It has long been recognized that asthma is a disease of eosinophilic airway inflammation. Nineteenth century postmortem studies on patients dying from status asthmaticus showed the following pathological features:

- Eosinophil infiltration in bronchial mucosa.
- Increased thickness of smooth muscle in bronchial walls.
- Mucous gland hyperplasia and hypertrophy.
- Occlusion of airways with thick mucus plugs.
- Loss of bronchial epithelium.

In living patients airway inflammation is suggested by:

- Charcot–Leyden crystals (derived from the cytoplasm of eosinophils).
- Creola bodies (clumps of desquamated epithelial cells).

In the last 20 years studies using bronchoscopy, bronchoalveolar lavage, and induced sputum have demonstrated:

- Increased eosinophil numbers (30).
- Increased mast cell numbers (31).
- Increased neutrophil numbers in chronic severe asthma.
- Excess prostaglandin and leukotriene secretion in the airways.
- Changes in cytokine profile and concentration.
- Evidence of airway remodelling (subepithelial fibrosis, myofibroblast accumulation, smooth muscle hypertrophy and hyperplasia, and epithelial disruption).

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**Pathology**

30 Eosinophils. Eosinophils (arrowed) and macrophages on bronchoalveolar lavage fluid (H & E staining). In normal individuals, eosinophils make up around 1–6% of the white blood cells; they are not normally found in the lung.

31 Mast cells. Mast cells in bronchoalveolar lavage fluid (toluidine blue staining). These are normally present in the lung mucosa and play a key role in the inflammatory process.
Airway inflammation in asthma

- The inflammatory response in asthma is a result of excessive activation of mast cells in the airways and their subsequent degranulation. There are two distinct phases, early and late (32).
- Mast cells (33) contain a host of pro-inflammatory mediators which are released when the mast cells degranulate.
  - This occurs when IgE molecules bound to the mast cell (i.e. following initial sensitization) become cross-linked by an appropriate allergen.
  - This in turn leads to an immediate hypersensitivity response and bronchoconstriction associated with release of histamine, proteases (e.g. tryptase and chymase), tissue necrosis factor, and various lipid mediators including platelet-activating factor and leukotrienes LTC4, LTD4, and LTE4.
  - This is referred to as the early asthmatic response and occurs within minutes of exposure to allergen.
- Mast cells also release chemokines and cytokines that recruit eosinophils, basophils, and T ‘helper’ lymphocytes to the local mucosa.
  - These cells then release other mediators, particularly interleukin-5 (IL-5), which attract more activated eosinophils.
- Eosinophils are laden with potent bronchoconstrictor substances, such as leukotrienes.
  - When activated eosinophils degranulate they release these substances into the airway causing bronchoconstriction.
  - This is known as the late asthmatic response and occurs some hours after allergen exposure.
- Ongoing inflammation results in structural change within the airways (34, 35, 36). This is referred to as airway remodelling, and includes epithelial damage, sub-basement membrane thickening, and hypertrophy of smooth muscle and mucous glands, leading to increased bronchial reactivity and airflow obstruction.

32 Early and late allergic response. Following allergen challenge, there is a rapid fall in PEF coinciding with the early asthmatic response. This can be blocked by beta-agonists but usually not by steroids. The late reaction then starts and may last for 24–48 hrs and be followed by a prolonged period of bronchial hyper-reactivity. This phase is usually blocked by steroids.

33 Mast cell (electron microscopy). These cells are found occasionally in bronchial mucosa and submucosa. They are morphologically similar to circulatory basophils and contain numerous granules within which are pre-formed mediators. When released, these mediators trigger the airway inflammation seen in asthma.

Allergen challenge produces both an early and a late response.
34 **Airflow obstruction.** Light microscopy (x 220) of an airway in asthma. Smooth muscle in the bronchial wall is contracted and the bronchial lumen contains a mucus plug.

35, 36 **Mechanisms in asthma.** When allergens bridge synthesized IgE receptors on mast cells (1), pro-inflammatory chemicals such as cytokines and leukotrienes are released (2). Further inflammatory mediators are released as eosinophils and neutrophils are activated and migrate into the airway (3). These act on the airway structures (right), damaging the epithelium, constricting the smooth muscle, causing vasodilation and plasma leakage, new vessel formation, oedema, mucous gland and goblet cell hyperplasia, and basement membrane thickening.
Origins of atopy

- The hypersensitivity reaction characteristic of asthma is termed atopy and is generally defined by the presence of elevated levels of IgE antibodies.
- It seems likely that this complex inflammatory process originally evolved for the purpose of controlling worm infestation.
- Parasitic worms, like allergens, present extrinsic free enzyme at mucosal surfaces and the consequent production of parasite-specific IgE and local eosinophilic inflammation produces protective immunity.

37 Inflammatory cell interactions. Mast cells respond to allergen invasion (1) by releasing cytokines (IL-4, IL-5), which activate eosinophils (2), and by producing pro-inflammatory mediators that, as well as affecting airway muscles, stimulate the differentiation of T-helper cells into Th1 and Th2 subtypes (3). Th2 cells also produce IL-4 and IL-5 (4), while Th1 cells are involved in B-lymphocyte defence mechanisms (5).

- In asthma, the role of T-helper lymphocytes and imbalance between different 'populations' (Th1 and Th2) of lymphocytes is of considerable importance.
- Maturing lymphocytes are believed to be pushed towards a 'Th2 state'. This is a state in which T-helper lymphocytes preferentially express cytokines such as IL-4 and IL-5, which promote allergic inflammation (37).
- The converse is a 'Th1 state', with preferential production of interferon and IL-2. This influences the immune system away from allergic disease and towards cell-mediated immunity, responsible for the control of intracellular infections such as mycobacteria and viruses.
Allergen exposure

- Allergens are well recognized triggers of asthma (38).
- It has been hypothesized that high exposure to allergens either in utero or in early childhood, in those predisposed, causes allergic sensitization (manifested as positive skin-prick tests or high levels of specific IgE in serum), which in turn leads to allergic disease.
- Increased allergen exposure in the last 30 years may be due to the following factors:
  ◦ There has been an increase in central heating, double glazing, and carpeted floors, all of which favour higher house dust mite levels.
  ◦ However, it has also been suggested that high levels of exposure to cat allergen early in childhood seem to protect against asthma rather than exacerbate it.
  ◦ Similarly in Sweden, where there has been a substantial reduction in carpets in houses in favour of wooden flooring, there has not been a consequent reduction in asthma prevalence.
- The house dust mite, Dermatophagoides pteronyssinus, is an arthropod about 0.3 mm in length which feeds on human epithelium. It has a life cycle of about 2–5 months during which the female lays two or three batches of 20–30 eggs. Mites are found in bedding and mattresses and it is the mite faeces (39, right) which cause the allergic reaction.

Asthma triggers

- Triggers for asthma are environmental factors that cause an acute asthma ‘attack’ as opposed to factors in the aetiology of asthma. Triggers can broadly be divided into allergic and nonallergic, irritant effects.
- Common allergic triggers include:
  ◦ House dust mite.
  ◦ Cat dander.
  ◦ Dog dander.
  ◦ Cockroaches.
  ◦ Grass pollens.
  ◦ Tree pollens.
- Common nonallergic triggers include:
  ◦ Viruses.
  ◦ Exercise.
  ◦ Cigarette smoke.
  ◦ Thunderstorms.
  ◦ Air pollution.
  ◦ Emotional trauma.

The faeces of the house dust mite are a common cause of allergic reaction.
**Atopy**

- Atopy is an inherited predisposition to develop allergic disease such as asthma, eczema or hayfever (allergic rhinitis).
- Atopic status can be determined by skin-prick testing (40), measuring serum levels of specific IgE or by simply observing whether a patient has a clear history of wheezing or hayfever on exposure to an allergen.

**Bronchial hyper-reactivity**

- Bronchial hyper-reactivity is a characteristic feature of asthma.
  - It is believed to occur because of the persistence of eosinophilic inflammation in the airway with release of potent bronchoconstrictor agents.
  - The true reason is likely to be more complex than this, however, as some patients have bronchial hyper-reactivity without demonstrable inflammation and some have airway inflammation without significant bronchial hyper-reactivity.
- Bronchial reactivity will also be increased if the diameter of the bronchial lumen is decreased.
  - This could occur either by intraluminal mucus produced by inflammation or by increasing the thickness of the bronchial mucosa and smooth muscle (airway remodelling).
- Airway remodelling (41) is a process that has been shown to occur even in mild asthma and, if persistent, eventually leads to a degree of fixed airflow obstruction.
  - Airway smooth muscle in asthma may not be inherently different from that in normal airways. However, the process of airway remodelling, which includes smooth muscle hyperplasia, may disrupt the equilibrium that exists between actin–myosin binding and unbinding. This is an attractive theory that goes some way to explaining the phenomenon of bronchial hyper-responsiveness in different asthma phenotypes.

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**Skin-prick testing.** This is performed by placing a drop of allergen on the forearm and lifting the skin lightly through the drop with the point of an intradermal needle. A wheal is a positive result and should be compared in size to that from the control solution.

**Airway remodelling within the bronchial wall.** This is a dynamic process involving gradual hypertrophy of the airway smooth muscle (a) beneath the airway epithelium (b) and submucosa (c).
Genetics of asthma

- A family history of asthma or atopy is an important risk factor for the development of asthma in an individual, and genetic factors are important in the aetiology of asthma.
  - Asthma genetics, however, do not show the classical Mendelian inheritance pattern.
- Asthma is a polygenic disease with a variety of genes interacting to increase the risk of developing asthma.
  - Monozygotic twins show only 50–60% concordance for atopic disease and only 26% concordance for asthma. This may be partly due to mutations in genes that influence the development of asthma, but also indicates that the environment has a major impact on whether an individual develops asthma.
- Linkage mapping has identified regions of chromosomes that are associated with asthma and allergy.
  - A region on chromosome 12 that contains the gene for interferon γ is linked to asthma, allergy, and total IgE. This is a logical association because interferon γ inhibits IL-4 activity, which promotes the development of allergic disease.
  - A region on chromosome 11 has also been found to be strongly linked to allergic disease and to contain the gene for expression of the high-affinity IgE receptor (FcεRI) – again a logical association.
- Recently, sequencing of the human genome and powerful techniques such as positional cloning have allowed identification of several genes that are strongly associated with asthma and atopy (see also chapter 11).
- Over 70 variants in candidate genes have been found to have linkage with the phenotypes of asthma and atopy.
- The main regions these variants have been found are on chromosomes 2q, 5q, 6p, 11q, 12q, 16q, and 17q.
- Five potential asthma susceptibility genes or complexes have been identified. These are ADAM33, DPP10, PHF11 and SETDB2, GPRA, and SPINK5.
  - The ADAM33 gene, found on chromosome 20p13, has been linked to asthma and bronchial hyper-responsiveness and codes for membrane-anchored metalloproteases which are involved in airway remodelling.
- It is hoped that identification of such genes associated with asthma will help identify proteins that are useful targets for future therapeutic agents.

Air pollution and smoking

- Air pollution may exacerbate pre-existing asthma, but is unlikely to actually cause asthma.
- The increase in prevalence of asthma and allergic disease in the UK in the last 30 years has coincided with a steady decline in levels of air pollution.
- Prior to the re-unification of Germany in October 1990, East Germany had high levels of atmospheric pollution, but a low prevalence of asthma, whereas in West Germany the converse was true.
- Epidemiological evidence does not, therefore, support air pollution as a cause for asthma.
- In contrast, several epidemiological studies have shown that maternal smoking in pregnancy is independently associated with asthma in the offspring (42).

Maternal smoking in pregnancy is associated with asthma in the offspring.

42 Maternal smoking. In this Swedish study, reported maternal smoking of one or more cigarettes daily during pregnancy and the first two years was greater for children with recurrent wheezing than for healthy children.
Viral infections are a well recognized and common cause of asthma exacerbations (43). However, there is no convincing evidence to suggest that viral infections cause asthma.

Infants hospitalized for acute respiratory syncytial virus (RSV) bronchiolitis often have recurrent wheezing episodes for several years afterwards, and there was speculation that RSV infection in childhood causes asthma.

Longitudinal prospective studies have shown that by the age of 10 years there is only a small excess of wheezing illness in those with RSV bronchiolitis in infancy compared with control children and no increase in the incidence of atopy.

It is now believed that RSV bronchiolitis causing a severe wheezing illness in some infants is simply a manifestation of a predisposition in these children to wheeze with viral infection (sometimes called ‘transient wheeze’ or ‘virus-associated wheeze’).

There are two main hypotheses which attempt to explain the rise in asthma prevalence over the past 30 years: the hygiene hypothesis and the diet hypothesis.

**The hygiene hypothesis**

- The rise in allergic disease over the last 30 years coincides with more widespread use of vaccinations and antibiotics to treat infections in childhood and in a general cleaner living environment.
- It has been postulated that vigorous avoidance and eradication of bacterial infections in childhood reduce Th1 activity in the immune system and consequently enhance Th2 activity, which leads to atopic disease.
- This is a logical argument and fits some of the epidemiological evidence:
  - It is well recognized that in large families the risk of atopic disease decreases with increasing birth order – younger siblings being presumed to be exposed to more bacteria and viruses from their older siblings.
  - Children in Guinea-Bissau, following a particularly severe epidemic of measles, were less likely to be sensitized to house dust mite allergens.
  - Japanese schoolchildren who responded strongly to BCG vaccination were less likely to become atopic.
- However, reports of clinical infections in infancy and childhood have not always been associated with subsequent absence of atopy:
  - The hygiene hypothesis fails to explain high asthma prevalence in poor areas of American cities, where there is often overcrowding and infestation with cockroaches and rodents.

**Antioxidants such as selenium, vitamins E and C, and n-3 PUFA may be protective against asthma.**
The possibility that the absence of parasitic infections in children growing up in the ‘developed world’ could have led to the rise in allergic disease has also been investigated with some mixed results.

- Some studies have shown that asthma prevalence is the same or increased in children with parasitic infections, whereas other studies have shown parasitic infections to be protective against asthma.
- The true situation is difficult to untangle because some parasitic infections cause asthma-like symptoms during their life cycle in the lung. However, most studies have not focused on one single parasitic species and there may be differences in the effects of different parasites.

**The diet hypothesis**

- Diet in westernized countries has changed substantially over the last 30 years, which coincides with the increase in allergic disease. In particular, children today eat less fresh fruit and fewer vegetables than previous generations.
- Antioxidants: selenium, and vitamins E and C, found in fresh fruit and vegetables, and n-3 PUFA (omega-3 polyunsaturated fatty acid), found in oily fish, are believed to be protective against asthma.
- This protective effect is likely to start *in utero*, when high maternal intake of these antioxidants is associated with reduced wheezing in infants and reduced proliferation in response to allergens of mononuclear cells from umbilical cord blood.
- Recent epidemiological studies have shown a higher prevalence of asthma in obese subjects.
- The widespread increase in asthma in recent years coincides with a rise in the incidence of obesity.
- The mechanism for any association is not known, but it is possible that the same dietary habits that have led to an increase in obesity have also led to an increase in asthma. This could be either by the presence of dietary substances that increase allergy or by the absence of substances, e.g. antioxidants, that protect against the development of asthma.

**Natural history of asthma**

- Study of the natural history of asthma is complicated by the different phenotypes.
  - For example, in early childhood it may be difficult to distinguish virus-associated wheeze from atopic asthma.
  - The former only wheeze in association with viral infection and do not have demonstrable atopy.
- It is well recognized that many children with atopic asthma ‘grow out’ of their asthma, although the extent of this is probably overestimated.
  - Epidemiological studies have shown that about 50% of children ‘outgrow’ their asthma in teenage years, but many of these children develop asthma again in their third and fourth decades of life.
  - Interestingly, some children who have apparently ‘outgrown’ asthma with no symptoms for at least 1 year continue to have eosinophilic airway inflammation. It may be that these individuals will go on to develop asthma again later in life.
- Factors associated with persistence of asthma into adolescence:
  - Severe childhood asthma.
  - Persistent symptoms (as opposed to episodic).
  - Strong family history of asthma.
  - Female gender.
- In adults, a distinction is sometimes made between atopic asthma (sometimes called extrinsic asthma) and nonallergic asthma (intrinsic asthma).
  - Nonallergic or intrinsic asthma tends to occur for the first time in individuals in their fourth and fifth decades, but may occasionally occur for the first time in old age. It is not possible, with current techniques, to find evidence of atopy in this phenotypic variety of asthma.
  - Debate continues as to whether intrinsic asthma is a distinct immunopathological entity or whether it simply represents one end of the spectrum of atopic asthma.