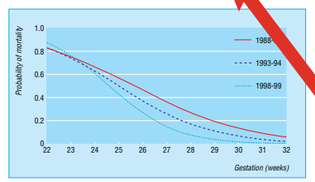
Maternal and fetal complications
About 15% to 25% of preterm infants are delivered because of maternal or fetal complications of pregnancy. The principal causes are hypertensive disorders of pregnancy and severe intrauterine growth restriction, which is often associated with hypertensive disorders. The decision to deliver these infants is informed by balancing the risks of preterm birth for the infant against the consequence of continued pregnancy for the mother and fetus. Over the past two decades improved antenatal and perinatal care has increased the rate of iatrogenic preterm delivery. During that time the incidence of still birth in the third trimester has fallen.

Outcomes after preterm birth

Broadly, outcomes improve with increasing gestational age, although for any given length of gestation survival varies with birth weight. Other factors, including ethnicity and gender also influence survival and the risk of neurological impairment.

The outcomes for preterm infants born at or after 32 weeks of gestation are similar to those for term infants. Most serious problems associated with preterm birth occur in the 1% to 2% of infants who are born before 32 completed weeks' gestation, and particularly the 0.4% of infants born before 28 weeks' gestation. Modern perinatal care and specific interventions, such as prophylactic antenatal steroids and exogenous surfactants, have contributed to some improved outcomes for very preterm infants. The overall prognosis remains poor, however, particularly for infants who are born before 26 weeks' gestation.

The outcome for preterm infants of multiple pregnancies can be better than that of singleton pregnancies of the same gestation. In term infants the situation is reversed. The

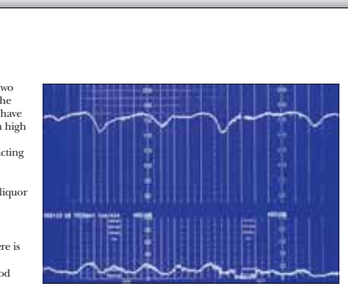


Mortality in UK neonatal intensive care cohorts of infants born before 32 weeks' gestation. Adapted from Parry G, et al. *Lancet* 2003;361:1789-91

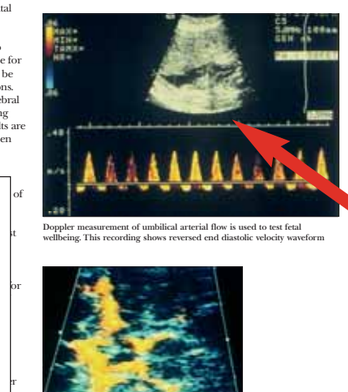
Outcomes for infants live born before 26 weeks' gestation in British Isles*

Gestation (weeks)	Survival to discharge (%)	Survival without handicap at 30 months (%)
22	1	0.7
23	11	5
24	26	12
25	44	23

*Adapted from Wood NS et al. *New Engl J Med* 2000;343:378-84



Monitoring the fetal heart rate can help determine the physiological wellbeing of the fetus. This cardiotocogram shows fetal tachycardia with reduced variability and decelerations



Doppler measurement of umbilical arterial flow is used to test fetal wellbeing. This recording shows reversed end diastolic velocity waveform

Doppler measurement of middle cerebral arterial flow. Abnormal waveforms can show cardiovascular adaptations to placental insufficiency

Induction of labour is most likely to be successful in a woman with a favourable cervix (as assessed by the Bishop score) who has had no caesarean sections and has a history of vaginal delivery

Please scroll down to see a sample chapter

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ASTHMA IN ADULTS – John Rees

1 Definition and pathology

Asthma is a common condition that has increased in prevalence throughout the world over the past 30 years. There is no precise universally agreed definition of asthma. The descriptive statements that exist include references to inflammation in the lungs, increased responsiveness of the airways, and reversibility of the airflow obstruction.

The clinical picture of asthma in young adults is recognisable and reproducible. The difficulties in precise diagnosis come in the very young, in older people, and in very mild asthma. Breathlessness from other causes, such as the increased tendency to obesity, may be confused with asthma.

The clinical characteristic of asthma is airflow obstruction that can be reversed over short periods of time or with treatment. This may be evident from provocation by specific stimuli or from the response to bronchodilator drugs. The airflow obstruction leads to the usual symptoms of shortness of breath. The underlying pathology is inflammatory change in the airway wall leading to irritability and responsiveness to various stimuli—and also to coughing, the other common symptom of asthma.

Asthma has commonly been defined on the basis of wide variations over short periods of time in resistance to airflow. Recent definitions have come to recognise the importance of the inflammatory change in the airways.

Low concentrations of non-specific stimuli—such as inhaled methacholine and histamine—produce airway narrowing. In general, the more severe the asthma the greater the inflammation and the more the airways react on challenge. Other stimuli—such as cold air, exercise, and hypotonic solutions—can also provoke this increased reactivity. In contrast, it is difficult to induce *significant* narrowing of the airways with many of these stimuli in healthy people. In some epidemiological studies increased airway responsiveness is used as part of the definition of asthma. Wheezing during the past 12 months is added to exclude those who have increased responsiveness but no symptoms.

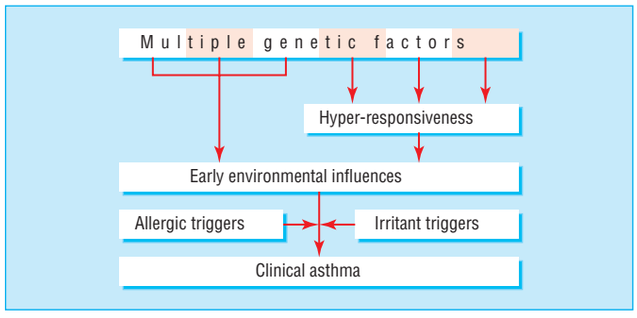
In clinical practice in the UK airway responsiveness demonstrated in the laboratory is not often used in the diagnosis of asthma. The clinical equivalent of the increased responsiveness is development of symptoms in response to dust, smoke, cold air, and exercise; these should be sought in the history.

Labelling

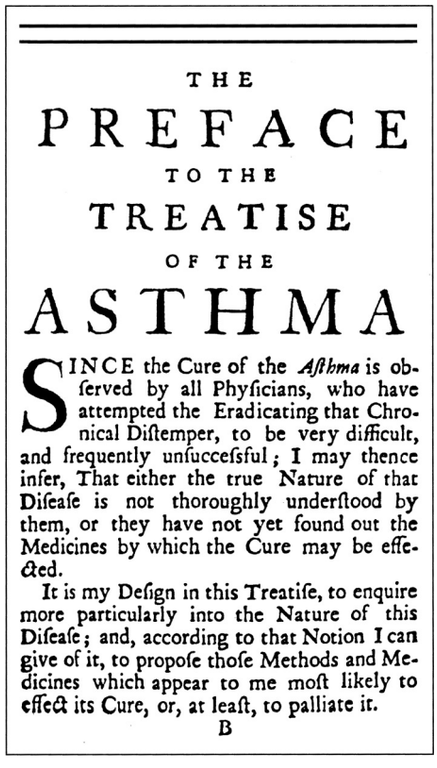
In the past there was a tendency to use the term "wheezy bronchitis" in children rather than "asthma" in the belief that this would protect the parents from the label of asthma.

More recently there has been a greater inclination to label and treat mild wheezing or breathlessness as asthma. These diagnostic trends have been seen in studies of prevalence. Studies through the 1970s and 1980s showed increasing prevalence, emergency room attendance, admission, and even mortality, but recent studies suggest a levelling off or decline in these more severe markers and of self reported wheezing, though the prevalence of the use of label of asthma has remained high or continued to increase.

The International Consensus Report on the Diagnosis and Management of Asthma gives the following definition: "Asthma is a chronic inflammatory disorder of the airway in which many cells play a role, in particular mast cells, eosinophils, and T lymphocytes. In susceptible individuals this inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night or in the early morning. These symptoms are usually associated with widespread but variable airflow limitation that is at least partly reversible either spontaneously or with treatment. The inflammation also causes an associated increase in airway responsiveness to a variety of stimuli."



Genetics and the environment influence asthma



THE
PREFACE
TO THE
TREATISE
OF THE
ASTHMA

SINCE the Cure of the *Aſthma* is obſerved by all Phyſicians, who have attempted the Eradicating that Chronical Diſtemper, to be very difficult, and frequently unſucceſsful; I may thence infer, That either the true Nature of that Diſeaſe is not thoroughly underſtood by them, or they have not yet found out the Medicines by which the Cure may be effected.

It is my Deſign in this Treatiſe, to enquire more particularly into the Nature of this Diſeaſe; and, according to that Notion I can give of it, to propoſe thoſe Methods and Medicines which appear to me moſt likely to effect its Cure, or, at leaſt, to palliate it.

B

The preface to *The Treatise of the Asthma* by J Floyer, published in 1717

The relevance of early environment has been increasingly evident in epidemiological studies. A considerable degree of the future risk of asthma and course of disease seems to depend on factors before or shortly after birth.

Self reported wheezing in the past 12 months is used as the criterion for diagnosing asthma in many epidemiological studies. Wheezing is a very common symptom, affecting three quarters of participants at some time in a recent study of people followed up to the age of 26.

In most people with asthma, available treatments can suppress symptoms to allow normal activity without significant adverse effects. These are the goals of most asthma guidelines. Treatments, however, are not always delivered efficiently, and many people with milder asthma remain symptomatic. Only a few people have difficult to control asthma or troublesome side effects of treatment. In contrast, though we understand more about the onset and natural course of asthma, little practical advance has yet been made in its cure or prevention.

In infants under the age of 2 wheezing is common because of the small size of the airways. Many of these affected infants will not go on to wheeze later. In adults who smoke, asthma may be difficult to differentiate from narrowing of the airways that is part of chronic bronchitis and emphysema caused by previous cigarette smoking.

The actual diagnostic label would not matter if the appropriate treatment were used. Unfortunately, the evidence shows that children and adults who are diagnosed as having asthma are more likely to get appropriate treatment than children with the same symptoms who are given an alternative label. In adults, attempts at bronchodilatation and prophylaxis are more extensive in those who are labelled as asthmatic. Asthma is now such a common and well publicised condition that the diagnosis tends to cause less upset than it used to. With adequate explanation most patients and parents will accept it. The correct treatment can then be started. Persistent problems of cough and wheeze are likely to be much more worrying than the correct diagnosis and improvement in symptoms on treatment. The particular problems of the diagnosis of asthma in very young children are dealt with in chapter 12 (p.51).

Treating older patients

In older patients the most common dilemma is differentiation from chronic obstructive pulmonary disease (COPD). As both conditions are common, some patients will have both. A degree of increased airway responsiveness is found in COPD in relation to geometry from the narrower airways and the 20% change defining responsiveness. Bronchodilators can be used for both conditions, although the agent may vary (p.36). Inhaled corticosteroids are a mainstay early treatment of asthma, but in COPD they are reserved for more severe disease or frequent exacerbations. When there is doubt they should be used.

Pathology

Since the 1990s there has been more interest in and understanding of inflammation in the asthmatic airway. Inflammation in the airway wall involves oedema, infiltration with various cells, disruption and detachment of the epithelial layer, and hypertrophy of mucus glands. Changes occur in the subepithelial layer, with the laying down of forms of collagen and other extracellular matrix proteins.

This remodelling of the airway wall in response to persistent inflammation can resolve but may result in permanent fibrotic damage, possibly related to the irreversible airflow obstruction that may develop in poorly controlled asthma.

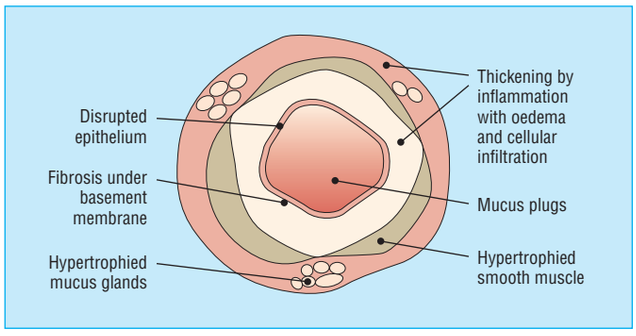
Differential diagnosis in adults

Chronic obstructive pulmonary disease
- May be difficult to differentiate from chronic asthma in older smokers
- The pathology differs, as does the degree of responsiveness to steroids

Large airway obstruction
- Caused by tumours, strictures, and foreign bodies; often misdiagnosed as asthma initially
- Differentiated by flow volume loop (see p.12)

Pulmonary oedema
- Once called "cardiac asthma"
- May mimic asthma, including the presence of wheezing and worsening at night

In smokers COPD may be difficult to distinguish from chronic asthma



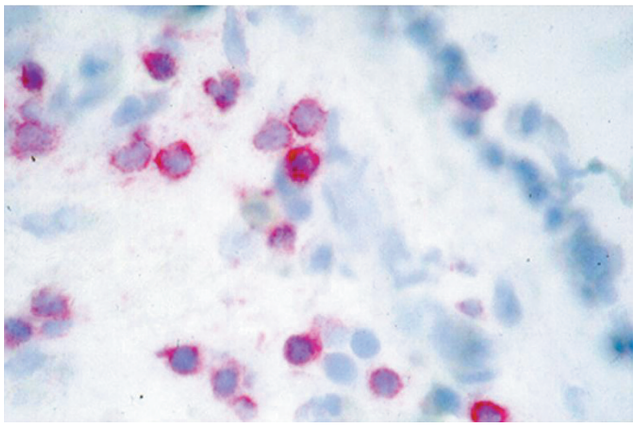
Inflammatory changes in the airway

There is evidence that symptoms in very early life are related to lifelong change in lung function. Early and prolonged intervention may be necessary to allow normal development of the airways and lungs and prevent permanent changes. In older children corticosteroids can suppress inflammation, but this returns, with associated hyper-responsiveness, when the drugs are stopped.

The inflammatory cells involved in asthma include eosinophils, mast cells, lymphocytes, and neutrophils. Dendritic cells, derived from monocytes, present antigen and induce proliferation in naive T cells and primed Th2 cells. Antigen cross links IgE to produce activation and degranulation of mast cells. T lymphocytes seem to have a controlling influence on the characteristic inflammation. Th2 lymphocytes that produce interleukin 4, 5, 9, and 13 are more common in the airway in asthma. Inflammatory cells are attracted to the airway by chemokines and then bind to adhesion molecules on the vessel endothelium. From there they migrate in to the local tissue.

In acute inflammatory conditions such as pneumonia the processes usually resolve. In asthma chronic inflammation can disrupt the normal repair process; growth factors are produced by inflammatory and tissue cells to produce a remodelling of the airway. There is proliferation of smooth muscle and blood vessels with fibrosis and thickening of the basement membrane. Thickened smooth muscle increases responsiveness and, together with fibrosis, reduces airway calibre. Some of these changes may be reversible, but others can lead to permanent damage and reduced reversibility in chronic asthma.

Some of the inflammatory changes in the airway wall can be reduced or prevented by suitable therapy. The point at which the changes become irreversible is uncertain



CD3 positive lymphocytes in mucosa (courtesy of Chris Corrigan)

Clinical evidence

Early evidence on the changes in the airway wall came from a few studies of postmortem material. The understanding advanced with the use of bronchial biopsies taken at bronchoscopy. These studies showed that, even in remission, there is persistent inflammation in the airway wall.

Cells from the alveoli and small airways obtained by alveolar lavage can give another measure of airway inflammation. However, this cannot be repeated regularly and is not practical as a monitor in clinical practice. Induced sputum, produced in response to breathing hypertonic saline, is an alternative more acceptable method.

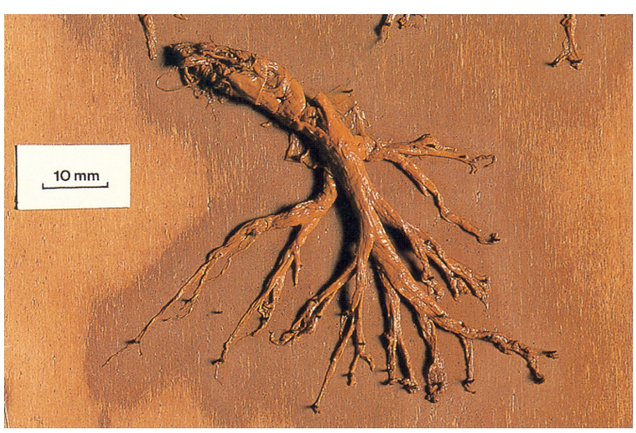
A key question is whether early, effective anti-inflammatory treatment can prevent inflammatory changes to the airway wall producing irreversible change

All these techniques sample different areas and cell populations and by themselves may induce changes that affect repeated studies. They have, however, provided valuable information on cellular and mediator changes and the effects of treatment or airway challenge.

A simpler method entails analysis of expired air. This has been used to measure exhaled nitric oxide produced by nitric oxide synthase, which is increased in the inflamed asthmatic airway. Other possibilities are measurement of pH of the expired breath condensate, carbon monoxide as a sign of oxidative stress, or products of arachidonic acid metabolism such as 8-isoprostane. These methods hold promise for simpler methods of measuring airway inflammation but are not routinely used.

Mucus plugging

In severe asthma, there is mucus plugging within the lumen and loss of parts of the surface epithelium. Extensive mucus plugging is the striking finding in the lungs of patients who die of an acute exacerbation of asthma.



Extensive airway plugs and casts of airways can occur in severe asthma

Asthma as a general condition

It has been suggested that asthma is a generalised abnormality of the inflammatory or immune cells and that the lungs are just the site where the symptoms show. This does not explain the

finding that lungs from a donor with mild asthma transplanted into a patient without asthma produced problems with obstruction of airflow, while normal lungs transplanted into a patient with asthma were free from problems. The link to the nasal mucosa, however, has been recognised more widely. The same trigger factors may affect both areas of the respiratory tract. A combined approach to treatment may be helpful in control of each area.

Types of asthma

Most asthma develops during childhood and usually varies considerably with time and treatment. Young patients usually have identifiable triggers that provoke wheezing, though there is seldom one single extrinsic cause for all their attacks. This "extrinsic" asthma is often associated with other features of atopy such as rhinitis and eczema. When asthma starts in adult life the airflow obstruction is often more persistent and many exacerbations have no obvious stimuli other than respiratory tract infections. This pattern is often called "intrinsic" asthma. Immediate skin prick tests are less likely to yield positive results because of a lack of involvement of allergens or a loss of skin test positivity with age.

Other categories

There are many patients who do not fit into these broad groups or who overlap the two types. There are other important types of asthma, including presentation with just a cough and asthma related to occupational exposure.

Presentation with a cough is particularly common in children. Even in adults it should be considered as the cause of chronic unexplained cough. In some series of such cases, asthma, or a combination of rhinitis and asthma, explained the cough in about half the patients who had been troubled by a cough with no obvious cause for more than two months.

Churg-Strauss syndrome is a rare systemic vasculitis associated with asthma. The asthma is usually severe and often precedes other elements of the condition. The diagnostic criteria include asthma, blood and tissue eosinophilia, and vasculitis. Treatment is with corticosteroids and other immunosuppressants, as well as appropriate treatment for the asthma, which may be difficult to control.

Types of asthma

Childhood onset
- Most asthma starts in childhood, usually in atopic children
- Tends to have considerable variability and identifiable precipitants

Adult onset
- Often a relapse of earlier asthma, but may have initial onset at any age
- Often more persistent with fewer obvious precipitants except infection

Nocturnal
- Common in all types of asthma
- Related to poor overall control and increased reactivity

Occupational
- Underdiagnosed
- Needs expert evaluation

Cough variant
- Cough is a common symptom and may precede airflow obstruction

Exercise induced
- Common precipitant
- May be the only significant precipitant in children

Brittle
- Two types:
  Chaotic uncontrolled asthma with variable peak flow
  Sudden severe deteriorations from a stable baseline

Aspirin sensitive
- May be associated with later onset and nasal polyps
- Only 2-3% have a history of asthma but formal tests identify asthma in 10-20%

Churg-Strauss syndrome
- An uncommon diffuse vasculitis characterised by severe persistent asthma
- Initial clue may be high eosinophilia (>1500/μl) or vasculitic involvement of another organ

Further reading

- Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004;59(suppl 1):1-232.
- International Consensus Report on the Diagnosis and Management of Asthma. *Clin Exper Allergy* 1992; suppl 1:1-72.
- Sears MR, Greene JM, Willan AR, Wiecek EM, Taylor DR, Flannery EM, et al. A longitudinal, population-based cohort study of childhood asthma followed to adulthood. *N Engl J Med* 2003;349:1414-22.