

Prevention of Allergy and Allergic Asthma

World Allergy Organization Project Report and Guidelines

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Prevention of Allergy and Allergic Asthma

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Prevention of Allergy and Allergic Asthma

World Allergy Organization Project Report and Guidelines

Volume Editors

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Introduction

The prevalence of asthma and allergy is increasing. It is estimated that over 20% of the world's population suffer from IgE-mediated allergic diseases such as asthma, rhinoconjunctivitis, eczema and anaphylaxis. Asthma, which in more than 50% of adults and 70–80% of children is allergic, occurs in around 5–15% in the paediatric population. Asthma is estimated by the World Health Organization (WHO) to affect 150 million people worldwide, placing an enormous strain on health resources in many countries, and is a major cause of hospitalisations for chronic diseases in children in the Western World.

Prevention of Allergy and Allergic Asthma was a collaborative project between the World Allergy Organization (WAO) and the WHO. This collaboration was commissioned to advance the strategic objectives of the WHO as outlined in its Strategy for the Prevention and Control of Chronic Respiratory Diseases.

WAO and WHO created a working group consisting of seven 'Chapter Chairpersons', each with co-authors, and a meeting of the group took place on December 5–6, 1999, at the WHO headquarters in Geneva. The Chairpersons of the working group invited a number of international experts to contribute to the chapters, enabling WAO and WHO to benefit from the widest possible expert opinion in the development of this document. A report of the second meeting of the working group was published in September 2003 [1].

The strategic guidelines and recommendations in this document have been developed for use by governments, health care professionals, research grant providers, lay organizations, and patients, and will be disseminated, amongst other routes, through the WAO educational program, Global Resources in Allergy.

What this Document Provides

The document provides guidelines and recommendations for the prevention of the allergen-specific immunological sensitisation necessary for disease, and advises that even where it exists, this sensitisation is not always expressed as disease. Allergic diseases can involve the respiratory system, e.g. asthma and rhinitis, the gastro-intestinal tract, e.g. food allergy, or the skin, e.g. eczema and contact dermatitis. In rare cases a generalised reaction, allergic anaphylaxis, develops, which can lead to shock and death. A source of potential confusion is that each allergic disease has a clinical mirror image, based on similar inflammatory reactions, but which is not initiated or mediated by specific immunological reactions.

In the westernised world, allergy and asthma have increased two- to three-fold over the last 40 years and have reached epidemic proportions. The increase in these diseases has occurred over a period of persistent environmental and lifestyle changes. Epidemiological studies have shown great variation in the prevalence of asthma and allergies between different nations. Valuable information may be derived from areas where a rapid increase in disease has occurred, to form the basis for prevention strategies in areas where the prevalence of these diseases is still low.

Most of the data on which the guidelines are based have been obtained from countries that have experienced this rapid increase in allergies and asthma, and so will require interpretation and adaptation to meet different local circumstances. Within any country or region, climatic and environmental variations, and differences between affluent and non-affluent groups, may require a broad range of strategies and advice to be available. It is hoped that the general principles of prevention proposed in this document will provide a useful basis for local guidelines to be developed. Further research is essential on many aspects which are still not fully understood, and further actions are recommended in each section to assist the strategic development of national and international research programmes.

Primary prevention (see Glossary on page XVII) of asthma may often be secondary prevention of allergy.

This document focuses mainly on primary prevention of the allergen-specific immunological sensitisation that is the basis for allergy and for much of asthma. Primary prevention measures should be implemented if they meet the following criteria:

They should be of potential benefit to the major part of the population.

They should be of no known harm to anyone.

They should not involve unreasonable costs.

Secondary prevention is also covered in some detail since adequate diagnosis and treatment of allergic diseases such as eczema and allergic rhinitis at a young age can prevent the later development of asthma.

Tertiary prevention is briefly mentioned; it is covered in detail elsewhere, for example in the Global Resources in Allergy program of the WAO, the ‘Global Initiative for Asthma’ [2], and ‘Allergic Rhinitis and Its Impact on Asthma’ [3]. The models of occupational respiratory and skin allergies are introduced as examples where primary and secondary prevention strategies have been successful.

Non-allergic asthma is mentioned in this report since some secondary prevention strategies may be of value in this disorder. Although the causes are less well defined, similar inflammation is present in the airways of patients with non-allergic asthma as in allergic asthmatics.

Evidence Base

In creating this document, authors were asked to code the referenced documents in accordance with the following WHO Categories of Evidence; on the basis of the categorisation of evidence, a strength of recommendation may be awarded to the ensuing guidelines. The Categories of Evidence are more easily applied to therapeutic interventions than to epidemiological and basic research studies, where randomisation or blinding may not be possible. A well-designed physiological study, for example, may not be able to be coded by these criteria. Thus, a recommendation awarded a ‘b’ cannot always be interpreted as a lesser recommendation than one coded ‘a’ – it is an indication only of the type of studies which have created the evidence base: a recommendation awarded ‘d’ may indicate that at the present time there is an absence of evidence. Accordingly, it was decided only to restrict strength of recommendation categories to the guidelines in chapters 5 and 6, where a clear interpretation of the evidence base is possible.

WHO Categories of Evidence

- Ia: Evidence from meta-analysis of randomised controlled trials
- Ib: Evidence from at least one randomised controlled trial
- IIa: Evidence from at least one controlled study without randomisation
- IIb: Evidence from at least one other type of quasi-experimental study
- III: Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies
- IV. Expert opinion of the Prevention of Allergy and Allergic Asthma working group

WHO Strength of Recommendations:

- A: Directly based on category I evidence
- B: Directly based on category II evidence or extrapolated recommendation from category I evidence
- C: Directly based on category III evidence or extrapolated recommendation from category I or II evidence
- D: Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Glossary and Definitions

The nomenclature of allergy is varied, and to address this important topic and ensure clear communication between health professionals, the WAO recommends the adoption of a global nomenclature for allergy. The terminology proposed by the European Academy of Allergology and Clinical Immunology publication, 'A Revised Nomenclature for Allergy' [4] has been updated by the WAO in its publication 'A Revised Nomenclature for Allergy for Global Use' [5]. The WAO nomenclature is used throughout this document.

Allergy. Allergy is a hypersensitivity reaction initiated by immunological mechanisms. Allergy can be antibody or cell mediated. In the majority of cases the antibody typically responsible for an allergic reaction belongs to the IgE isotype, and these individuals may be referred to as suffering from an IgE-mediated allergy. Not all IgE-associated 'allergic' reactions occur in 'atopic' subjects. In non-IgE-mediated allergy the antibody can belong to the IgG isotype, e.g. anaphylaxis due to immune complexes containing dextran, and the classical, nowadays rare, serum sickness previously referred to as a type III reaction. Both IgE and IgG antibodies are found in allergic bronchial pulmonary aspergillosis. Allergic contact dermatitis is representative of allergic diseases mediated by lymphocytes.

Allergens. Allergens are antigens which cause allergy. Most allergens reacting with IgE and IgG antibody are proteins, often with carbohydrate side chains, but in certain circumstances pure carbohydrates have been postulated to be allergens. In rare instances low-molecular-weight chemicals, e.g. isocyanates and anhydrides acting as haptens, are still referred to as allergens for IgE antibodies. In the case of allergic contact dermatitis, the classical allergens are low-molecular-weight chemicals, e.g. chromium, nickel and formaldehyde, reacting with T cells.

Atopy. Atopy is a personal and/or familial tendency, usually in childhood or adolescence, to become sensitised and produce IgE antibodies in response to

ordinary exposure to allergens, usually proteins. As a consequence, such individuals can develop typical symptoms of asthma, rhinoconjunctivitis, or eczema. The terms 'atopy' and 'atopic' should be reserved to describe the genetic predisposition to become IgE sensitised to allergens commonly occurring in the environment and to which everyone is exposed but to which the majority do not produce a prolonged IgE antibody response. Thus, atopy is a clinical definition of an IgE antibody high-responder. The term atopy cannot be used until an IgE sensitisation has been documented by IgE antibodies in serum or by a positive skin prick test. Allergic symptoms in a typical atopic individual can be referred to as atopic, e.g. atopic asthma. However IgE-mediated asthma in general should not be called atopic asthma. Neither a positive skin prick test nor presence of IgE antibody to a less common allergen, e.g. Hymenoptera sting or a drug, which are high-dose exposures, is a diagnostic criterion for atopy.

Hypersensitivity. Hypersensitivity causes objectively reproducible symptoms or signs, initiated by exposure to a defined stimulus that is tolerated by normal subjects.

Non-Allergic Hypersensitivity. Non-allergic hypersensitivity is the preferred term to describe hypersensitivity in which an immunological mechanism cannot be proven.

Prevention

Primary Prevention: Prevention of immunological sensitisation (i.e. the development of IgE antibodies).

Secondary Prevention: Preventing the development of an allergic disease following sensitisation (and the progression from eczema or rhinoconjunctivitis into severe diseases such as asthma).

Tertiary Prevention: Treatment of asthma and allergic diseases.

Disease Nomenclature

Asthma (as defined by the Global Initiative for Asthma). Asthma is a chronic inflammatory disorder of the airways 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 and/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. This inflammation also causes an associated increase in airway responsiveness to a variety of stimuli.

Occupational Asthma. It is characterised by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to

a particular occupational environment and not to stimuli encountered outside the workplace.

Allergic Asthma. It is the basic term for asthma mediated by immunological mechanisms. When there is evidence of IgE-mediated mechanisms the term IgE-mediated asthma is recommended. IgE antibodies can initiate both an immediate and a late asthmatic reaction. However, as in other allergic disorders, T-cell-associated reactions seem to be of importance in the late and delayed reactions. Depending on the duration of symptoms, asthma can be referred to as either intermittent or persistent (as recommended in the document 'Allergic Rhinitis and Its Impact on Asthma' [3]).

Non-Allergic Asthma. This is the preferred term for non-immunological types of asthma. It is recommended that the old terminologies, 'extrinsic', 'intrinsic', 'exogenous' and 'endogenous' should no longer be used to differentiate between the allergic and non-allergic sub-groups of asthma.

Rhinoconjunctivitis. Symptoms of an immunologically mediated hypersensitivity reaction in the nose and conjunctiva should be referred to as allergic rhinoconjunctivitis. Most cases are IgE mediated. Based on the duration of symptoms, it can be useful to differentiate between intermittent and persistent allergic rhinoconjunctivitis.

Dermatitis. The umbrella term for a local inflammation of the skin should be dermatitis. What is generally known as 'atopic eczema/dermatitis' is not one, single disease but rather an aggregation of several diseases with certain characteristics in common. A more appropriate term is eczema. The subgroup related to allergic asthma and rhinoconjunctivitis, i.e. eczema in a person of atopic constitution, should be called atopic eczema.

Close contact with low-molecular-weight chemicals may provoke a predominantly Th1-lymphocyte-mediated allergic contact dermatitis. The non-allergic variety can also be described by terms like irritant/toxic contact dermatitis.

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The Heritability of Atopic Disease

Over recent years, considerable amounts of data have become available on the genetics of asthma in general, allergic asthma and other allergic diseases. These data have been derived from studies on twins, parental history, family studies, from other studies of IgE-mediated allergic diseases and from genetic studies of different types of allergic asthma, e.g. certain types of occupational asthma, as well as non-allergic asthma, such as aspirin-induced asthma (table 1). By careful review of these data, it is now possible to provide practical, useful, genetic information for physicians, patients and families. However, the complexity of the system limits the clinical application of the scientific knowledge.

The term ‘atopy’ (from Greek ‘strangeness’) was originally used by Coca and Cooke [1a(NC)] in 1923 to describe a particular predisposition to develop hypersensitivity to common allergens associated with an increase of circulating reagenic antibody, now defined as IgE, and with clinical manifestations such as whealing-type reactions, asthma and hay fever. Today, atopy is regarded as a constitutional trait, defined in the EAACI Revised Allergy Nomenclature Position Statement and the Report of the WAO Nomenclature Review Committee as ‘a personal and/or familial tendency to produce IgE antibodies in response to ordinary exposure to allergens, usually proteins’ [2, 3(NC)]. Thus, atopy is a clinical definition of an IgE-antibody high-responder genetic constitution. In this document IgE-mediated disease in atopic individuals is referred to as atopic disease. If the definition of atopy in a study discussed is not clear, this is indicated by citation markers, e.g. ‘atopy’.

In industrialised countries atopy is sometimes considered to be correlated with an increased total serum IgE level. Because of their complex clinical phenotype, IgE-mediated allergic diseases have been studied using intermediate or surrogate, disease-specific measurements, such as elevated total serum IgE for atopy, and bronchial hyperresponsiveness (BHR) for asthma (table 2). For studies of allergy this approach is unfortunate, since total serum IgE is not a good enough marker for IgE antibody sensitisation, and both allergic and non-allergic asthma are characterised by BHR. Phenotypes have been defined in several ways ranging from subjective measures (e.g. symptoms), objective measures (e.g. BHR or serum IgE level) or both. In addition some studies have utilised quantitative scores, which are derived from both physical measures such as serum IgE and BHR, and also questionnaire data [4(NC), 5(III)]. Again, these scores are not specific for IgE-mediated, atopic allergy. The intention is that these scores should enable the evaluation in a quantitative way of complex traits that result in the development of asthma symptoms. The use of such scores enables the utilisation of potentially more powerful methods for genetic analysis that rely upon the use of quantitative, rather than dichotomous traits. It is a lack of understanding of atopic phenotypes that presents the biggest problem when reviewing studies of the genetic basis of atopy, with multiple definitions of the same intermediate phenotype being used in different studies.

Is Atopy a Heritable Condition?

Some historical notes might be of interest. Eighty-two years ago the first comprehensive study of the heritability of atopy was undertaken by Cooke and van der Veer [6(III)] in the Department of Medicine of the Postgraduate Hospital and Medical School of New York in their study of 621 'atopic' probands and 76 'non-atopic' controls and their families (a respectable sample size even for current studies of atopy genetics). After initially determining the frequency of potentially allergic sensitisation, defined as 'hay fever... and also clinical manifestations of bronchial asthma, urticaria, angio-neurotic edema and acute gastro enteritis following the ingestion of certain foods but excluding... eczema, migraine and epilepsy until further observation warrants their inclusion' at approximately 10% in their population, Cooke and van der Veer [6(III)] showed that 48.4% of their 'atopic' probands had a positive family history for atopy compared to 14.5% in the control population. They discussed the effect of a family history for atopy on the age of onset of clinical symptoms and the nature of the inheritance; whether there is transmission of a definite allergen-specific IgE antibody sensitisation from parent to child, or whether the child merely inherits the capacity or tendency to form IgE antibodies specific to an allergen. While the 'atopic conditions' they included, and those excluded (such as eczema, transitionally termed the atopic eczema/dermatitis syndrome),

Table 1. Is atopic disease heritable?

-
- 1 Individuals with a family history of atopy have an increased risk of developing IgE sensitisation.
 - 2 The risk of developing atopic IgE-mediated diseases (e.g. allergic asthma, rhinitis and eczema) is related to a family history of IgE-mediated disease.
 - 3 Studies have estimated the contribution of genetic factors to the development of IgE sensitisation and to a family history of an IgE-mediated disease at 70–80%.
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may be open for debate today, the conclusions nonetheless remain the same. There is a high heritable component to the development of ‘atopy and atopic disease’ and, as is more clearly understood biologically now, this is an inheritance of a tendency to generate IgE antibody responses to common protein allergens. Subsequent to the work of Cooke and van der Veer, the results of many studies have established that ‘atopy’ and representative clinical entities such as asthma, rhinitis and eczema have strong genetic components. Family studies have shown an increased prevalence of ‘atopy’, and phenotypes associated with ‘atopy’, among the relatives of ‘atopics’ compared with ‘non-atopic subjects’ [7(III), 8(III)].

In a study of 176 normal families, a striking association was found between asthma, hay fever and ‘eczema’, in the parent and in the child [9(III)]. These findings suggest that end organ sensitivity is one of the components of the allergic diathesis that is inherited. This hypothesis is borne out by a questionnaire study involving 6,665 families in southern Bavaria. Children with ‘atopic diseases’ had a positive family history in 55% of cases compared with 35% in children without ‘atopic disease’ ($p < 0.001$) [10(III)]. Subsequent work on the same population set out to investigate familial influences unique to the expression of asthma. It was found that the prevalence of asthma alone (i.e. without hay fever or eczema) increased significantly if the nearest of kin suffered from asthma alone (4.7 vs. 11.7%, $p < 0.0001$). A family history of eczema or hay fever and excluding asthma was unrelated to asthma in the offspring [11(III)].

One method which can be used to determine the relative contribution of genes and the environment in complex genetic disorders is to study the concordance of a trait in mono- and dizygotic twins. Monozygotic twins have identical genotypes, whereas dizygotic twins share on average only one half of their genes. Therefore a disease that has a genetic component is expected to show a higher rate of concordance in monozygotic than in dizygotic twins. Numerous twin studies [12(III), 13(III), 14(III), 15(III), 16(III), 17(III), 18(III)] have shown a significant increase in concordance amongst monozygotic twins compared with dizygotic twins, providing evidence for a genetic component to

Table 2. Phenotypes used for genetic analysis of allergic disease

1 <i>Complex</i>
Affection status
Atopy
Asthma
Eczema
Rhinitis
Quantitative scores
2 <i>Intermediate</i>
Skin prick tests
Size of wheal, number of positives
Presence of IgE antibodies
Number of positives
Level of positivity to individual allergens
Sum of specific IgE levels for multiple allergens
Total IgE
Measures of lung function
FEV ₁ , BHR (methacholine and histamine)
Measures of disease severity
Medication usage
Quality of life

atopy. IgE-mediated asthma has also been widely studied, and twin and family studies have also shown a strong heritable component to this phenotype [12(III), 16(III), 17(III), 19(III), 20(III), 21(III)].

In a recent study using a twin-family model, in families with asthma in successive generations, genetic factors alone explained as much as 87% of the development of asthma in offspring. The incidence of the disease in twins with affected parents is fourfold compared with the incidence in twins without affected parents [22(III)] (parents were not separated into allergic and non-allergic asthma). This indicates that asthma in general is reoccurring in families due to shared genes rather than to shared environmental risk factors. This has been further substantiated in a recent study of 11,688 Danish twin pairs. Using additive genetic and non-shared environmental modelling it was suggested that 73% of susceptibility was due to the genetic component. However a substantial part of the variation liability of asthma in general was due to environmental factors, and there was no evidence for genetic dominance or shared environment effects [23(III)].

Segregation analysis is a method of determining the pattern of inheritance of a disease or trait by observing how it is distributed within families. The

observed frequency of a trait in offspring and siblings is compared to the distribution expected with various modes of inheritance. If the distribution is significantly different than predicted, that model is rejected. The model that cannot be rejected is, therefore, considered the most likely. Segregation analysis has been applied to IgE and BHR as well as to the individual IgE-mediated diseases. Several different modes of inheritance of high IgE levels have been suggested including autosomal recessive, autosomal dominant and polygenic inheritance [24(III), 25(III), 26(III), 27(III), 28(III), 29(III), 30(III)]. One study looked at eight traits, log IgE, BHR, skin prick test, eczema, hay fever, wheeze, asthma in general (i.e. with no distinction between allergic and non-allergic asthma) and 'atopy' on a cohort of 131 families recruited at random from the population of Wessex, UK. Complex segregation analysis showed that it was unlikely that any major genes underlay any of these traits, with the data favouring a two-locus model [4(NC)]. The prevalence of BHR in the non-asthmatic members of families with an asthmatic proband has also been investigated [21(III), 31(III), 32(III)]. In each of these studies, a high proportion of clinically 'normal' first-degree relatives of asthmatic children demonstrated bronchial reactivity, suggesting a genetic component to the trait. However, segregation analysis of bronchial response to methacholine on 51 families ascertained through a proband with asthma revealed no evidence for genetic segregation at a single locus and implied that a large environmental component was involved in the expression of the trait [33(III)]. Segregation analysis of physician-diagnosed asthma in Hispanic and non-Hispanic white families rejected an environmental model and supported the hypothesis that the inheritance of asthma in general is mediated by a major autosomal co-dominant gene [34(III)]. From these studies it is clear that both atopy and asthma are complex diseases in which it is the interaction between both genetic and environmental factors that plays a fundamental role in the development of IgE sensitisation and in the subsequent development of disease. The development of IgE responses by an individual, followed by allergic disease, is the function of several genetic factors. These include the regulation of basal serum immunoglobulin production, the regulation of the switching of immunoglobulin-producing B cells to IgE, and the control of the specificity of responses to antigens.

The genetic influences on the development of symptoms of IgE-mediated asthma are even more complex, involving not only genes controlling the induction and level of an IgE-mediated response to allergen, but also triggering of mast cells, release and activation of mediators, chemokines and interleukins, expression of inflammation and its effect on target organs and finally individual 'symptom sensitivity'. This also applies equally to other clinical manifestations of atopy such as rhinoconjunctivitis and the IgE-associated subgroup of eczema (table 3).

Table 3. How can genetic effects influence IgE-mediated disease?

-
- 1 *Determine susceptibility to IgE-mediated disease 'Th2' or 'IgE switch' genes*
 - 2 *Determine specific target organ disease in atopic individuals*
 - Asthma susceptibility genes
 - 'Lung-specific factors' that regulate susceptibility of lung epithelium/fibroblasts to remodelling in response to allergic inflammation
 - Eczema susceptibility genes
 - Genes that regulate dermal inflammation and immunity (common loci with psoriasis)
 - 3 *Influence the interaction of environmental factors with atopy and IgE-mediated disease*
 - Regulation of specific IgE responses (what allergen will you respond to?)
 - e.g. MHC class II alleles, TCR V gene usage
 - Determining immune responses to factors that drive Th1/Th2 skewing of the immune response
 - e.g. CD14/TLR4 polymorphism and early childhood infection
 - Changing interaction between genetic effects and environmental exposures in the initiation of disease
 - e.g. β_2 AR polymorphism, cigarette smoke and asthma susceptibility
 - Altering interaction between environmental factors and established disease
 - e.g. genetic polymorphism regulating responses to RSV infection and asthma symptoms
 - 4 *Modify severity of disease*
 - e.g. TNF- α polymorphisms and asthma severity
 - 5 *Regulate response to therapy*
 - Pharmacogenetics
 - e.g. β_2 AR polymorphism and response to β_2 -agonists, clinical variability in response to anti-leukotriene therapeutics
-

Molecular Regulation of Atopy and Atopic Disease

Susceptibility Genes

Approaches to Genetic Studies of Complex Genetic Diseases

There are two main approaches to identifying genes predisposing to disease. The first of these is the candidate gene approach in which genes, selected for their relevance to the pathophysiology of the disease, are directly tested for their involvement by linkage or association with the disease. This is then followed by the identification of causative mutations or polymorphisms. The second is termed a 'genome scan' or 'positional cloning', in which the entire genome is screened using a panel of polymorphic DNA markers spaced across the genome to identify specific regions linked to specific phenotypes. This is then followed by the identification of the gene (or genes) within this region,

and polymorphisms within these gene(s), that contribute to the development of the disease.

The aim of linkage studies is to localise the gene responsible for a disease through demonstration of inheritance of a DNA marker, with a known position in the genome, with the phenotype of the disease. Thus, linkage studies can identify a region of the chromosome in which the disease gene may be located. If the whole genome is assessed for linkage with the disease phenotype of interest, this is termed a genome-wide screen. The aim of association studies is to show that affected individuals in a population are more likely to have a particular allele (variant) of a gene than the unaffected individuals in the same population. A positive association may indicate a causal relationship between the allele and the disease, but it can also occur if the allele is in linkage disequilibrium with another disease causing polymorphism in the same or a nearby gene. Furthermore a positive association may occur as a result of a population admixture. In a mixed population, any trait present at higher frequency in an ethnic group will show a positive association with any allele that also happens to be more common in that group. Thus to prevent false-positive associations, association studies should be performed within relatively homogeneous populations or alternatively tests of association in family-based cohorts can be used such as the Transmission Disequilibrium Test [35(NC)].

Genome-Wide Screens

Several genome-wide screens for atopy and atopic disorder susceptibility genes have been completed. In Australian and UK populations six regions of potential linkage on chromosomes 4, 6, 7, 11, 13 and 16 with 'atopy' and BHR have been described [36(III)]. Recently, the same group has shown positive linkage of serum IgA levels to a marker on chromosome 13 previously linked to 'atopy' [37(III)]. The Collaborative Study on Genetics of Asthma (CSGA) [38(III)] is a large, multicentre, ongoing study in the USA. In its first report, describing the analysis of 237 affected sib pairs, the linkage between asthma and six novel regions in three racial groups was described: 5p15 and 17p11.1–11.2 in African Americans; 11p15 and 19q13 in Caucasians, 2q13 and 21q12 in Hispanics. They also detected linkage in five regions previously reported to be linked to asthma phenotype: 5q, 6p, 12q, 13q and 14q in Caucasian and 12q in Hispanics. A further report from the CSGA study [39(III)] using 199 single pedigree and 67 extended pedigrees with ethnicity-specific analyses, which allowed for different frequencies of asthma susceptibility genes in each ethnic population, provided the strongest evidence for linkage at 6p21 in the Caucasian population, at 11q21 in the African American population, and at 1p32 in the Hispanic population. Conditional analysis and affected-sib-pair two-locus analysis provided further evidence for linkage, at 5q31, 8p23, 12q22 and 15q13 [39(III)].

Genome scans have also been completed in a sample of 97 German and Swedish families, including 156 sib pairs and 107 French families. In the German asthma genetics study, four candidate regions were identified that showed linkage to asthma: the region of chromosome 2 around the marker D2S2298; chromosome 6p21.3–23; chromosome 9 (proximal to D9S1784), and chromosome 12q13–21. Linkage to these regions was also seen with total or allergen-specific IgE [40(III)]. In the French Epidemiological Study of the Genetic and Environmental Factors in Asthma, Bronchial Hyper-Responsiveness and Atopy (EGEA) study a two-stage analysis led to the detection of three regions: 11p13 for IgE, 12q24 for eosinophils and 17q12–21 for asthma and skin tests. The EGEA study also found evidence of four other regions previously linked in genome scans: 1p31 for asthma, 11q13 for IgE, 13q31 for eosinophils and 19q13 for BHR [41(III)].

Three genome scans for asthma have been undertaken in genetically isolated populations. The advantages of genetically isolated populations is that being relatively homogeneous, the molecular mechanisms underlying a complex disease such as asthma might also have reduced heterogeneity and therefore be easier to dissect than in mixed populations. In the Hutterites, a genetically isolated population of European ancestry, an initial sample of 361 individuals and a replication sample of 292 individuals were evaluated for asthma phenotypes, and 12 markers in 10 regions were identified that showed possible linkage to asthma or an associated phenotype. Linkage was found in both the initial and replication samples in four regions (5q23–31, 12q15–24.1, 19q13 and 21q21) that have also shown linkage to asthma phenotypes in other samples. In addition one novel region linked to asthma phenotypes, 3p24.2–22, was also identified [42(III)]. A study of a population from eastern central Finland (Kainuu province) found strong evidence for linkage in a 20 cM region of chromosome 7p14–p15 for three phenotypes: asthma, a high level of total serum IgE (>100 kU/l) and the combination of the two phenotypes (i.e. asthma and high serum IgE levels). The strongest linkage was seen for high serum IgE (non-parametric linkage score 3.9, $p = 0.0001$) [43(III)]. In a study of a genetically isolated population on the island of Tristan da Cunha [44(NC)], AxyS Pharmaceuticals identified linkage between asthma and chromosome 11p13. Subsequently two transcription factors (*ASTH1I* and *ASTH1J*) were identified at this locus, and single-nucleotide polymorphisms (SNPs) within these genes were reported to be associated with asthma [45(NC)]. Asth1J contains a polymorphism in the CAAT box of the promoter that affects the transcription of the gene. Asth1J is identical to a previously described gene ESE-3 and appears to be involved in regulating epithelial differentiation [46(NC)].

Three genome scans have also been completed for childhood ‘atopic dermatitis’ and allergic rhinitis resulting in the identification of four candidate

loci, 3q21 [47(iii)], 1q21 and 17q25 [48(III)] and 4q24–27 [49(III)]. Some of these loci overlap closely with loci previously identified as susceptibility loci for psoriasis [48(III)]. This suggests that ‘atopic dermatitis’, most likely eczema, may be influenced by genes with general effects on dermal inflammation and immunity.

Thus the results of the genome-wide screens for asthma susceptibility genes reflect the genetic and environmental heterogeneity seen in allergic disorders and illustrate the difficulty of identifying susceptibility genes for complex genetic diseases. In addition, as discussed above, the phenotype is not always clearly defined. Different genetic loci will show linkage in a population of different ethnicity and differing environmental exposure. Identifying the gene(s) underlying the linkage observed is therefore a major challenge.

It is also clear from these studies that the propensity to express the atopic constitution is influenced by different factors than those that influence disease. However, these disease factors require interaction with IgE antibodies (or something else) to trigger disease. For example, in asthma, disease is triggered mostly by an eosinophilic inflammation in the lung, but in some people who may have ‘asthma susceptibility genes’ but not the atopic constitution, asthma is triggered by other factors such as toluene diisocyanate etc. This is reflected in the three novel asthma susceptibility genes recently identified, with *PHF11* [50(IIb)] and *DPP10* [51(IIb)] being associated with measures of atopy and related to allergic inflammation in general and *ADAM33* being an asthma-specific factor related to BHR (see below).

Novel Asthma Susceptibility Genes Identified through Genome Scans

The A disintegrin and metalloprotease 33 (ADAM33) gene is a member of a sub-group of the zinc-dependant metalloprotease family. ADAM family members are involved in a wide range of biological processes including the shedding of cell-surface proteins such as cytokines and cytokine receptors. In a genome-wide scan of 460 Caucasian families for doctor-diagnosed asthma, evidence for linkage between polymorphic genetic markers on chromosome 20 was found, the statistical significance of which further increased when BHR was included in the definition of asthma [52(IIb)]. In contrast, when asthma was conditioned for serum total IgE and allergen-specific IgE, the level of statistical evidence fell, indicating the presence of genes more closely linked to altered airway function than to allergic inflammation per se. Physical mapping and direct cDNA selection identified 40 genes in the region under the peak of linkage at 20p13 [52(IIb)]. SNPs in the region were then identified and were typed in cases and controls. 24 SNPs were localised to a cluster of three genes showing significant association with both asthma and BHR. Fourteen of these lay within a single gene identified as ADAM33 [52(IIb)].

The association of polymorphism in ADAM33 with asthma has since been confirmed in several other populations [53(III), 54(III)]. Although as might be expected for a complex disease the replication of these findings has not been universal [55(III), 56(NC)].

ADAM33 is the most recently reported member of the ADAM gene family of zinc-dependant matrix metalloproteases [57(NC)]. ADAMs have a complex organisation involving eight domains, the first six encoding signal sequence and pro-, catalytic, disintegrin, cysteine-rich and epidermal growth factor domains [58(NC)] which are anchored at the cell surface or Golgi apparatus by a transmembrane domain followed by a cytoplasmic domain with signalling-specific sequences. ADAM33 belongs to the ADAM 12, 15, 19 and 28 sub-family, all of which possess proteolytic activity [58(NC), 59(NC)]. ADAM33 is expressed in a number of lung cell types including bronchial smooth muscle, myofibroblasts and fibroblasts, but not in bronchial epithelial cells, T cells or inflammatory leukocytes.

Asthma is a chronic disorder in which T-cell-mediated inflammation causes thickening of airway walls, smooth muscle contraction, and narrowing of the airways. Epithelial damage, smooth muscle hyperplasia and increased matrix deposition are important characteristics of asthmatic airways that are thought to contribute to airway responsiveness [60(NC)]. This remodelling process has been linked to activation of the epithelial-mesenchymal trophic unit leading to the proliferation of biosynthetically active fibroblasts, myofibroblasts and smooth muscle, a feature of BHR [61(NC)]. A role for ADAM33 in airway remodelling and BHR is supported by its expression in human lung fibroblasts and bronchial smooth muscle. The pattern of expression of ADAM33 suggests that alterations in the activity or expression levels of ADAM33 may underlie abnormalities in airway function rather than the immunological components of asthma. In addition, the known functions of ADAM family members in promoting myogenic fusion [62(NC)] and the release of proliferative growth factors [59(NC)] further support a role for ADAM33 in airway remodelling. The identification of ADAM33 as a susceptibility gene for asthma and BHR illustrates that the positional cloning approach for complex disease can be successful, leading to the identification of a novel gene and pathway involved in disease pathogenesis.

Less than a year from the identification of ADAM33 as an asthma susceptibility gene, a second asthma gene was identified through a positional cloning strategy. Polymorphism of the gene *PHF11* was recently identified as accounting for a proportion of variation in total serum IgE levels and to be associated with severe asthma. In a multistage process involving identification of a region of linkage on chromosome 13q14 to serum IgE levels in a genome-wide scan [36(III)], confirmation of this linkage in other cohorts [63(III), 64(III)] and fine

mapping of the region with additional microsatellite markers [65(NC)] showed that the locus linked to total serum IgE levels was located within a 7.5-cM region centred on the genetic marker *D13S161*. Positive association was observed between IgE levels and the microsatellite *USAT24G1* [66(III)]. This suggested that the gene responsible for the observed linkage and association lay within 100 kb of this marker. Within this region 54 additional genetic markers were typed (49 SNPs, 4 insertion-deletion polymorphisms and 1 microsatellite), and strong association was found between SNPs centred on the gene *PHF11* and extending to two flanking genes (*SETDB2* and *RCBTB1*) [50(IIb)]. After further analysis, 3 SNPs (b5_2, b4_2 and b5_3) all within *PHF11* were shown to have independent effects on IgE levels [50(IIb)]. This association was confirmed in a number of other cohorts including a panel of randomly recruited Australian families and families with 'atopic dermatitis'. In unrelated British adults, the SNP b4_2 was most strongly associated with severe asthma [50(IIb)]. *PHF11* contains two PHD zinc-finger DNA binding motifs and is probably a transcription factor regulating the expression of other genes. It is widely expressed in many different tissues including the lung, immune tissues and B cells. It is tempting to speculate that it may regulate B-cell immunoglobulin switching but as with *ADAM33*, understanding the biology is going to take as long as finding the gene.

A third asthma susceptibility gene, *DPP10*, has been more recently identified. The *DPP10* gene encodes a homologue of dipeptidyl peptidase and is located on chromosome 2q14 [51(IIb)]. Its role in the pathogenesis of asthma may be through the cleavage of signal peptides from cytokines and chemokines. All three asthma/atopy susceptibility genes identified through genome scans, *ADAM33*, *PHF11* and *DPP10*, will require considerable further research into the role that these gene products play in the pathogenesis of the disease. However in the future, this may provide new opportunities for therapeutic intervention in asthma.

Candidate Regions

A large number of candidate regions have now been studied for both linkage to and association with a range of atopy-related phenotypes. In addition, single nucleotide polymorphism in the promoters and coding regions of a wide range of candidate genes has been examined. These genes have been chosen both due to their chromosomal location and their product function in IgE-mediated disease processes. There are now over 200 studies that have examined polymorphism in over 100 genes for association with asthma and allergy phenotypes. The description below, while not an exhaustive summary of these studies, outlines the current understanding of the role of a number of candidate genes/gene regions in determining susceptibility to express atopy. For readers wanting a more comprehensive summary of all studies of the genetic

basis of allergy and asthma, one can be found on the Asthma Gene Database website (<http://cooke.gsf.de/asthmagen/main.cfm>) [67(NC)]. When assessing the significance of association studies it is important to consider several things. These include the size of the study: Was it adequately powered if negative results are reported? The selection of cases and controls: Were the cases and controls appropriately matched? Could population stratification account for the associations observed? Definition of phenotypes: What phenotypes have been measured (and which haven't)? How were they measured? Correction for multiple testing: Have the authors taken multiple testing into account when assessing the significance of association? Recent publications by Weiss [68(NC)], Hall [69(NC)] and Tabor et al. [70(NC)] review these issues in depth.

Chromosome 11q13

The first evidence for linkage of 'atopy' with a specific chromosomal region was reported in 1989. In a group of seven families a linkage was seen between 'atopy' (defined by high total serum IgE and/or specific IgE response to a group of common allergens and/or positive skin prick test) and the D11S97 marker on chromosome 11q13, with a maximum lod score for all seven families of 5.58, although the majority of the lod score came from a single large family [71(III)]. This linkage was supported by a second study in a sample of 64 nuclear families [72(III)]. Subsequently, using their previous definition of atopy and an expanded population sample, the same group found a maternal bias in the inheritance of 11q13 marker in affected sib pairs [73(III)]. Other workers found that 11q13 was linked to log IgE and a skin prick test index, but not to a composite 'atopy' phenotype. In a second sample, the same marker was linked to asthma but not to IgE or the skin prick test index [36(III)]. Mapping of the 11q13 region identified a putative candidate gene for 'atopy', the β chain of the high-affinity IgE receptor (Fc ϵ RI- β), at this locus, and it was shown to be linked to 'atopy' [74(III)]. Fc ϵ RI- β was linked to serum IgE antibody levels but not to total serum IgE levels in 121 Australian Caucasian families [75(III)]. Studies of linkage between 11q13 markers and 'atopy' or IgE-mediated diseases are still controversial as many investigators have not replicated the 1989 results referred to above. It is difficult to make a comparison between these studies due to different methods of subject ascertainment, phenotype and disease definitions, and small sample sizes [76(III), 77(III), 78(III), 79(III), 80(III)]. Other investigators have found linkage to the original markers D11S97 but not to Fc ϵ RI- β , indicating the possible presence of another 'atopy' susceptibility gene in 11q13 [81(III), 82(III)]. Similar negative results have been reported for BHR, with an exception of a weak linkage of BHR to one marker in one study [83(III)]. Linkage to 11q13 has also been seen in one study of families with eczema [84(III)], however this was not replicated in another study [79(III)].

The β -chain of Fc ϵ RI is thought to amplify the signal resulting from cross-linking of the receptor [85(NC)]. As such, polymorphisms of the β -chain may increase mast cell activation and the release of IL-4 stimulating IgE synthesis. Sequence analysis of the Fc ϵ RI- β gene has identified three nucleotide substitutions in the sixth exon resulting in leucine substitutions at positions 181 and 183 within the fourth transmembrane domain of Fc ϵ RI- β [86(III)]. The Leu181 polymorphism was identified in 17% of 60 unrelated nuclear families with allergic asthmatic probands, was maternally inherited in each family, and showed significant association with positive IgE responses. The Leu183 variant was not identified in any family or individual. A subsequent study in a general Western Australian population identified the Leu181/183 polymorphisms at a frequency of 4.5% and showed that when inherited maternally, this haplotype constituted a genetic risk factor for 'atopy' and BHR [87(III)]. Children with maternal-inherited Leu181 have increased levels of total IgE and a positive IgE response to grass pollen compared to children ('atopic' and 'non-atopic') without Leu181. However, no association was found between Leu181 and clinical manifestations of atopy such as allergic asthma in these families [88(III)].

Arguing against the direct involvement of the Leu181 polymorphism in the expression of atopy is the fact that several studies have failed to identify the Leu181 mutation in a number of different population groups [89(NC)]. In addition, there is no evidence of functional differences in receptor function between 'atopic' subjects with Leu181 compared to other atopic individuals [90(NC)]. Therefore association between Leu181 and atopy may merely reflect linkage disequilibrium with another variant of Fc ϵ RI- β , or another tightly linked gene.

Further to this, an additional polymorphism of the Fc ϵ RI- β , an A $\rightarrow$ G substitution that changes amino acid residue 237 from glutamic acid to glycine (E237G) was subsequently identified in 5% of a previously studied Australian population. In this population E237G was shown to be associated with 'atopy' and BHR [91(III)]. In addition, E237G has also shown association with asthma and BHR in a Japanese population [92(III)]. Restriction fragment length polymorphism markers (*Rsa* I restriction sites in exon 7 and intron 2) have shown association with total serum IgE in an Australian Aborigine population [93(III)], and with IgE-mediated asthma and IgE, but not with BHR in a Japanese population [92(III)], while in an Italian population the same polymorphism was associated with BHR but not IgE [94(III)]. This association with 'atopy' could not be confirmed in a second Japanese population [95(NC)] nor in a Spanish population [96(III)]. A recent study involving two groups of patients with eczema showed a strong association of both Fc ϵ RI- β , *Rsa* I polymorphisms with the disease but only in maternally derived alleles [97(III)] and also showed a significant association of these polymorphisms with allergic asthma. Conversely, no association between E237G polymorphism and eczema or asthma was found.

The conflicting results of different studies in different populations make it uncertain whether any of the identified polymorphisms of FcεRI-β are casual mutations or in linkage disequilibrium with other polymorphisms in the same or a closely linked gene. One such closely linked candidate gene is uteroglobin (UGB; also called CC10 or CC16) which is expressed in the Clara cells of bronchial mucosa and has an inflammatory and immune modulation role [98(III)]. An adenine to guanine substitution at position 38 (A38G) in the promoter region of the gene has been reported to be associated with asthma in an Australian population [99(III)]. However, two following association studies did not find any positive association between asthma and CC16 genotypes in Japanese and British populations [100(III), 101(III)].

Chromosome 5q31–35

The first reported linkage of atopy with chromosome 5 was by Marsh et al. [102(III)]. In this study of 11 large Amish pedigrees, selected on the basis of serum IgE antibodies to common allergens in at least one child, there was linkage between five markers located on chromosome 5q31 and total serum IgE, with the linkage being centred around the IL-4 locus. No linkage was seen between IgE antibodies and the same markers. There are a number of genes on chromosome 5q that may be important in the development or progression of inflammation associated with atopic disease including the cytokines IL-3, IL-4, IL-5, IL-9, IL-12 (β-chain), IL-13 and GM-CSF.

Further evidence for the role of this Th2 cytokine cluster has been provided by Meyers et al. [30(III)]. Using a similar phenotype, linkage has been reported between several markers on 5q31–33 and total IgE in 92 Dutch families. Further segregation analysis of these families provided evidence for a second major locus regulating serum IgE levels [103(III)] unlinked to that on 5q31–33. In addition a positive linkage between several markers on 5q and BHR [104(III)] was also seen in this population, with the strongest linkage evidence for both phenotypes being centred around the β₂-adrenergic receptor (β₂AR). A space strong association has been identified between total IgE and the IL-9 locus, but not with BHR, in a UK random population [105(III)]. In 68 Japanese families ascertained through asthmatic children a positive linkage has been found between ‘atopy’ and asthma and gene markers in or near the IL-4 and IL-9 genes and D5S393 on chromosome 5q31–33 [106(III)]. In a study involving 121 Australian families, two markers in this region, 393 and 399, were found to be linked to total serum IgE and IgE antibody levels but not to BHR [75(III)]. The CSGA genome-wide scan also found linkage of asthma to 5q in Caucasian families [38(III)]; however a previous study using the same approach found no linkage between IgE or BHR and 5q markers in a UK and Australian population sample [36(III)]. A more recent

study from the same investigators of linkage and association with multiple markers concluded that there might be as many as three asthma/‘atopy’ loci in the 5q13–33 region, each with a relatively small effect [107(III)].

Other groups of investigators have also been unable to detect evidence of linkage between polymorphic markers on chromosome 5q31–33 and IgE; studies of large ‘atopic families’ in Minnesota [108(III)] and of 119 sibling pairs recruited from an Australian population [109(III)], using the polymorphic marker D5S399, failed to detect any evidence of linkage with asthma or ‘atopy’. A study using sixteen polymorphic markers, spanning 5q31–33, failed to detect any linkage to either serum IgE level or asthma in 157 families from Finland [110(III)]. Another study examining the association between 11 polymorphic markers spanning the region 5q31.1–33.1 and total serum IgE and BHR traits also failed to detect any associations between these markers and either IgE or BHR [111(III)].

The Consortium on Asthma Genetics (COAG) has attempted to pool information from different studies on chromosome 5 and asthma, each of which had published its principal results, to allow a meta-analysis of the data [112(NC)]. The results of the COAG5 study, which utilised data from 1,037 families from 11 centres, suggest that there is a major gene for asthma in the 5q31–33 region which contributes 15–23% of the genetic risk of asthma, with the highest lods at the centromeric end of the Th2 cytokine cluster, but this study provided little evidence for a gene predisposing to ‘atopy’ in this region [113(III)]. There are a number of problems with such retrospective collaborations, not least the differences in ascertainment of subjects, phenotyping, and genetic markers between studies. Providing these difficulties can be adequately resolved, the sample size of studies such as COAG5 may help resolve many of the conflicting results and lead to identification of the gene (or genes) that underlie linkage to chromosomal regions such as 5q31–33.

The inconsistency of these results may be attributable to differences in populations, such as ethnicity and ascertainment of the families studied and/or differences in definition of phenotype. However the linkage between 5q31 and ‘atopy’ and asthma phenotypes is the most reproduced of all the possible linkages reported. Based on the results of 5q31–33 linkage studies, studies have begun to identify polymorphisms in candidate genes at this locus and to examine possible association of these polymorphisms with disease traits.

IL-4 and the IL-4 Receptor

IL-4 plays an essential role in the IgE-mediated immune response, as it induces IgE synthesis in B cells and differentiation to the Th2 phenotype in T cells. This makes the IL-4 gene itself, or factors which regulate its expression, a strong candidate gene for atopy and asthma. An IL-4 promoter

polymorphism, a C $\rightarrow$ T substitution at -589 bp from the open reading frame, in 20 asthmatic and 5 control families has been identified. This polymorphism has been shown to be associated with high serum IgE levels and to increase the transcriptional levels of the IL-4 gene in a CAT assay [114(NC)]. However, the role of this polymorphism is still controversial. Two large populations, 230 nuclear families from Australia, and 124 unrelated 'atopic' asthmatics and 59 unrelated 'non-atopic', non-asthmatic controls from the UK have been studied. Only a weak association of this polymorphism with IgE antibody to house dust mite and to wheeze was found in the first population, while no association with any measure of asthma or 'atopy' was found in the UK population [115(III)]. A study of two populations, one of families ascertained through an asthmatic child, and one a randomly ascertained population as a control, found no significant difference in the prevalence of the polymorphism between the two groups. No difference was observed in total IgE or IgE antibody levels, whether the individual was homozygous for the C allele, heterozygous or homozygous for the T allele. However, using the Transmission Disequilibrium Test a significant association between the T allele and asthma was found in the family sample [116(III)]. Finally, a recent study has shown an association between C-589T polymorphism and the severity of asthma measured by FEV₁ [117(III)]. The IL-4 C-589T polymorphism has also been studied in 'atopic dermatitis' patients. The T allele has been found to be transmitted preferentially to the offspring of patients with eczema and the number of T allele homozygotes was significantly increased in eczema patients when compared to controls [118(III)].

IL-4 acts its biological effects by binding to the IL-4 receptor (IL-4R) [119(NC)]. The IL-4R is composed of two subunits: an α subunit required for IL-4 binding and signal transduction, and a γ subunit common to several cytokine receptors [120(III)]. The IL-4R α chain consists of one extracellular domain, that contains the IL-4 binding site, and a large cytoplasmic domain.

The IL-4R α gene is located on chromosome 16p(16p12.1) [121(III)], and a study using four microsatellite markers flanking the IL-4R α gene on chromosome 16p found significant linkage between three markers and specific sensitisation to common inhalant allergens in two populations of 'atopic' families, stressing the significance of IL-4R α as a candidate gene for 'atopy' [122(III)]. Several polymorphisms have been identified in the coding part of the IL-4R α gene, some of them leading to amino acid changes of the gene products [123(NC)]. An extracellular variant of IL-4R α chain (I50V) consisting of a substitution of valine at amino acid 50 for isoleucine has been shown to upregulate receptor response to IL-4 with an increased STAT 6 activation, CD23 expression and increased IgE synthesis. Ile50 was also associated with atopy (measured as total IgE and mite-specific IgE), and allergic asthma [124(III)],

125(NC)]. However, a recent study in a similar Japanese population failed to find any association between I50V polymorphisms and ‘atopy’ or asthma [126(III)].

A polymorphism in the intracellular domain of IL-4R α , Q576R, has been shown to enhance signalling of the IL-4R resulting in an increase in CD23 expression and to be associated with hyper-IgE syndrome and severe eczema. The Q576R, located in the STAT6 binding region, is adjacent to tyrosine residue Y575 that binds to SHP-1, a phosphotyrosine phosphatase involved in signal termination. Q576R may alter the binding of SHP-1 to phosphorylated Y575 leading to an exaggerated signalling [127(NC)]. Investigation of four polymorphisms of the IL-4R α , including Q576R, and their association with ‘atopic’ phenotypes, found that Q576R is associated with lowered total IgE levels and that this effect is magnified by the simultaneous presence of another polymorphism, S503P, located in the I4R motif. While the presence of S503P alone does not influence the signal transduction it is possible that the presence of both polymorphisms (S503P/Q576R) may alter the conformation and charge of the receptor, abolishing the propagation of IL-4 signals leading to decreased B-cell proliferation and IgE synthesis. Conversely, a recent study showed that Q576R does not have a direct effect on IL-4 signal transduction [128(NC)]. Therefore, further functional studies are required to establish the mechanisms through which these polymorphisms may alter the IL-4R α signalling and predispose to IgE sensitisation.

The most comprehensive study of IL-4R α variation, atopy and asthma susceptibility has been undertaken in the Hutterite and CSGA genome scan study populations. All the population samples showed evidence of association to ‘atopy’ or to asthma (p values 0.039–0.0044 for atopy and 0.029–0.0000061 for asthma), but the alleles or haplotypes showing the strongest evidence differed between the groups [129(III)]. The authors concluded that while the IL-4R α gene is an ‘atopy’ and asthmasusceptibility locus, it is likely that variation outside the coding region of the gene influences susceptibility. Therefore at this stage it is difficult to identify which polymorphism(s) of IL-4R α contribute to the association seen with ‘atopy’, and which merely show linkage disequilibrium with other disease-causing polymorphisms.

Interleukin-13

IL-13 is a closely related cytokine to IL-4 that is also produced by Th2 cells. IL-13 along with IL-4 can switch B cells to produce IgE, however unlike IL-4, IL-13 cannot induce Th2 cell differentiation. In adults only 50% of asthma is associated with atopy, yet all forms of the disease are characterised by enhanced T-cell secretion of Th2 cytokines in the airways. Severe chronic asthma is characterised by the deposition of interstitial collagens in the lamina

reticularis beneath the epithelial basement membrane associated with an increased number of myofibroblasts, epithelial damage and increased mucus production-airway remodelling. Of importance in asthma, IL-4 and IL-13 are also key regulators of this response, with wide-ranging effects on epithelial cells, fibroblasts, and smooth muscle. Evidence suggesting a critical role for IL-13 in asthma comes from well-characterised experimental models of allergic asthma. Sensitisation and subsequent challenge of mice with allergen results in airway hyperresponsiveness (AHR), increase in IgE antibody, mucus secretion and airway eosinophilia. Daily administration of IL-13 to the airways of mice has been shown to induce AHR, increased total IgE, mucus secretion, goblet cell metaplasia and airway eosinophilia [130(NC), 131(NC)]. Transgenic expression of IL-13 in the lungs of mice has been shown to cause similar phenotypes [132(NC)].

The IL-13 gene is also encoded in the Th2 cytokine cluster, a cluster on chromosome 5q31–33 located within 12 kb of IL-4 [133(NC)] and shares 40% homology with IL-4. A number of polymorphisms have now been identified in the IL-13 gene. A single base pair substitution in the promoter of IL-13 adjacent to a consensus NFAT binding site has been identified. Using an oligonucleotide ligation assay in a sample of 101 asthmatics and 107 controls, the authors showed an increased frequency of homozygotes in the asthmatic group (13/107 vs. 2/107, $p = 0.002$, odds ratio = 8.3). In vitro experiments showed that the polymorphism was associated with less inhibition of IL-13 production by cyclosporin and increased binding of NFAT [134(III)]. As well as promoter polymorphisms of IL-13, an additional amino acid polymorphism of IL-13 has been identified, Arg110Gln [135(III), 136(III), 137(NC)]. Protein modelling suggests that this polymorphism may influence binding of IL-13 to the IL-4R α /IL13R α 1 receptor complex.

Strong associations have been shown between IL-13 polymorphisms and ‘atopy’-related phenotypes in two studies of children [135(III), 138(III)], however, neither of these studies examined associations with asthma. In contrast, in adults, polymorphisms in IL-13 are associated with asthma *not* IgE levels [136(III), 139(III)]. Thus, it is possible that polymorphisms in IL-13 may confer susceptibility to airway remodelling in asthma, as well as to allergic inflammation in early life.

The conflicting reports of positive and negative associations between polymorphisms in the IL-4 and IL-13 genes highlight a number of issues that need to be addressed when interpreting the results of association studies. Polymorphisms that are physically close to one another in the genome are often in association with each other (linkage disequilibrium) and therefore are not inherited independently. Consequently association seen between polymorphism A and a disease phenotype may not indicate that polymorphism A is affecting

gene function but rather that it is merely in linkage disequilibrium with polymorphism B that is exerting an effect on gene function or expression. Given that both IL-13 and IL-4 are good functional candidates for atopy and asthma, polymorphism in either or both of them may be affecting disease susceptibility. Therefore to gain a true understanding of the roles of individual polymorphisms it will be necessary to type polymorphism across the two genes in a single population and assess the significance of association of different haplotypes (combinations of polymorphisms).

In at least one study haplotypes consisting of IL-4 promoter polymorphisms and polymorphism lying in the intergenic region between the IL-4 and IL-13 genes have shown significant association with asthma [140(III)]. Interestingly several highly evolutionary conserved non-coding regions in the IL-4/IL-13 gene locus including an 86-bp element located 5' of the IL-13 gene which is 91% identical with another non-coding element in the human 5q31 region, and a further 400-bp element located between the IL-4 and IL-13 genes (which is 85% identical in humans and mice) have recently been identified [133(NC)]. In human YAC transgenic mice lacking the 400-bp conserved element, production of human IL-4 and IL-13 is markedly reduced when compared to mice harbouring a wild-type YAC, strongly supporting its involvement in regulating the human IL-4 and IL-13 genes [141(NC)]. Therefore it is possible that polymorphism outside both the IL-4 and IL-13 genes may affect regulation of both genes.

β_2 -Adrenergic Receptor

β_2 AR is a transmembrane protein which following agonist binding activates G-protein-mediated signal transduction leading to airway smooth muscle relaxation and protection of the airways from bronchoconstriction. It has long been hypothesised that a defective β_2 AR may be a pathogenic factor in asthma, and a linkage between IgE and BHR and markers on chromosome 5q around the β_2 AR has been shown [104(III)]. The two most common polymorphisms [142(III)] are at amino acid 16 (R16G) and at amino acid 27 (Q27E). Studies in vitro have shown that the Gly16 increases down-regulation of the β_2 AR after exposure to a β_2 -agonist. By contrast the Glu27 polymorphism appears to protect against agonist-induced downregulation and desensitization of the β_2 AR [143(NC), 144(NC)]. While a number of studies have indicated that β_2 AR polymorphism may have disease-modifying effects in asthmatic patients, their contribution to atopy and the heritable component of asthma susceptibility is still not clear. The Glu27 β_2 AR polymorphism has been associated with elevated IgE levels in asthmatic families [145(III)], and the haplotype Gly16-Gln27 has been associated with BHR [146(III)], however an association between either the Gly16 or Glu27 β_2 AR polymorphism and an increased risk

of asthma or IgE sensitisation per se is not clear [147(III), 148(III), 149(III), 150(III)]. Recent studies suggest however that there are gene environment interactions between both cigarette smoking [151(III)] and exercise/obesity [152(III)] with β_2 AR genotype determining susceptibility to asthma [151(III)].

CD14

Atopic disease is the result of interaction between genetic and environmental factors. Recent studies have suggested that bacterial infections in infancy may protect against the development of allergy, possibly by promoting Th1 immune responses and therefore suppressing the Th2 responses, which regulate IgE production. CD14 is a multifunctional receptor with specificity for lipopolysaccharides and other bacterial-wall-derived components, and its engagement is associated with an increased production of IL-12 and thus a Th1 differentiation of T cells. The CD14 gene is located on chromosome 5q31.1. A C $\rightarrow$ T substitution in the promoter region at position -159 from the transcription has been identified and associated with an increased level of soluble CD14 and lower IgE levels but not atopy per se in school children from America [153(III)]. Subsequently studies in an adult Dutch population have shown that while sCD14 C-149T is not associated with allergy per se, it is associated with the number of positive skin tests and total serum IgE levels in skin-test-positive individuals [154(III)]. This suggests that sCD14 is not a gene for atopy but may predispose to a more severe atopic phenotype. Equally, polymorphisms of other genes whose products play an important role in neonatal immune responses to bacteria may also play a role in determining atopy severity and susceptibility.

Polymorphisms of other genes in the lipopolysaccharide-sensing pathway may also be important in altering expression of atopy and susceptibility to asthma. Polymorphism in the TLR4 gene has been shown to alter both severity of atopic sensitization [155(III)] and susceptibility to asthma. Furthermore the study by Werner et al. [156(III)] demonstrates the importance of assessing environmental exposure of subjects when undertaking genetic studies of complex disease. They demonstrated that subjects with the usual (wild-type) TLR4 alleles had an increased prevalence of asthma with elevated endotoxin levels in house dust, whereas those individuals who carried hyporesponsive TLR4 alleles had an attenuated risk of asthma with increasing endotoxin exposure. Thus, in addition to rigorous study design (adequate power, relevant genes in a pathway, haplotypes of polymorphisms within each gene and relevant phenotypes), genetic studies should ideally include environmental measures to detect gene-environment interaction. Variation in the level of exposure to endotoxin between populations has also been postulated to account for some of the variability in the studies of the CD14 -159 polymorphism [157(III)].

SPINK5/LEKTI

One approach to genetic analysis of complex disease that has proved successful in other complex genetic disorders such as type II diabetes is to identify genes in rare, severely affected sub-groups of patients in whom disease appears to follow a pattern of inheritance that indicates the effect of a single major gene. The assumption is that mutations (polymorphisms) of milder functional effect in the same gene in the general population may play a role in susceptibility to the complex genetic disorder. The only example of this approach in studies of atopic disease has been the identification of the gene *SPINK5* encoding the serine proteinase inhibitor *LEKTI* on chromosome 5q32 as the cause of the Netherton syndrome [158(NC)]. The Netherton syndrome is a severe autosomal recessive disorder characterised by congenital ichthyosis with defective cornification, a specific hair shaft defect and severe atopic manifestations including atopic eczema, hay fever, high total serum IgE and hypereosinophilia. Six coding polymorphisms have now been identified in *SPINK5* and one, E420K, has been shown to be significantly associated with atopy and atopic eczema in two independent family cohorts [159(III)].

Chromosome 12

Chromosome 12q contains several candidate genes which may be important in the expression of atopy including interferon- γ , mast cell growth factor, insulin-like growth factor-1 and the constitutive form of nitric oxide synthetase 1. A series of studies have identified a positive linkage between markers on 12q and IgE and asthma. 12q24.3 has been identified as a potential area of interest in a study of 191 families using a single-locus non-parametric linkage [5(III)]. A linkage has been shown between 12q15-q24.1 and both asthma and total serum IgE in 29 Afro-Caribbean families and also a linkage to IgE levels in isolated Amish kindreds [160(III)]. Another study using the same set of markers confirmed the linkage to IgE level in a German population [161(III)]. CSGA, using a genome-wide search, found evidence of linkage of asthma to 12q, but only in Caucasian and Hispanic population groups [38(III)], while the German and Asthma Genetics Group genome scan also found linkage between asthma and 12q13 [40(III)], with the French EGEA study finding linkage between eosinophils and 12q24 [41(III)]. However, despite the extensive evidence of linkage between IgE and asthma phenotypes to chromosome 12q, to date polymorphism of no candidate gene has been positively shown to account for the observed linkage.

Human Leukocyte Antigen and T-Cell Receptor- α / β

As the human leukocyte antigen (HLA) class II molecules play a crucial role in the immune response binding antigen-derived peptides and presenting

them to T lymphocytes via the T-cell receptor (TCR), several studies have investigated associations between both HLA class II molecules and TCR genes, and IgE responses to specific allergens. The HLA gene complex is located on chromosome 6p and consists of the class I, class II and class III genes containing the highly polymorphic genes for HLA class I and II molecules, as well as other genes such as tumor necrosis factor- α . The TCR consists of two chains, either α and β or γ and δ chains. The β/γ chain gene complex is on chromosome 7q35 while the α/δ gene complex is on chromosome 14q11.2.

The strongest reported association between HLA and IgE antibody responses is that between Amb a 5 allergen and DRB*15 [162(III)] and is still the only consistently seen association in several studies [163(III)]. Some studies have investigated the association between HLA class II genes and atopy and asthma. A study of 52 subjects with ragweed pollen 'atopy' found an association between DR2 and asthma, but not rhinitis, and between HLA B8, DR3 haplotype and rhinitis alone [163(III)]. A study of an extended French Caucasoid family demonstrated that DRB1*04 and DRB1*07 (DR53-associated haplotype) were associated with 'atopy' and asthma [164](NC), 165(III)]. However, these results were not confirmed in a study of 22 HDM-positive Caucasian families [166(III)]. An investigation of the responses of 431 subjects from 83 families to six common aeroallergens described weak associations of HLA-DR alleles to IgE responses, suggesting a minor role of HLA in 'atopy' [167(III)]. The data from the CSGA genome-wide scan for genes controlling IgE antibody response to *Dermatophagoides pteronyssinus* (*Der p*) in Caucasian and African-American families has recently been analysed. Linkage was confirmed between *Der p* allergen-specific IgE responsiveness and three previously identified regions on chromosome 6p21 (HLA-D region), 13q32–34 and 5q23–33, and also identified two new regions on chromosome 2q21–23 and 8p23-p21 that may be involved in the pathogenesis of the IgE antibody response to *Der p* II [168(III), 169(III)]. The study was extended to identify further linkage of IgE antibody responses toward common inhaled allergens, and found linkage with both 5q31–33 and 11q13. A linkage has been shown between the TCR- α/δ complex and IgE antibodies to *Der p* 1 and *Fel d* 1 in two Australian and British populations; no evidence of linkage was found to the β -chain in either population [170(III)]. However, a recent study in Japanese families ascertained through asthmatic children provided evidence for linkage of the TCR- β/α genes and nearby genes on chromosome 7q35 to both IgE sensitisation and asthmatic phenotype, but no evidence for linkage of IgE sensitisation or asthma to TCR- α was detected [171(III)].

These studies reveal the complexity of genetic factors regulating the IgE antibody response and that non-HLA genes as well as environmental factors play an important role in the allergen-specific IgE responsiveness in some

populations. However, despite much research, it is still unclear to what extent HLA class II and TCR γ genes play a role in regulating IgE responses to specific allergens.

In summary, in the last 10 years there have been many linkage and association studies examining genetic susceptibility to the atopic constitution and atopic disease. As yet no single gene has been identified as a risk factor with any degree of certainty. Further research is needed to confirm previous studies. Larger family-based cohorts and the pooling of data across studies as well as more specific markers for IgE-mediated allergy should help in the enormous task of identifying the gene(s) that underlie regions of linkage. Large population samples including longitudinal cohorts will prove essential in determining not only the contribution of identified polymorphisms to susceptibility, but also how these polymorphisms interact with the environment to initiate IgE-mediated disease.

Disease-Modifying Genes

The concept of genes interacting to alter the effects of mutations in susceptibility genes is not unknown. A number of genetic disorders caused by mutations in single genes are known to exhibit inter- and intra-familial variability [172(NC)]. A proportion of inter-familial variability can be explained by differences in environmental factors and differences in effect of different mutations in the same gene. Intra-familial variability, especially in siblings, cannot be so readily accredited to these types of mechanisms. There is increasing evidence that many genetic disorders are influenced by 'modifier' genes which are distinct from the disease susceptibility locus. For example not all individuals with insulin-dependent diabetes mellitus develop diabetic nephropathy, but the relative risk of this complication is increased 2-fold in relatives of patients with insulin-dependent diabetes mellitus and nephropathy [173(NC)].

Genetic Influences on Disease Severity

Very few studies of the heritability of IgE-mediated disease have examined phenotypes relating to severity. Sarafino et al. [15(III)] studied 39 monozygotic twin pairs and 55 same-sex dizygotic twin pairs for the heritability of asthma and asthma severity. Asthma severity (as measured by frequency and intensity of asthmatic episodes) was examined in twin pairs concordant for asthma. Severity was significantly correlated for monozygotic pairs but not for dizygotic pairs. In contrast, a more recent study [174(III)] examined the family prevalence of 'atopy' and IgE-mediated diseases including asthma. Although the prevalence of asthma in children of parents with asthma was significantly

increased when compared to children whose parents did not have asthma (55 vs. 29% for the eldest child), when the severity of a child's asthma was compared with that of the parents, there was no correlation between the severity of the child's asthma and either the severity of the parents' asthma or the number of parents with asthma.

There have been several other studies of familial correlation with asthma severity. A large epidemiological study (661 children and their parents) of family patterns of asthma and AHR [175(III)] identified a modest correlation between severity of parents' AHR and those of the child ($R = 0.51$, $p = 0.04$). A positive family history of asthma was the only significant predictor of asthma severity in a study of children aged 5 with a history of severe wheeze in childhood [176(III)]. A study of factors relating to asthma and severity in adolescents concluded that genetic factors may contribute to severity by altering susceptibility to environmental factors such as sensitisation to allergens.

A number of studies have examined associations between asthma severity and polymorphisms in candidate genes. These have included tumor necrosis factor- α [177(III)], IL-4 [117(III), 178(III)] and IL-4RA [178(III)] but the conclusive identification of genetic factors contributing to asthma severity has been hampered by the lack of clear, easily applied, accurate phenotype definitions for asthma severity that distinguish between underlying severity and level of therapeutic control. For example it has been shown that β_2 AR polymorphisms could influence asthma severity, as Gly16 polymorphism is over expressed in patients with nocturnal asthma [179(III)] and in steroid-dependant asthmatics [142(III)]. It is not clear whether this reflects β_2 AR polymorphism affecting patients' responses to β_2 -agonists and hence leading to poor therapeutic control, or whether, irrespective of their effects on treatment, polymorphism of the β_2 AR leads to more severe chronic asthma. The development of such phenotypes in conjunction with more extensive studies of the genetics of asthma severity may allow identification of at-risk individuals, and targeting of prophylactic therapy.

Genetic Regulation of Response to Therapy – Pharmacogenomics

Genetic variability may not only play a role in influencing susceptibility to express an IgE-mediated allergy, but may also modify its severity, or influence the effectiveness of therapy [180(NC)]. Clinical studies have shown that β_2 AR polymorphisms influence the response to bronchodilator treatment. Asthmatic patients carrying Gly16 have been shown to be more prone to develop a bronchodilator desensitisation [181(III)], while children who are homozygote or heterozygote for Arg16 are more likely to show positive responses to bronchodilators [182(III)]. However, some studies have shown that response to bronchodilator treatment is genotype independent [183(III), 184(IIa)].

A study of 190 asthmatics examined whether the β_2 AR genotype affects the response to regular versus as-needed albuterol use [185(IIa)]. During a 16-week treatment period there was a small but significant decline in morning peak flow in patients homozygous for the Arg16 polymorphism who used albuterol regularly. The effect was magnified during the 4-week run out period when all patients returned to albuterol as needed, with Arg16 homozygotes on regular albuterol having a morning peak flow 30.5 ± 12.1 l/min lower than Arg16 homozygotes, who took albuterol only as needed ($p = 0.012$). These findings are difficult to explain in the light of the studies above linking the Gly16 allele with BHR, β_2 -agonist effectiveness and asthma severity.

There are also a number of other candidate genes that may be involved in modifying the response to anti-asthma drugs. Glucocorticoids are a potent and effective treatment for asthma. However, there is a small group of asthmatics in whom glucocorticoids, even when given in high doses, are not effective. Polymorphisms in the receptor may influence glucocorticoid resistance; however in a limited study of 6 steroid-sensitive and 6 steroid-resistant asthmatics, no mutations in the GCR gene were identified in either group [186(NC)]. More recently it has been shown that there is increased expression of glucocorticoid receptor (GR)- β -positive cells in steroid-insensitive subjects with severe asthma [187(NC)]. Insensitivity to steroids may be a major contributing factor in fatal asthma, and GR- β is an alternatively spliced form of the GR that inhibits GR- α activity. It is possible that polymorphisms in splice junctions may alter the ratio of different splice forms of this receptor, leading to steroid insensitivity. A single nucleotide polymorphism of the GCR, N363S, has been shown to lead to increased sensitivity to glucocorticoids in vivo [188(NC), 189(NC)], however its effect on treatment of asthma with inhaled glucocorticoids has not been investigated.

Genetic polymorphism may also play a role in regulating responses to the class of anti-asthma drugs known as the anti-leukotrienes. Clinical responsiveness to anti-leukotriene therapy varies between patients but is relatively consistent in individual patients over time [190(NC)]. A repeat length polymorphism in the promoter of the 5-lipoxygenase gene has been reported to modify transcription factor binding and reporter gene expression [191(NC)]. This polymorphism also seems to be associated with a reduced response to 5-lipoxygenase inhibitor therapy [192(IIa)]. Polymorphisms have also been identified in a number of other genes encoding for leukotriene biosynthetic enzymes and their receptors including leukotriene C_4 synthase [193(NC), 194(NC)], 5-lipoxygenase-activating protein [195(NC)] and the cysteinyl/leukotriene receptors, CysLT₁ [196(III)] and CysLT₂ [197(III)]. While only limited studies have been carried out to date, some of these polymorphisms have been correlated with altered responsiveness to

anti-leukotriene therapy [196(III), 198(IIa)]. Further research is needed in this area.

Conclusions

In reality we know little more in genetic terms that we did in 1916 – namely that atopy and atopic disease are heritable disorders, that there are separate genetic influences determining susceptibility to expression of atopy and development of specific atopic disease, and that interaction with environmental exposures is important. Despite intensive effort and the advances of molecular biology over recent years, few genes involved in the pathogenesis of IgE sensitisation and asthma have been clearly identified with any certainty. The major difficulties in genetic studies of atopy and other IgE-mediated disorders have included phenotype definition and sample ascertainment. Examples such as the IL-13 Arg110Gln polymorphism also illustrate that the same polymorphisms may be associated with different phenotypes at different stages of life (atopy in childhood and asthma in adulthood). Thus studies of the same polymorphism or genetic region that use different methods of subject ascertainment (atopy vs. asthma or eczema, adult vs. child probands, incorrectly defining atopy as high total IgE or only based on case history for example) and different measures of phenotype are unlikely to replicate one another. These issues are now being addressed seriously, and much effort is being directed at consensus between groups, and co-operation in research efforts. An attempt to address some of these issues has been undertaken in the form of COAG. This was a multicentre collaborative initiative launched in June 1998 with the limited goal of determining what could be learnt about the genetics of asthma by pooling information from different studies, each of which had published its principal results, to allow meta-analysis of the data. Another such project can be found in the asthma gene database [67(NC)] (<http://cooke.gsf.de/>), which is a database of studies (both published and unpublished) relating to asthma genetics.

The Future

The ongoing research into genetic factors behind the expression of atopy and the development and pathogenesis of allergic disease will in due course provide us with a greater understanding of the fundamental mechanisms of these disorders. Study of these genetic factors in large longitudinal cohorts with extensive environmental information will allow the identification of both the environmental factors that in susceptible individuals trigger allergic disease,

and the periods of life in which this occurs, potentially leading to prevention of disease by environmental modification. Identification of genetic variants that predispose to allergic disease will result in several outcomes. Firstly, the greater understanding of the susceptibility factors for the disease will allow the development of specific new drugs both to relieve and prevent symptoms. In addition, different genetic variants may also influence the response to therapy, and the identification of individuals with altered response to current drug therapies will allow optimization of current therapeutic measures. Secondly, the identification of susceptibility factors for allergic disease will allow early identification of susceptible individuals, allowing them to be targeted at early age for both for therapy and environmental intervention such as avoidance of allergen exposure. Genetic screening in early life may thus become a practical and cost-effective option in preventing allergic disease.

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Environmental Influences on Asthma and Allergy

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Background

Environmental influences on asthma were recognised by Hippocrates more than 2,000 years ago. In the 19th century, known associations with asthma included the weather, air temperature, humidity, thunderstorms, environmental tobacco smoke (ETS), 'fenny' country, season, occupation, diet, exercise, feather beds, animals, pollen and 'the passions'. The only major risk factor not noted in the 19th century was infection, due to the lack of germ theory. However, there was no formal asthma and allergy epidemiology until the 20th century.

Evolution in the Understanding of the Relationship between Environmental Factors and Allergic Disease

The understanding of the relationship between different environmental factors and allergic disease has changed over the last few decades. In 1984, Finnish investigators set out to test the hypothesis that early infection increased rather than decreased the risk of allergic symptoms. 'Atopy probably cannot be prevented by protecting small children from infection' [1(III)]. However, in 1989 Strachan [2(IIIC)]¹ proposed in the 'hygiene hypothesis' that allergic

¹The code 'IIIC' will be used throughout this chapter to denote cohort studies which are considered to provide stronger evidence than other epidemiologic study designs.

diseases could be prevented by infection in early childhood and this hypothesis has dominated thinking and research since the early 1990s. In the early 1980s increasing outdoor air pollution was related to troublesome asthma and therefore considered as a possible cause of increasing asthma [3(NC)]. Although outdoor air pollution aggravates established asthma, heavy air pollution is now recognised to be a potentially protective factor for population prevalence of asthma and allergies [4(III)].

More recently, research has moved from studying factors that aggravate asthma and allergies and risk factors within populations, to exploring factors that influence the development in populations by studying these conditions between populations.

Research Approaches

In reviewing this topic it is clear that most relevant studies are observational population-based studies. These studies are mainly cross-sectional and therefore they are most suitable for generating hypotheses. Some studies are hypothesis-testing clinical experiments, and there are few randomised-controlled trials or meta-analyses. Strong evidence-based recommendations for the prevention of asthma and allergy are unable to be made except for ETS.

It is also obvious that the majority of studies come from developed countries, where rates of asthma and allergic disease are generally higher than in developing countries from where there has been relatively little research. However, the situation is changing and new research is emerging from developing countries, stimulated by studies like the International Study of Asthma and Allergies in Childhood (ISAAC) [5(NC), 6(III), 7(III), 8(III), 9(III)]. This is important, because there may be the most to learn from places where these conditions are rapidly emerging, and rising in prevalence as environments change, rather than from already high prevalence locations where the pace of change is slower.

Determinants of variations between individuals within a population may be different from the determinants between populations [10(NC)]. Rose [10(NC)] suggested that one type of question is where individuals lie on the population distribution of a characteristic. A second type of question is the position of the distribution (e.g. mean), which may differ between populations. A small change in relative risk, applied to a large number of people, could bring a large absolute benefit, and therefore be worth having. He labelled this the prevention paradox; 'a preventive measure that brings large benefits to the community offers little to each participating individual' [10(NC)]. 'When many people receive a little benefit, the total benefit may be large'. If the benefit to the individual is small, we are looking for interventions which are not

inconvenient or hazardous [11(NC)], but rather are safe, low cost and easy to implement. The recommendations at the end of this chapter fit these criteria.

Rose stated that ‘The primary determinants of disease are mainly economic and social, and therefore its remedies must also be economic and social’ [10(NC)]. This proposition could be expanded to include features of lifestyle, such as diet and housing. If the environment is important, the appropriate analysis should be at the environmental level [11(NC)].

The population environmental studies, which advance the picture, are ecological studies comparing groups rather than individuals. This approach has recognised limitations compared with individual level studies [12(NC), 13(NC)]. A particular limitation is ecologic bias, which is the failure of expected ecologic effect estimates to reflect the biologic effect at the individual level. However ecological analyses are appropriate for attempting to explain why prevalence varies throughout the World and for putting the results of individual level epidemiological studies within populations in context. Marmot [11(NC)] has said ‘Thus, ecological analyses are not second rate but are the most useful way to examine the effect of social environment on health’.

However, Pearce et al. [14(NC)] have written that the problem of information bias is of particular concern in asthma epidemiology issues because of the difficulties in defining and measuring asthma, allergic rhinoconjunctivitis and atopic eczema, and the difficulties in obtaining exposure information in the aetiologically relevant time period. However, provided that the information has been collected in a standardized manner, then misclassification will be non-differential, and any bias it produces will usually be towards the null value.

The term ‘exposure’ means the presence of a substance in the external environment, and in allergy and asthma refers to any attribute or agent that may increase the risk of, or protect against the development of sensitisation, disease, or worsening disease. Methods of exposure measurement with good validity in regard to current exposures include personal interviews, or self-administered questionnaires, diaries, observation, routine records, physical or chemical measurements of the environment, or physical or chemical measurements of the person which can relate either to an exogenous exposure such as airborne dust, or internal dose such as plasma cotinine. Questionnaires have a long history of successful use in epidemiology. They may be combined with environmental exposure measurements (e.g. pollen counts) to obtain a quantitative estimate of individual exposures. Questionnaires and environmental measurements have good validity and reproducibility [14(NC)].

The Diseases

Immunologically mediated hypersensitivity disorders are referred to as allergy, a term that unfortunately is not always used in this strict sense. This

sometimes makes interpretation of published data difficult. This report uses the terms allergic asthma and allergic rhinoconjunctivitis (hay fever). What was previously referred to as 'atopic dermatitis', i.e. the umbrella term for the clinical group of eczema/dermatitis, is termed eczema, while the IgE-associated subgroup of eczema is referred to as atopic eczema. For details, please see the glossary. When it is not clear from a study whether reference is given to the IgE-associated subgroup of eczema the term 'atopic eczema' is given in inverted commas.

Although, asthma, allergic rhinoconjunctivitis and eczema are related, ISAAC showed that most symptomatic children had symptoms of only one disorder in the previous year, rather than two or three. Observations like this indicate that factors required for the clinical expression of each of these disorders may differ in timing or effect [6(III)].

The differences between the conditions are illustrated by their different geographical distribution. In Britain, the pattern of hay fever at the county level did not closely resemble that of 'atopic eczema', whereas the geographical distribution of asthma prevalence by county exhibited some similarities with the distribution of 'atopic eczema' [15(III)]. The worldwide picture from ISAAC shows that there are differences in the geographical distribution of high, medium and low prevalences for the three conditions [6(III)].

Asthma in children is commonly described as an allergic, IgE-mediated disease. The proposed process is that allergen exposure produces IgE sensitisation and that continual exposure leads to clinical asthma through the development of airway inflammation, bronchial hyperresponsiveness (BHR) and reversible airflow obstruction. This proposal does not explain the children with asthma who do not have the atopic constitution. Recently Pearce et al. [16(NC)] have challenged the closeness of the relationship between asthma and atopy. The epidemiological evidence suggests that only 50% of the adult population with asthma have IgE-mediated disease (allergies or asthma). Comparisons across populations or time periods show only a weak and inconsistent association between the prevalence of atopy and asthma. Non-allergic asthma may be a separate entity from allergic asthma and a different set of preventive studies may be required for this type of asthma. The aetiology of non-IgE-mediated asthma therefore needs to be explored further [16(NC)]. Thus, non-allergic asthma must be considered as a potentially separate entity, which may need a different set of preventive strategies from allergic asthma. Little research has been done in this direction.

Most of the studies on the relationship between the environment and IgE-mediated disease relate to asthma, and there are a few studies on allergic rhinoconjunctivitis and eczema. However, the recent review on 'atopic eczema' by McNally et al. [17(NC)] confirmed that environmental factors play a crucial

role in disease expression. In Britain specific risk factors for IgE sensitisation include house dust mite, but the review recommends investigation of changes in other population exposures to other things over the last few decades (e.g. changing patterns of exposure to common viruses, decreases in helminthic infestation, trends in immunisation, home environment, and lifestyle factors including the use of central heating, fuel source for heating and cooking, type of bedding, the use of carpets, hygiene and dietary habits, and factors in the macro-environment such as pollution, water supply, and rurality). These environmental factors are also considered in reviewing possible contributing or causative factors in the development or exacerbation of asthma.

Preventive Strategies

The prevention of allergic asthma, allergic rhinoconjunctivitis and atopic eczema requires environmental strategies aimed at reducing both the development of allergic sensitisation, and the subsequent development of asthma in those who have already become sensitised [18(NC)]. Strategies for primary prevention of non-allergic asthma are not clear and may be different from allergic asthma. Measures to prevent all these conditions are likely to be effective only if introduced early in life, because of genetic predisposition from conception, and evidence that the processes begin in the foetus or in the first few months or years of life.

Major Changes in Population Prevalence Suggesting Environmental Influences

The increase in prevalence of allergic diseases, including allergic asthma, over time is too large to be explained by any genetic variation. There are many studies which show that asthma, allergic rhinoconjunctivitis and 'atopic eczema' are increasing over time. The reasons for this need exploration [19(NC)].

Seven studies in Britain have shown increasing prevalence. In South Wales, UK, over a 15-year period there were increases in the prevalence of exercise-induced bronchospasm, wheeze, asthma, eczema and (hay fever) allergic rhinoconjunctivitis in children [20(III)]. In England over a 13-year period there were increases in the prevalence of wheezy children and persistent wheezing [21(III)]. In a small study in adults in London, UK, over a 14-year period there was an increase in the prevalence of skin prick test reactivity [22(III)]. In another study in London, over a 13-year period, there were increases in the prevalence of wheezy children and persistent wheezing suggesting a change in the environmental determinants of asthma [23(III)]. In England and Scotland

over a 10-year period there were increases in the prevalence of wheezy children [24(III)]. In Aberdeen, Scotland, over a 25-year period there were increases in the prevalence of wheezing, (hay fever) allergic rhinoconjunctivitis and eczema in school children [25(III)]. Further increase in wheezing was seen over a subsequent 5-year period [26(III)]. In a comparison of two prospective birth cohort studies in Britain 12 years apart there was an observed rise in the prevalence of hay fever and eczema [27(III)].

Increases have been reported in several other countries. In two German studies, increases have been found. In Leipzig in the former East Germany the prevalence in children of (hay fever) allergic rhinoconjunctivitis and IgE sensitisation increased significantly between 1991–1992 and 1995–1996 [28(III)]. A recent study from Münster (Germany) found an increase in symptoms of asthma, rhinoconjunctivitis and eczema over 5 years [29(III)]. In three Australian studies there have been increases. In Melbourne over a 26-year period the prevalence of wheeze in the last 12 months significantly increased [30(III)]. In two centres in New South Wales, Australia, over a 10-year period there were increases in the prevalence of wheezy children and airway hyperresponsiveness (AHR) but not skin prick test positivity. Numbers of house dust mites in household dust increased fivefold [31(III)]. In the ISAAC Australia study wheezing increased over a 4-year period [32(III)]. In Lower Hutt, New Zealand, a study reported a near doubling of the prevalence of parentally reported asthma among 11- to 13-year-old children between 1969 and 1982 [33(III)]. In Auckland, New Zealand, the prevalence of respiratory symptoms, but not the diagnostic label 'asthma' increased significantly from 1985 to 1991 among school children of European ethnicity [34(III)]. In a study of children in Japan the prevalence of asthma increased over a 10-year period [35(III)].

These large increases in prevalence over short time periods of time are most likely to be explained by environmental than genetic factors.

The wide variation in prevalence found around the world, and in people of similar genetic stock in different environments, is too large to be explained by genetic variation. In the largest geographical description ever undertaken, ISAAC collected information concerning symptoms of asthma, allergic rhinoconjunctivitis and 'atopic eczema', actually eczema since the diagnosis is based only on a questionnaire, on more than 700,000 children (6–7 years) and adolescents (13–14 years) in 156 centres located in 56 countries around the world. Centres varied by up to 15-fold for symptoms of asthma, up to 28-fold for symptoms of allergic rhinoconjunctivitis and up to 22-fold for symptoms of eczema. Explanations for these large variations are likely to be environmental rather than genetic [6(III), 7(III), 8(III), 9(III)].

The European Community Respiratory Health Survey was a large study of adults (140,000 people from 22 countries, mainly in Europe). Large geographical

differences were found in the prevalence of asthma, atopy and BHR, with high prevalence rates in English-speaking countries and low prevalence rates in the Mediterranean region and Eastern Europe [36(III)].

There have been a few other studies between regions of the world. The prevalence of symptoms of asthma was studied in centres in three countries with differing language and culture. The prevalence of wheezing in the last 12 months was much lower in St. Gallen, Switzerland, (7.4%) than in Melbourne, Australia, (23.1%) or La Serena, Chile (26.5%) [37(III)]. In another comparison, the prevalence of symptoms of asthma and exercise-induced bronchospasm among children in New Zealand, Wales (UK), South Africa and Sweden, was highest in New Zealand (16.8% for a history of asthma), lower in Wales and South Africa (12.0 and 11.5%, respectively) and lowest in Sweden (4.0%) [38(III)]. Large variations in prevalence have been found within regions. An analysis of the ISAAC data for the Latin America region showed that large differences in prevalence existed for centres in a developing region and that in some cases prevalence was as high as that experienced in centres in industrialised countries [39(III)]. A comparison of respiratory symptoms and BHR in children between Auckland, New Zealand and two locations in New South Wales, Australia showed similar prevalence in Auckland and inland New South Wales, but lower prevalence in coastal New South Wales [40(III)]. In a study of three south-east Asian locations, hay fever, eczema and wheeze were higher in Hong Kong than Kota Kinabalu in Malaysia and San Bu in China [41(III)].

A survey of 12-year-old children in New Zealand and South Wales, Britain, showed higher prevalence of a history of 'asthma and wheeze ever' in New Zealand. Similar results were found for exercise-induced bronchospasm [42(III)].

In the UK up to twofold geographical variations in the distribution of reported and examined 'atopic eczema' exist at the regional level, not explained by social class. Suggested explanations for further research include climatic factors, industrial and traffic exhaust pollution, pollen levels, and mineral deposits [15(III)].

The fall of the Berlin wall in 1989 offered the unique opportunity to compare populations of similar genetic stock and geographic background which had been living under quite different environmental exposure conditions for over 40 years, and the papers have been reviewed recently [43(III)]. During 1989–1991 there were lower prevalences of hay fever and symptoms of rhinitis in Leipzig in the former East Germany compared to Munich (former West Germany) [4(III)]. In a comparison of children in Münster (former West Germany) and Greifswald (former East Germany) during 1994–1995, asthma, (hay fever) allergic rhinoconjunctivitis and 'atopic eczema' were generally higher in Münster. Protective factors in former East Germany may include

wood or coal heating [44(III)], although there may be other protective factors. In a comparison of children in Dresden, Munich and Leipzig, Germany in 1995–1996, symptoms and signs of ‘atopic eczema’ were more common in Dresden (former East Germany) compared with Munich. However, in Dresden the prevalence of asthma and BHR were lower [45(III)].

Comparisons between urban and rural areas in the same country have pointed to environmental factors. These studies have concentrated in Africa. In Ghanaian children, exercise-induced bronchospasm was found more commonly in ‘urban-rich’ than in ‘urban-poor’ or ‘rural’ children, suggesting that environmental factors such as wealth, lifestyle and housing are important [46(III)]. In a comparison of rural and urban Zimbabwean children, urban living and higher material standards are associated with higher prevalence of reversible airway obstruction [47(III)]. In Kenyan children, exercise-induced bronchospasm and symptoms of asthma were found more commonly in urban than rural children, suggesting that urbanisation has various environmental exposures on increasingly susceptible populations [48(III), 49(III)]. Wheeze and asthma are especially rare in rural subsistence areas in Ethiopia, and failure to express an atopic constitution may be associated with reduced prevalence of these symptoms in this environment. In urban Jimma, self-reported asthma symptoms began to emerge in the mid-1980s [50(III)].

In New Zealand adults symptoms of asthma were generally found more commonly in urban areas compared with rural although some rural areas did show comparatively high prevalence values [51(III)].

A study of the prevalence of asthma in the highlands of New Guinea published in 1974 reported a very low prevalence of 0.2–0.3% in adults. This area of New Guinea first experienced contact with Europeans in 1933 and had experienced considerable material and cultural change since the 1950s. Asthma is extremely uncommon. These low rates were attributed to a low degree of exposure to allergens [52(III)].

Studies of migration have provided further evidence of powerful environmental influences. In a longitudinal study in Tucson, Ariz., USA recent migrants into the area had a lower prevalence of skin test positivity initially and a much greater increase than existing residents after 8 years in residence [53(IIIC)]. Among Asian immigrants from Pakistan, India and East Africa in Blackburn, UK, there was an increasing rate of asthma symptoms with increasing duration of stay in the UK [54(III)]. Among adult Asian immigrants from Pakistan, India, Sri Lanka and East Africa in London, UK, immigrants had a later age of onset of asthma but similar skin prick test positivity, to existing residents [55(III)].

Tokelauan children were studied in two environments in 1975–6. Asthma was more than twice as common among Tokelauan children in New Zealand

than in Tokelau. There was no significant difference in the prevalence of asthma between those born in New Zealand and those born in Tokelau [56(IIa)].

In Australia the prevalence of asthma, allergic rhinoconjunctivitis and skin prick test positivity has been studied in Asian immigrants of Chinese origin in Melbourne. The prevalence of wheeze was higher in Australian-born Asians and non-Asians than in Asian immigrants. The prevalence of allergic rhinoconjunctivitis and asthma was strongly associated with the length of stay in Australia, suggesting environmental factors are important in the pathogenesis of these diseases [57(III)]. In teenagers in Melbourne, Australia, there was a dose effect on the prevalence of symptoms in subjects born outside Australia and now living in Melbourne [58(III)]. In the ISAAC Australia study, asthma was higher among Australian-born children than among those born elsewhere [32(III)].

Thus there is evidence from prevalence studies over time, between regions of the world, and within and between countries, and of migrants, which suggest that these variations in prevalence found are too large to be explained by genetic variation, and are therefore likely to be due to environmental factors.

Diet

The incidence of many non-communicable diseases throughout the world has been linked to diet. Many nutritional factors may influence disease, including changes to the production and availability of food, changing food preferences, increased supply of processed foods for consumption as well as supplies for food aid, use of fertilisers and pesticides, land availability, increased prices of staple foods, urbanisation, migration, economic factors and market fluctuations. Traditional nutritional patterns and patterns of health are changing as are other aspects of lifestyles of populations. Over the past few decades, 'westernisation' has seen many countries moving away from the traditional diet of locally grown foods to a more western diet. For example, processed foods and refined carbohydrates are the meal staples in urban Tonga, compared with fish and vegetables in rural Tongan adults [59(III)]. There have been dramatic changes in eating habits and food preparation in many locations. Others have reported a lower incidence of chronic disease to be associated with the consumption of a more traditional form of diet [60(NC), 61(NC)]. Asthma is classified as a non-communicable disease but there has been little study of its relationship to dietary factors.

Throughout human development dietary patterns have evolved and now vary greatly in different parts of the world. The diet of economically developed countries and urban areas of the developing world are now relatively low in

cereals, tubers and other starchy foods, and relatively high in sugar, fat, protein of animal origin, salt, meat, dairy products and alcohol. Plant-based carbohydrate-rich diets have been associated with lower rates of other non-communicable diseases [60(NC), 62(NC)]. Mediterranean countries have a relatively high proportion of energy from cereals, vegetables and fruits, relatively less meat consumption than in northern Europe, and greater reliance on vegetable than animal fat [60(NC)].

Migration and food aid (including processed food) have been associated with the rapid increase in asthma prevalence, suggesting a potent environmental factor [57(III), 63(IIa)]. The prevalence of asthma, (hay fever) allergic rhinoconjunctivitis and other IgE-mediated diseases has been studied in Asian immigrants of Chinese origin in Melbourne. The prevalence of wheeze was higher in Australian-born Asians and non-Asians than in Asian immigrants. The prevalence of (hay fever) allergic rhinoconjunctivitis and asthma was strongly associated with the length of stay in Australia, suggesting environmental factors are important in the pathogenesis of these diseases. They noted that there is often a change in dietary habits after migration and many Asian immigrants replace their traditional rice-based, low-salt, high-fibre diet, with an emphasis on fish and vegetables, and move to a diet with foods containing high salt, high saturated fat, low fibre, and food additives and preservatives. Most subjects originated from Hong Kong, Malaysia and Vietnam [57(III)]. A discussion of these different food groups will be found later in this section. Thus, in seeking explanations for the large worldwide variations in the prevalence of asthma, allergic rhinoconjunctivitis and eczema, and the increases within populations over the last few decades, dietary factors are a potentially important field for study.

Most of the dietary studies have a cross-sectional design, and therefore they are more suited for raising questions and hypotheses than in giving evidence. Nevertheless ISAAC's ecological study of diet was a relatively powerful tool, because data from 53 countries were analysed, looking at all food groups. The relationship between per capita food intake and the prevalence of symptoms of asthma, rhinoconjunctivitis and eczema were reported [64(III)]. This worldwide analysis of per capita food intake and symptoms of asthma, allergic rhinoconjunctivitis and eczema in the 13- to 14-year age group showed a consistent negative association between all three allergic conditions and calorie intake, protein, vegetables and specific vegetable nutrients (vitamin A, vitamin E, protein, mono-unsaturated fatty acids, poly-unsaturated fatty acids, PUFA, and saturated fats), starch, calories from cereal and rice, total fibre, protein from cereals and nuts, total seafood, all fish (fresh and frozen) and olive oil. There were no consistent associations for other foods. The video questionnaire results showed similar, but weaker associations with the diet variables. For the 6- to 7-year age group, the

negative and positive associations generally remained as for the older age group, but were also weaker. This may indicate that the diet of 13- to 14-year-old children is more accurately reflected in the average per capita per day intake of food and may account for the stronger associations seen for the older age group.

There was over a 1,500-fold difference between the two countries at the extreme for olive oil consumption, a 25-fold difference for the two countries at the extremes for vegetable consumption and nearly a 3-fold difference for the two countries at the extremes for calories from cereal and rice. The between-country variability of calories as a percent of total energy consumption from cereal and rice showed the country with the lowest consumption (Germany, 21% of total energy consumption) to the country with the highest consumption (Ethiopia 72% of total energy consumption). Although the country range is relatively small, the analysis showed a significant negative association with current and severe wheeze, allergic rhinoconjunctivitis and eczema. It is striking that when adjusted for Gross National Product (GNP), the negative association of total calories, protein, vegetables, vegetable fats and vegetable micronutrients, starch, total fibre, calories from cereal and rice, protein from cereals and nuts, total seafood, all fish and olive oil was consistent for symptoms of all three conditions, asthma, allergic rhinoconjunctivitis and eczema. There was no consistent pattern for any other food category, so it seems unlikely that these findings simply reflect systematic bias or confounding by other unknown dietary factors [64(III)]. The timing of exposure to relevant dietary factors is not clear, but these studies are inclusive of all possibilities.

The ISAAC analysis used reliable data from standardised sources (ISAAC) and FAOSTAT, a data base of the Food and Agricultural Organisation of the United Nations. Food balance data provide direct information about the availability of foods, but only indirect information about dietary intake. In particular, an association at the country level may be due to complex biases and may not apply at the individual level, since dietary variations between countries are likely to reflect broader cultural and environmental differences and may not be directly causal. The timing of the effects of diet could not be elucidated from this analysis. Nevertheless, an ecological approach has certain advantages in examining possible relationships between diet and disease. In so far as diet varies more widely between countries than within them, associations may be detectable when comparisons are made between different countries that would not be evident within any one country [10(NC)]. Ecological studies also avoid the regression dilution bias that arises in studies of individuals whose diet varies over time.

Fish

It has been postulated that increased consumption of oily fish, rich in omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) which

have anti-inflammatory effects, reduces the synthesis of proinflammatory cytokines. Theoretically, eicosapentaenoic acid could either prevent the development of asthma or reduce its severity by altering airway inflammation and AHR [65(III)]. Although the ISAAC diet analysis showed a consistent negative association between total seafood and all fish (fresh and frozen) and the three conditions, this association was insignificant except for severe wheeze [64(III)]. In a random cross-sectional study of Australian school children, regular consumption of fresh, oily fish was observed to be associated with reduced risk of asthma symptoms in children [65(III)]. It is not clear why consumption of canned and processed fish did not show this benefit, but they postulated that it is possible that processing may alter the integrity or activity of the fatty acids in fish oils.

Clinical studies (of fish oil supplements) have not always shown the expected benefits on airway functioning. In a small randomised double-blind crossover controlled study of adults in Finland, fish oil and evening primrose oil supplementation were found to be ineffective in the treatment of asthma [66(Ib), 67(III), 68(NC)]. In a further Australian study of asthmatic children, enrichment of their diet by supplementation with omega-3 and omega-6 fatty acids was done over a 6-month period. They found the omega-3 fatty acid supplementation increased plasma levels of these fatty acids, and reduced stimulated tumor necrosis factor- α production, but showed no effect on the clinical severity of asthma [69(Ib)]. However in France, a double-blind randomised study treated a group of 12 asthmatic adults with fish oil (docoahexaenoic acid and eicosapentaenoic acid) or placebo for 1 year. A significantly positive effect on forced expiratory volume in 1s (FEV₁) in the treatment group was found after a period of 9 months [70(Ib)]. In a study of adults in USA, chronic dietary intake of fish was associated with higher levels of pulmonary function [67(III)]. In a randomised controlled study in Japanese children with asthma, treated for 10 months with either fish oil or olive oil, asthma symptoms scores and AHR decreased in the fish oil group and plasma levels of eicosapentaenoic acid increased [71(Ib)].

Vegetables, Fruit and Antioxidants

There is an increasing body of evidence that dietary antioxidants may be protective against the development of asthma, allergic rhinoconjunctivitis and 'atopic eczema' in children. Decreased consumption of fruit and vegetables in the United Kingdom has been postulated to be associated with an increase in prevalence of asthma and rhinitis through their antioxidant properties, which may protect against inflammation [72(NC), 73(III)]. In particular, vitamins A and E are known antioxidants that are essential in the lung defence mechanisms against reactive oxidant propagation. They are also inhibitors of

oxidant propagation and scavenge hydroxyl radicals and singlet oxygen [72(NC)]. These antioxidant defences may be important in reducing airway inflammation and lung permeability in response to cigarette smoke, air pollutants and ozone [72(NC)]. There is evidence that oxidants produced endogenously by overactive inflammatory cells contribute to ongoing asthma. Vitamin C is the major antioxidant substance present in the airway surface liquid of the lung. Vitamin E has been shown in a mouse model to promote the Th1 subtype. One of the functions of vitamin C is to regenerate vitamin E from the oxidised tocopheroxyl radical. Moreover both vitamins may act to protect airways against oxidant attack [74(NC)]. The ISAAC analysis found a consistent negative association between vegetables, vegetable-derived vitamin A and E and asthma, allergic rhinoconjunctivitis and eczema. However, although vitamin C may have similar properties [75(NC)], no consistent association was found in the ISAAC analysis [64(III)].

Fresh fruit and vegetable intake are particularly low in Britain [72(NC)], and therefore it is of interest to examine studies in that country. In a British study, adults with brittle asthma had lower median dietary intakes of vitamins A and E than controls, although serum levels were within the normal range [76(III)]. In a nested case-control study in Scotland intakes of vitamin E and plasma levels of ascorbate and the α -tocopherol:triglyceride ratio were inversely related to adult-onset wheeze [73(III)]. In British adults wheeze was inversely associated with intake of fresh fruit and vegetables although the effect seemed to be restricted to smokers [77(IIIC)]. In a longitudinal study in British adults, changes in fresh fruit consumption were positively associated with FEV₁, and fell more among those who reduced their fresh fruit consumption the greatest [78(IIIC)]. In elderly people in the UK, an increase in vitamin E in the daily diet was associated with an increase in FEV₁ [79(III)].

In a cross-sectional study of children in northern and central Italy, intake of citrus or kiwi fruit, rich in vitamin C, was a highly significant protective factor for wheeze for those eating fruit 5–7 times a week compared with less than once a week [80(III)]. In a cross-sectional study in children in urban and rural Saudi Arabia low intake of vitamin E, magnesium and sodium were associated with a 2- to 3-fold risk of having symptoms of asthma [74(III)]. A further series of studies published this year in abstract form support the notion of a protective effect of fruit and vegetables [81(III), 82(III), 83(III), 84(III), 85(III), 86(III), 87(III), 88(III)].

However, although there is evidence that intake of antioxidants via fresh vegetables and fruit may be protective against asthma and allergic diseases, interventions based on specific micronutrient supplementation have not yet been proven and further studies are needed in this area [68(NC)]. The whole constituents of fresh fruit and vegetables need consideration – constituents

other than antioxidant levels in the food may be crucial factors. While it is desirable to know all the precise mechanisms of benefit before considering dietary recommendations, it is not essential.

The effect of reduction in antioxidant activity has been explored in another way, by exposure to paracetamol, which depletes the antioxidant glutathione. In adults in Britain there was a positive relationship between paracetamol use and asthma [89(III)]. Paracetamol sales per capita have been examined in relationship to ISAAC data in 36 countries, and European Community Respiratory Health Survey data in 18 countries. There were positive correlations between paracetamol sales and symptoms of wheeze, rhinoconjunctivitis and eczema. An increase in paracetamol sales of 10 g/capita was associated with an increase of 5.2% in asthma symptoms in 13- to 14-year-olds and 2.6% in adults [90(III)].

Cereals and Rice

Components in whole grains that may be protective include antioxidants and trace minerals [62(NC)]. Many of the protective compounds in whole grains (wheat, rice and corn being the main ones) are also found in fruit and vegetables, but some plant compounds are more concentrated in whole grains.

Of interest in the ISAAC analysis is the strong, consistent, negative association between calories from cereal and rice and protein from cereal and nuts and the three conditions, and it was speculated that, if the daily per capita amount of calories from cereal and rice consumed were to be increased by 10% of total energy consumption, it may be possible to achieve a 3.2% decrease in the prevalence of current wheeze, a 0.4% decrease in severe wheeze, a 2.4% decrease in allergic rhinoconjunctivitis and a 0.6% decrease in eczema [64(III)]. As mentioned above, plant-based carbohydrate-rich diets have been associated with lower rates of other non-communicable diseases [60(NC), 62(NC)] and it is of interest that this association has been found for asthma, allergic rhinoconjunctivitis and eczema. Although it is speculated that antioxidants contained in cereal, rice and vegetables may be a reason for this protective effect, other mechanisms need to be explored.

Although it is speculated that antioxidants contained in cereal, rice and vegetables may be a reason for this protective effect, this and other mechanisms need exploration and it is of interest that this association has also been found for asthma, allergic rhinoconjunctivitis and eczema.

Polyunsaturated Fat

With the emphasis on reducing our intake of saturated fats and cholesterol, more polyunsaturated fat is consumed. Animal fats have been replaced with vegetable oils, in food manufacture, fast-food frying, and even in home

preparation. There has been a doubling from 8 to 15% in the percentage of the polyunsaturated linoleic acid in body fat [61(NC)]. Increased consumption of linoleic acid, found in PUFA, is thought to be linked to asthma in general, eczema and allergic rhinitis [28(III), 61(NC)]. It is also postulated that an increase in consumption of linoleic acid leads to an increase in the synthesis of prostaglandin E₂, resulting in allergic sensitisation [91(NC)].

To test the hypothesis that the increased consumption of altered PUFA (for example, margarine) has an influence on the increasing prevalence of IgE-mediated disease, a cross-sectional study of over 2,000 German children looked at what they used as a spread, comparing margarine with butter. The results showed that margarine was associated with IgE sensitisation, and with rhinitis symptoms in boys [92(III), 93(III)].

However, PUFA derived from vegetables show a different picture. The ISAAC analysis revealed a significant association between vegetable-derived PUFA and decreased symptom prevalence of the three conditions, as well as vegetable-derived mono-unsaturated fatty acids and decreased symptom prevalence of current wheeze and eczema, supporting the hypothesis that it is industrially derived PUFA that is responsible, rather than naturally derived PUFA from vegetables. Whether this is an independent association between vegetable-derived PUFA or is dependent on the association with vegetables as a whole is not clear [64(III)].

Trans Fatty Acids

Trans fatty acids are mainly derived from industrially hydrogenated fats in spreads, although they are also found in dairy products and in the fat of ruminant animals. It has been reported that trans fatty acids influence the desaturation and chain elongation of n-6 and n-3 fatty acids into precursors of inflammatory mediators, such as leukotrienes, and that these effects may be stronger for trans fatty acids from hydrogenated vegetable fat than from animal fat [94(NC)]. Furthermore, among infants, increased trans fatty acid plasma levels have been associated with changes in the fatty acid composition of plasma lipids [95(III)] similar to those seen in individuals with IgE-mediated diseases [96(III)]. A European ISAAC investigation found a significantly positive association between trans fatty acids and the prevalence of childhood asthma, allergic rhinoconjunctivitis and eczema [97(III)]. The associations seen tended to be stronger when the analyses were restricted to the estimates of trans fatty acids from sources that contained predominantly hydrogenated vegetable fat, such as oils, biscuits, cakes and potato chips. Trans fatty acids have become a typical part of the 'western' diet and the hypothesis that they may play a part in the development of childhood asthma and allergies seems worth pursuing [97(III)].

Chemicals and Trace Elements

Sodium. It has been hypothesised that diets high in salt may accentuate bronchial reactivity. Several groups of researchers have investigated the relationship between sodium intake and asthma. These data have demonstrated a small adverse effect of increased sodium intake on bronchial reactivity, but no significant effect on clinical symptoms of asthma has been shown, consequently there is little support currently for the adoption of low-salt diets by patients with asthma [68(NC)].

Selenium. Selenium acts as an antioxidant. It is an essential component of the enzyme glutathione peroxidase, which reduces hydrogen peroxide and other organic peroxides to harmless substances, thereby preventing peroxidation and subsequent instability of cell membranes. Inflammatory cells in asthmatic airways produce oxygen-derived free radicals and peroxides. Studies to examine a possible relationship between low selenium levels and asthma have yielded inconsistent results. There are no current data demonstrating a beneficial effect of selenium supplementation on asthma. There is therefore no clear evidence that selenium is important in the aetiology of asthma [68(NC)].

Magnesium. Although the mechanism of the proposed effect of magnesium on asthma is unknown, it may involve a direct action on bronchial smooth muscle, producing airway dilatation. Intravenous magnesium may have a minimal role in the treatment of acute severe asthma, but it does not appear to be of value in the treatment of chronic asthma. Magnesium deficiency has not been shown in asthma patients and there is no clear evidence that magnesium is important in the aetiology of asthma [68(NC)].

Food Preservatives and Additives

It has been noted that there is often a change in dietary habits after migration, including the addition of preservatives and food additives such as metabisulphates, benzoate and tartrazine, which have also been implicated in asthma exacerbations [57(III)]. There are observations that some traditional diets of locally grown foods are being replaced with a more 'westernised' diet containing processed foods and refined carbohydrates, as these become more accessible [59(III), 63(IIa)]. Traditional diets have less food preservatives and additives, and it has been reported that a lower incidence of chronic disease is associated with the consumption of a more traditional form of diet [60(NC), 61(NC)]. There have been no studies of the separate effect of food preservatives and additives on asthma and allergy.

Breast-Feeding

The role of breast-feeding in asthma and allergic disease has been extensively reviewed recently by Peat et al. [98(NC)]. Intuitively, breast-feeding

should be healthy for babies and prevent disease, but is this true for the non-infectious diseases of asthma and allergies? The constituents of breast milk include immunological factors and allergens. Although there are factors in breast milk which may stimulate the development of asthma and IgE-mediated disease such as Th2 cells, cytokines, and antigens, other factors in the milk may protect against asthma and IgE-mediated disease and act by influencing the infant gut.

Patterns of breast-feeding have changed radically in the last few decades, particularly in affluent countries, where the rates became particularly low 3–4 decades ago, but have gradually increased since. There are differences in rates between countries, with rates being lower in Australia, USA and UK than in The Netherlands, Denmark, Sweden and Norway [98(NC)]. Could these variations contribute to the variations in the prevalence of asthma and allergic diseases?

There is popular belief that breast-feeding helps to prevent asthma and IgE sensitisation, and thus the expression of the atopic constitution, but there is little evidence to support this. However, protection against the development of allergic symptoms by exclusive breast-feeding has not been apparent in all studies. A recent review found no studies that have demonstrated a preventive effect of dietary measures as regards asthma under 4 years [99(IIIC)]. In a prospective British cohort study, breast-feeding had an apparent protective effect, but this effect was reduced and no longer significant after adjustment for socio-economic status [100(IIIC)]. A protective relationship between breast-feeding and the development of allergy symptoms, wheezing illness and asthma has been shown in a Finnish cohort study which followed healthy infants from birth to the age of 17 years. Breast-feeding was found to be protective against ‘atopic eczema’, food allergy, wheezing and symptoms of allergic rhinoconjunctivitis throughout childhood and adolescence [101(IIIC)]. In a historical cohort study in Guinea-Bissau, participants who had been breast-fed for more than 1 year were less likely to have a positive skin test to house dust mites [102(IIIC)]. In a prospective birth cohort study in New Zealand there was no evidence to indicate that early breast-feeding or early solid feeding practices reduced the risk of subsequent asthma [103(IIIC)], but risks of eczema were increased by early solid feeding of 4 or more types of solid food under 4 months of age [104(IIIC)]. In a prospective cohort study in Western Australia, the introduction of milk other than breast milk before 4 months of age was a significant risk factor for all asthma- and atopy-related outcomes in children aged 6 years [105(IIIC)]. In a randomized controlled trial in England, feeding pre-term neonates on cow’s milk based formula did not increase the overall rate of asthma or wheezing at age 18 months. However, in the subgroup with a family history of atopy, early exposure to cow’s milk increased the risk of a wide range of allergic reactions, especially ‘atopic eczema’ [106(Ib)].

In small prospective studies in India and Newfoundland, Canada, in newborn siblings of children with 'atopic disease', exclusively breast-fed for a minimum of 6 weeks, the incidence of 'atopic eczema', recurrent wheezing, elevated serum IgE, and various IgE antibodies to cow's milk proteins were significantly lower compared with a formula-matched control group [107(IIIC)]. 'Atopic eczema' in infants from high socio-economic status with a high atopy risk can be avoided by breast-feeding. Introduction of allergenic foods in later infancy promotes the development of 'atopic eczema' in formerly breast-fed infants. Prolonged breast-feeding as well as high socio-economic status may even be indicators of a high atopy risk. The effect of early food avoidance programs on the prevalence of 'atopic eczema' does not last for more than 2 years [108(IIa)]. In a prospective cohort study in Tucson, Ariz., USA, in a cross-sectional analysis, breast-feeding appeared to have a paradoxical relationship with IgE in childhood, depending on the maternal IgE level – lower maternal IgE was associated with lower serum IgE in the child, and higher maternal serum IgE with higher serum IgE in the child [109(IIIC)].

Children who become allergic at an early age are at much greater risk for the development of clinically important asthma in later years. Methods that delay allergen-specific IgE sensitisation in early life such as prolonged breast-feeding are likely to result in an overall down-regulation of asthma morbidity in later life [98(NC)]. The hypothesis is that infants at high risk for development of asthma because of a family history of allergic illness are very likely to have allergic symptoms of some type, but these symptoms will be less severe if the infants are breast-fed in the first few months of life.

The relationship between breast-feeding and various formula feeds and solids has been explored. In a prospective double-blind randomised controlled trial in India among 72 infants with a family history of atopy among first-degree relatives, exclusive breast-feeding for more than 4 months was found to be partially protective against 'atopic disease', with this effect being enhanced when the mother excluded common allergenic foods from her diet during lactation. Among those not breast-fed, feeding a milk/whey hydrolysate formula reduced the incidence of 'atopic disease'. This approach was significantly beneficial compared with feeding a soy-based formula, or a conventional cow's milk formula, and even compared to exclusive breast-feeding without maternal dietary restriction [110(Ib)]. Several prospective studies in high risk infants exclusively fed breast milk and/or fed extensively hydrolysed formula combined with avoidance of cow's milk proteins and solid foods during at least the first 4 months of life a reduction in the cumulative incidence of food allergy and 'atopic eczema' in the first 2–4 years of life is found [99(NC)].

Peat et al. [98(NC)] stated that 'Previous studies suggest that breast-feeding is especially important in preventing the onset of allergic illness for male children,

certain ethnic groups, children who share a room and babies of mothers who smoke. It is important to keep this particular evidence in perspective and remember that it is only clinically relevant from a mechanistic view point and not from a public health perspective. The multitude of potential health and psychological benefits that breast feeding confers both to the infant and to the mother/infant relationship confirms that effective promotional strategies need to be directed at the entire community to optimise the health of all babies. In trying to establish a relationship between breast feeding and allergic disease, the inherent problems of epidemiologic studies, for which there are few reliable methods with which to measure exposures to different infant feeding modes have been frustrating. The lack of reliable methods has meant that consistent evidence of the relationship between breast-feeding and allergic disease that health professionals find convincing has taken more than a decade to assemble. An added complication has been that breast-feeding does not end when formula feeding is introduced. Rather there is a gradual change over the weaning period that may last between one week to several months. Thus it has been impossible to disentangle the risk conferred by formula feeding from the protection afforded by breast-feeding. It will be extremely difficult to collect evidence for the long term independent effects of exclusive breast feeding and partial formula feeding.' [98(NC)].

Maternal Diet during Lactation

Some high-risk infants may benefit from modulation of maternal diet during lactation. A few studies indicate that the preventive effect of breast-feeding on the development of 'atopic eczema' may be enhanced by maternal avoidance of potential food allergens (milk, egg and fish) during the lactation period, but other studies do not confirm this finding [99(NC), 107(IIIC), 111(II)]. The effects on the infant of other variations in the diet of a breast-feeding mother have not been studied, such as increased antioxidant intake.

Maternal Diet in Pregnancy

The intrauterine environment is now thought to play an important part in the development of chronic disease in later life [112(IIIC)], although there is no documented beneficial effect of maternal diet during pregnancy [99(NC)]. Indirect effects on intrauterine growth are discussed in the next section. This effect may prove to be either protective or aggravating, for example nutritional deficiency in utero may irrecoverably constrain the growth of the airways. Birth weight, head circumference and gestational age, markers of the intrauterine environment that are routinely measured and recorded in birth records, could be markers of future chronic diseases. Diet during pregnancy could potentially influence asthma and expression of atopy adversely, with antigens passing through the placenta leading to programming of the developing immune

system by stimulating cells and cytokines. However there were no advantages found in a randomised controlled trial of elimination of cow's milk and egg in the last trimester [113(I), 114(Ib)].

The effects on the infant of other variations in the diet of the pregnant mother have not been studied, such as increased antioxidant intake.

Growth

Low Birth Weight

Lower birth weight has been associated with worse adult lung function, but its relationship to asthma needs clarification [112(IIIC)]. In a prospective British cohort, low birth weight is a risk factor for early childhood wheezing, independent of maternal smoking [100(IIIC)]. This may be mediated through under-nutrition in utero causing small airways. In a Norwegian population-based study there was an inverse association between birth weight and numbers of respiratory symptoms [115(IIIC)]. In a study from Israel, 17-year-old adolescents had a higher risk of asthma if they had birth weights less than 2,500 g. This may be mediated through lung function [116(IIIC)]. In a New Zealand study there was no association between birth weight, respiratory symptoms and IgE but the numbers were small [117(IIIC)]. In a study of 50-year-old men and women in Lancashire, UK, there was no relationship between birth weight and allergy [118(IIIC)]. Children with bronchopulmonary dysplasia (chronic lung disease of prematurity) have an increased likelihood of wheezing in early life, and have hypertrophied bronchial smooth muscle. However, there is no evidence that these children are more likely to develop asthma and allergy. The relationship between low birth weight and asthma could be explored further, especially with studies from developing countries.

Disproportionate Foetal Growth

Foetal under-nutrition during critical periods in early development can have lifelong effects on structure, physiology and metabolism. This phenomenon is known as programming. An imbalance in thymus-derived lymphocytes may be linked to persistent IgE responses. In a study of 50-year-old men and women in Lancashire, UK subjects with higher IgE concentration had a larger head circumference at birth [118(IIIC)]. In a cohort study from Dunedin, New Zealand, infants with a larger head circumference at birth had a higher serum total IgE at 11 years. The reasons for this association are not clear, but relative over-nutrition in utero could be a factor [117(IIIC)]. However, it should be remembered that increased serum IgE concentrations is not necessarily related to allergen-specific IgE sensitisation.

Obesity

The prevalence of obesity among children and adolescents has increased in Western countries, due to changes in diet and physical activity. In a cross-sectional study in the USA, television viewing affected overweight among youth, and the attributable risk indicated that more than 60% of overweight incidence could be linked to excess television viewing time [119(III)].

Evidence for a positive relationship between body mass index (BMI) and reported asthma is not clear. In a longitudinal cohort study in Tucson, there was no association between BMI at age 6 year and wheezing prevalence at any age. Girls becoming overweight between 6 and 11 years of age were 7 times more likely to develop new asthma symptoms at age 11 or 13 years [120(IIIC)]. In New York children, being overweight was associated with more symptoms of asthma [121(III)]. In a national sample in the USA, increased weight was associated with increased asthma symptoms [122(III)]. In a cross-sectional study in Australian adults, severe obesity (BMI >35 kg/m²) was associated with wheeze in the last 12 months, but not AHR or atopy; however the underweight group (BMI <18.5 kg/m²) appeared to have more respiratory problems, with a higher prevalence of symptoms, and increased AHR [123(III)]. The relationship between BMI and wheeze and BHR has been investigated in a cross-sectional study in Taiwan. The prevalence of BHR was lower in the lowest quintile of BMI than in other girls. BMI was positively associated with symptoms of rhinitis in girls [124(III)]. A cross-sectional study examining the association between obesity and asthma in England and Scotland showed an association between BMI and asthma although the association was stronger in girls than boys, and was stronger in an inner city sample compared with the general population. No association was found with skinfold thickness [125(III)]. The nature of the association has yet to be clarified and it cannot be concluded that obesity has contributed to the rise in asthma [126(NC)]. Recent studies published as abstracts show either no association [127(III)], a protective effect [128(III)], or a deleterious effect of obesity on asthma symptoms [129(IIIC), 130(III), 131(III)].

Physical Fitness

In a prospective community-based study of Danish children there was a weak correlation between physical fitness and reduced risk for the development of asthma, but not hay fever. The risk for developing asthma during adolescence was reduced 7% by an increased maximal workload of 1 W/kg [132(IIIC)]. In a cross-sectional Norwegian study, children with asthma who exercised less had more BHR than those who exercised less, but the cause of this relationship is not clear [133(III)]. Adult onset asthma in women may be associated with reduced levels of activity and the Gly16 allele [134(IIIC)]. The relationship

between physical fitness and possible protection from the development of asthma is worthy of further exploration.

Infection

The relationship between infection and IgE sensitisation has intrigued clinicians, epidemiologists and other scientists for the last 2 decades. A retrospective study of children attending day care for at least 3 months during the first 2 years of life, compared with children cared for at home in Helsinki, Finland, showed a higher prevalence of otitis media and other infections among the day care children. The day care children had similar prevalence of eczema, cumulative allergic disease by age 7 and positive skin prick tests as children cared for at home. When the groups were combined, an increased prevalence of cumulative atopic disease and positive skin prick tests was found in children who had infections in infancy. However, the authors concluded that infections in infancy were not associated with IgE-mediated allergy later in life, suggesting that an unknown factor could modify the relationship [1(III)].

A 1989 review of the role of viral infections indicated that there is evidence that viral infections are associated with onset of allergic symptoms among predisposed individuals. The type and timing of infection may be important in the development of asthma. A similar association has been observed with respect to asthma and respiratory viral infection. There are multiple effects of respiratory viral infection on allergic sensitisation and airway reactivity, including IgE sensitisation, epithelial injury, inflammation and enhanced mediator release. All of these effects act to enhance the factors which participate in inflammation [129(NC)]. A subsequent (1995) review suggests that infants with wheeze fall into two groups: infants with viral-infection-associated wheeze who have lower than normal lung function shortly after birth, who will become symptom free during the pre-school years; and children who will continue to wheeze. The factors that determine which group will be persistent wheezers are not well understood but viral infections are unlikely to play a major part [135(NC)].

The 'hygiene hypothesis' was first proposed by Strachan [2(IIIC)] in 1989: that allergic diseases could be prevented by infection in early childhood. This arose from the observation that hay fever at 11 and 23 years of age was inversely related to the number of children in the household at age 11 years, with the number of older children being more influential than birth order, and that eczema in the first year of life was independently inversely related to the number of older siblings. He proposed that allergic diseases could be 'prevented by infection in early childhood transmitted by unhygienic contact with older siblings or acquired

prenatally from a mother infected by contact with her older children. Later infection or reinfection by younger siblings might confer additional protection against hay fever' [2(IIIC)]. The first decade of the 'hygiene hypothesis' has recently been carefully reviewed by David Strachan [136(NC)].

General Burden of Childhood Infections

Several large cross-sectional studies of school children have shown no substantial inverse relationships between the nature or frequency of infections early in childhood and prevalence of allergic diseases and skin test positivity [137(III), 138(III)]. Longitudinal studies, showing a relationship, are open to various interpretations [139(IIIC), 140(IIIC), 141(IIIC)]. The picture is not clear-cut. A recent prospective cohort study in Germany showed that children with 2 or more episodes of runny nose before 1 year of age were less likely to have been diagnosed as asthmatic by a doctor or have wheeze by 7 years, and were less likely to be atopic by 5 years. One or more viral infections of the herpes type before 3 years of age were also inversely associated with asthma at age 7. Conversely, repeated lower respiratory tract infections in the first 3 years was associated with an increased risk of wheeze at age 7 [142(IIIC)]. In another review it was stated that epidemiological evidence suggests that early infection may decrease the risk of IgE-mediated allergic diseases, but not apparently asthma [74(NC)]. In his recent review, Strachan states that 'the totality of current evidence from cross-sectional and longitudinal studies, of common specific and non-specific infectious illness in infancy and childhood, offers no support for the 'hygiene hypothesis' [136(NC)].

Day Care

Inconsistent results have emerged from studies investigating exposure to children outside the home [136(NC)]. One relatively small German study found a reduced risk of allergic diseases among children who had entered day nursery at an early age [143(III)]. A larger Finnish study reported a significant association in the opposite direction [144(III)]. An earlier Finnish study found no difference in allergic symptoms or skin test positivity with respect to day care attendance [1(III)]. In the British 1958 birth cohort attendance at a pre-school nursery did not influence the prevalence of allergic sensitisation in early adult life [145(IIIC)]. Among European adults day care attendance in childhood was not associated with an increase in IgE-mediated allergic diseases [146(III)]. However, a recent analysis of the Tucson cohort showed that day care under 6 months was protective against the development of asthma. Day care during the first 6 months also increased the risk of frequent wheeze (more than 3 episodes in the previous year) at age 2 years, but decreased the risk of frequent wheeze at ages 6–13 years [147(IIIC)].

Family Size and Sibling Order

One of the most striking epidemiological features of allergy is the inverse association with family size, which has been consistently found in studies of hay fever, skin prick positivity and allergen-specific IgE [148(NC)]. Many, but not all, studies find a stronger protective influence for older siblings than for younger siblings, for (hay fever) allergic rhinoconjunctivitis, but not asthma [136(NC), 149(III)]. The influence of family size and structure was seen for (hay fever) allergic rhinoconjunctivitis and 'atopic eczema' in two national British birth cohorts [2(IIIC)]. Studies from several European countries have shown the same inverse association of skin prick tests or circulating levels of aeroallergen-specific IgE with family size [137(III), 140(IIIC), 146(III), 150(III), 151(III)]. Higher socio-economic status and lower sibling number are determinants of atopy (skin prick test positivity) in an Italian population [137(III)]. Birth order has been specified in a few studies [137(III), 145(IIIC)]. In two large studies no differences emerged between older and younger siblings [146(III), 152(III)]. Possible modifying influences of household structure, including birth order, sibling gender, and parental ages still require clarification [136(NC)]. The balance of evidence does not suggest a relationship between allergic diseases and early child contacts outside the home [136(NC)].

Specific Infections

Respiratory Syncytial Virus. Respiratory syncytial virus (RSV) has warranted special consideration because it is the commonest cause of bronchiolitis, an acute wheezy illness of infants. A study of children in Sweden, which used a case-control methodology, showed a positive association between RSV infection in infancy requiring hospitalisation, and allergic sensitisation at age 7.5 [153(IIIC)]. A study of children enrolled in the longitudinal cohort study, the Tucson Children's Respiratory Study (USA), showed that RSV lower respiratory tract infections before 3 years were associated with an increased risk of infrequent wheeze, and frequent wheeze at age 6. Risk decreased with age and was not observable at age 13. RSV lower respiratory tract infections were also associated with lower forced expired volumes, but there was no difference after inhalation of salbutamol [154(IIIC)].

Tuberculosis. Recent experimental evidence suggests that exposure to *Mycobacterium tuberculosis* may reduce the risk of developing asthma. In a partly longitudinal study of children in Japan, an inverse relationship was found between tuberculin skin response, allergen-specific IgE and symptoms of asthma. However it is unclear whether Bacille Calmette Guérin (BCG) vaccination, primary tuberculous infection in childhood, or sensitisation to harmless environmental mycobacteria were responsible [155(III)]. (BCG vaccination is discussed below under 'Immunisation'.)

A case-control study of individuals notified to the Finnish National Tuberculosis Registry between 1966 and 1969 compared with matched controls, showed lower prevalence of persistent asthma among women who were notified as having tuberculosis younger than age 16 after 28–32 years follow-up. Women were also less likely to have other allergic conditions. In contrast men who had contracted tuberculosis were more likely to have persistent asthma [156(III)].

In a cross-sectional study in Sweden the frequencies of skin test reactivity to the atypical mycobacteria *M. avium* and *M. scrofulaceum* were higher rather than lower in allergic compared to non-allergic children. There was a tendency toward a lower frequency of more strongly positive skin reactions to mycobacteria in allergic rather than non-allergic children. These results do not support the hypothesis that early mycobacterial infections have a suppressive effect on the development of ‘atopic disease’ [157(III)].

An ecological analysis of ISAAC Phase One has shown an inverse association between tuberculosis notification rates and the lifetime prevalence of wheeze and asthma and the 12-month prevalence of wheeze assessed from a video questionnaire, adjusted for GNP. A decrease in tuberculosis notifications of 25 cases per 100,000 was associated with a 4.7% increase in the prevalence of wheeze ever [158(III)].

Measles Infection. In a historical cohort study in Guinea-Bissau, measles infection was associated with a large reduction in the risk of skin test positivity to house dust mites, compared with children who had been vaccinated against measles and not acquired the infection [102(IIIC)]. The mechanism of this effect is difficult to fit into the ‘hygiene hypothesis’ because measles causes sequential Th1 and Th2 cytokine responses. Measles vaccination leads to an enhanced Th2-like effect, with suppression of delayed-type hypersensitivity reactions [159(NC)].

A cross-sectional study in Finland showed a positive association between measles infection and allergic diseases (asthma, rhinoconjunctivitis and eczema) [160(III)]. In contrast, in a prospective British cohort, measles infection in childhood appeared to reduce the risk of hay fever at age 16 years in children with multiple older sibling contacts [161(IIIC)].

Orofaecal Infections. A cross-sectional retrospective study of young Italian men showed that IgE-mediated allergy was less common among men who were seropositive for the hepatitis A virus antibody [162(III)]. Among Italian young men respiratory allergy was less frequent in people heavily exposed to orofaecal *Helicobacter pylori*, hepatitis A virus and *Toxoplasma gondii*. The authors proposed that hygiene and a westernised, semi-sterile diet may facilitate IgE sensitisation by influencing the overall pattern of commensals and pathogens that stimulate the gut-associated lymphoid tissue [163(III)].

Pertussis. In an Italian population, a history of bronchitis or bronchiolitis before 2 years of age was weakly associated with an increased 'risk of atopy', whereas a history of pertussis or pneumonia was not [137(III)]. In a randomised double-blind controlled trial of pertussis vaccine in Sweden, there was a positive association between whooping cough and asthma by 2.5 years of age, and asthma occurred more commonly in un-immunised children [164(Ib)].

Anthroposophical Lifestyle

An anthroposophical lifestyle is one in which participants follow a system of beliefs and practice based on the teachings of Rudolph Steiner, maintaining that by correct training and personal discipline, one can attain experience of the spiritual world. Features of an anthroposophical lifestyle may include a choice not to immunise children, restricted use of antibiotics, increased exposure to childhood infections and dietary patterns which may influence the intestinal microflora [165(III), 166(III)]. A cross-sectional study comparing children in two Rudolph Steiner schools near Stockholm, Sweden, with children in neighbouring schools showed lower prevalence of atopy among children from the Steiner schools [166(III)]. There is further comment on this in Chapter 3.

Immunisation

It has been postulated that immunisation in early life may either promote or protect against asthma and IgE-mediated diseases in childhood. Studies showing that immunisation may increase the incidence of IgE-mediated disease include a study showing that the pertussis toxin stimulated the production of IgE in mice [167(IIa)]. Several studies involving children have shown similar results. In a retrospective cohort study in Oxfordshire, immunisation with whole-cell pertussis vaccine was associated with the development of IgE-mediated disorders, but the authors suggested that this finding should be interpreted cautiously because of the possibilities of confounding effects and reverse causation [141(IIIC)]. In a small cross-sectional study carried out in London, UK, asthma was found more commonly in immunised than un-immunised children [168(III)]. A large cross-sectional study in the USA found that diphtheria/pertussis/measles or tetanus vaccine appeared to increase the risk of asthma ever, and symptoms of allergic rhinoconjunctivitis, but not wheezing in the last 12 months [169(III)].

In another study a group of adults was immunised with the live measles vaccine, this resulted in activation of Th2 cells producing interleukin-4 [170(IIa)]. In a small retrospective cohort study in Christchurch, New Zealand, involving school-aged children, there were lower rates of asthma or allergic disease among the 1.8% of un-immunised children [171(IIIC)].

Other studies have found that immunisation has no effect or even a protective effect on IgE-mediated disease. In contrast to the studies that found that the pertussis vaccine increased IgE-mediated disease, two studies found that the pertussis vaccine had no effect on asthma and allergies. In a large prospective cohort study in the Avon health Authority, United Kingdom, there was no increased risk for wheezing illnesses in vaccinated children [172(IIIC)]. In a randomised double-blind controlled trial of pertussis vaccine in Sweden, the cumulative incidence of IgE-mediated disease was similar in the three vaccination and placebo groups [164(Ib)].

BCG has also been found to have no effect on IgE sensitisation or even may have a protective effect. A retrospective case-controlled cohort study in children born in Stockholm found that the BCG vaccination in infancy, beyond the neonatal period, had no primary preventive effect on the development of IgE sensitisation in children with atopic heredity [173(IIIC)]. The effects of BCG in early life in non-atopic families have not been studied. A study in Guinea-Bissau showed that children who were vaccinated with BCG in early infancy were less likely to be atopic, defined as positive skin prick testing at 3–14 years of age than children who had not been vaccinated [174(IIIC)]. In a partly longitudinal study of children in Japan, an inverse relationship was found between tuberculin skin response and atopy, including allergen-specific IgE and symptoms of asthma and IgE-mediated allergy but it is unclear whether BCG vaccination, primary tuberculous infection in childhood, or sensitisation to harmless environmental mycobacteria were responsible [155(III)]. In a cross-sectional study in Sweden the prevalences of atopic eczema, allergic rhinoconjunctivitis and asthma were lower among BCG-vaccinated children who were born in other countries, but there was no effect on those born in Sweden [157(III)]. A prospective British cohort study found that the measles vaccination in childhood appeared to reduce the risk of (hay fever) allergic rhinoconjunctivitis at age 16 years in children with multiple older sibling contacts [161(IIIC)].

An ecological analysis of the ISAAC phase One data using immunisation rates for the year of birth of the ISAAC participants, adjusted for GNP, showed no association between symptoms of asthma, allergic rhinoconjunctivitis and eczema and national immunisation rates for diphtheria and tetanus toxoids and pertussis, measles and BCG [175(III)]. However, for local immunisation rates in 13- to 14-year-olds there were significant negative associations of symptoms of all three conditions and diphtheria/tetanus toxoids/pertussis and measles, but BCG had no effect [175(III)]. No associations were seen in the 6- to 7-year age group between any symptoms and any of the three immunisations [175(III)]. This large worldwide study is reassuring for population immunisation programmes.

Microbial Exposure in Early Life

Intestinal Microflora Protective

The role of the intestinal microflora has recently been reviewed [176(NC)]. It is recommended that a search for factors that enhance the induction of tolerance would be more worthwhile than concentration on factors that increase sensitisation. When animals are colonised with bacteria of the normal commensal intestinal flora, oral tolerance and immune deviation towards Th1 responses develop rapidly. The intestinal microflora is the most likely candidate for the hypothesis that microbial pressure would enhance Th1 type responses [176(NC)]. Primary gut flora in infants in Finland born by caesarean section may be disturbed for up to 6 months after the birth with a delay in Bifidobacterium- and Lactobacillus-like bacteria and less *Bacteroides fragilis* groups than babies born by vaginal delivery [177(IIa)]. In a prospective study of the development of allergy to environmental factors, a small number of Estonian and Swedish children differed in their colonisation with Lactobacilli. The allergic children in Estonia and Sweden were less often colonised with Lactobacilli as compared with non-allergic children in each country [178(III)]. In the allergic children there were higher counts of aerobic micro-organisms, particularly coliforms and *Staphylococcus aureus* and the proportions of aerobic bacteria of the intestinal flora were higher in the allergic children while the opposite was true for anaerobes and Bacteroides. Thus, differences in the indigenous intestinal flora might affect the development and priming of the immune system in early childhood [179(IIIC)].

Among Finnish infants the bacterial cellular fatty acid profile in faecal samples differed significantly between infants in whom atopy was and was not developing. Atopic subjects had more Clostridia and fewer Bifidobacteria. The differences in neonatal gut microflora precede the expression of atopy, suggesting a crucial role of the balance of indigenous intestinal bacteria for the maturation of human immunity to a non-atopic mode [180(IIIC)].

Differences have been found in the intestinal micro-flora between countries with a high and low prevalence of allergies [178(III)] and between allergic and non-allergic children [179(IIIC)], suggesting that differences in the indigenous intestinal flora might affect the development and priming of the immune system in early childhood. The authors suggest that if further study proves this to be the case, then the administration of probiotic bacteria could be a possible intervention for primary prevention of allergy.

Probiotics

The concept of probiotics – live microbial food ingredients that have a beneficial effect on human health – was first proposed in the early 1900s by

Russian Nobel Prize winner Elie Metchnikoff who suggested that Bulgarian peasants lived long healthy lives because they consumed fermented milk products. *Lactobacillus*, he proposed, had a positive effect on the microflora of the colon, decreasing toxic microbial activities [181(NC)]. Probably the most striking alteration in the early immune exposures of infants throughout human history has been the wholesale change in initial gut colonisation during the past century. The dominance of *Bifidobacteria* and *Lactobacillus* in the initial flora of the developing world infant has been increasingly replaced by a variety of other organisms in the developed world. The exact mechanisms by which probiotics may affect IgE-mediated disease remain speculative, but their potential effects on the immune system are an intriguing area for further exploration [182(IIa), 183(NC)].

In a double-blind randomised placebo-controlled trial in Finland, mothers were randomly given capsules of either *Lactobacillus* daily, or placebo 2–4 weeks before expected delivery [184(Ib)]. Postnatally, capsules were given for 6 months either to breast-feeding mothers or to the children directly if not breast-feeding. In the probiotic group of babies (both routes of delivery combined) the frequency of eczema, but not of other allergic diseases, was half that of the placebo group. There were no differences in IgE antibody concentrations or skin prick test positivity. A similar study from another Finnish group did not find any difference [185(Ib)]. Long-term follow-up of these cohorts will be of interest.

In the first clinical demonstration of specific probiotic strains modifying the changes related to allergic inflammation (i.e. tertiary prevention), a randomised double-blind controlled trial was carried out in Finland. A small number of infants who manifested ‘atopic eczema’ while exclusively breast-feeding were weaned to probiotic supplemented (*Bifidobacterium lactis* or *Lactobacillus*) extensively hydrolysed whey formulas, or to the same formula without probiotics. A significant improvement in skin condition occurred in patients given probiotic-supplemented formulas. The concentration of soluble CD4 in serum and eosinophilic protein X in urine were reduced, indicating that probiotics may counteract inflammatory responses beyond the intestinal milieu [186(Ib)].

However, the safety of probiotics must be considered including the possibility of adverse effects in athymic neonates. Probiotics have a favourable profile but there have been sporadic cases of septicemia and liver abscess in immunodeficient patients [184(Ib)]. Thus understandable enthusiasm should be tempered with caution before probiotics become mainstream ‘allergy-proofing’ regimens.

Antibiotics

Sales of antibiotics in Europe vary more than fourfold with France, Spain, Portugal and Belgium having the highest sales, and the Netherlands,

Denmark, Sweden and Germany the lowest [187(III)]. One unwanted effect of antibiotics is major depletion of the commensal microflora of the gut. Prospective studies on the link between the early-life receipt of antibiotics and the development of IgE-mediated disorders are needed [188(NC), 189(NC)].

Most of the studies are retrospective, and potentially one of the largest problems with the retrospective studies is the concept of self-selection. Children who wheeze with lower respiratory infections in early childhood may be more likely to receive antibiotics. Thus it is not necessarily the antibiotic treatment that leads to asthma, but may merely be a marker for children who are more likely to wheeze in the first place.

In a retrospective cohort study in Oxfordshire, oral antibiotics in the first 2 years of life predicted 'atopic disorders'. Receipt of macrolide and cephalosporin antibiotics was more predictive of subsequent IgE-mediated allergy than the narrower spectrum penicillins. However the authors suggested that this should be interpreted cautiously because of the possibilities of confounding effects and reverse causation [141(IIIC)]. In a Bavarian population, the use of antibiotics was related to a higher prevalence of asthma and hay fever. The less frequent use of antibiotics by farmers' offspring, compared with other children, may result in an enhanced infectious burden which has been suggested to protect against the development of asthma and allergies [190(III)]. A study in New Zealand of children attending Rudolph Steiner schools showed that more than one course of antibiotics in the 1st year of life was significantly associated with a history of asthma but not with current wheeze. There was no significant association with (hay fever) allergic rhinoconjunctivitis or eczema [191(III)].

A study among children in Dresden, Germany, using the ISAAC phase Two protocol showed that repeated episodes of fever and antibiotic use in early life were strongly positively associated with prevalence of asthma and wheeze at school age. Among asthmatic children the number of fever episodes and antibiotics courses were strongly inversely associated with the prevalence of IgE-mediated allergy and BHR. Asthmatic children with recurrent early childhood infections were less likely to be symptomatic at school age. The highest risk of asthma with early childhood infections was for non-allergic asthma [138(III)].

The prospective Boston Home Allergens and Asthma Study [192(IIIC)] was a birth cohort study which followed 448 infants, at high risk for atopy, from birth to 5 years. This study excluded children who were treated with antibiotics for wheezing. There was no association between antibiotic use and asthma, allergic rhinitis or eczema at age 5.

Farming Environment

In Switzerland children growing up on a farm were compared to non-farming families in the same villages. Farming as parental occupation was significantly associated with lower rates of sneezing attacks during pollen season and IgE sensitisation, but not wheeze and itchy skin rash. The risk of IgE sensitisation was lower in children of full-time farmers than in children of part-time farmers [193(III)]. Among farmers in Switzerland and farming children in Bavaria lower rates of sensitisation to pollen and animal dander, and self-reported (hay fever) allergic rhinoconjunctivitis have been observed. High exposure to allergens may contribute to the development of tolerance [193(III), 194(III)].

In a cross-sectional study of Finnish children the childhood farm environment reduced the risk of allergic rhinoconjunctivitis, asthma and wheezing. The authors proposed that environmental exposure to immune-modulating agents such as environmental mycobacteria and actinomycetes favours manifestation of a non-atopic phenotype [144(III)].

Among Austrian children living in a rural area, children living on a farm had less (hay fever) allergic rhinoconjunctivitis, asthma and other IgE-mediated allergies than those in a non-farming environment. Possible explanations include the development of immunotolerance or the stimulation of Th1 cells and suppression of Th2 cells by increased exposure of farm children to microbial antigens in the stables or farmhouses [195(III)].

In Bavaria, Germany, farmers' children had lower prevalences of (hay fever) allergic rhinoconjunctivitis, asthma and wheeze than their peers not living in an agricultural environment. The risk was lower among families of full-time farmers compared with part-time farmers. Increasing exposure to livestock was related to a decreasing prevalence of IgE-mediated diseases. Factors related to environmental influences on a farm, such as increased exposure to bacterial compounds in stables where livestock is kept, prevent the development of allergic disorders in children. Farming and use of coal and wood as a heating source were highly correlated. Although indoor dampness increased the risk for IgE-mediated disorders in this population, farmers within the population reported more indoor dampness with a lower disease prevalence, supporting the notion that a strong protective factor operates in the agricultural environment. The consumption of whole, but not skim milk was associated with a decreased prevalence of (hay fever) allergic rhinoconjunctivitis and asthma. The authors proposed that increased consumption of whole milk may reflect an increased uptake of milk originated directly from the farm. This 'raw' unpasteurised milk may contain a higher microbial load, particularly of *Lactobacillus*, than industrial-processed skim milk. Although farmer's children used less antibiotics and homeopathic medication and drank more whole milk

than their peers, none of these factors explained the protective ‘farming effect’ in the multivariate models. A strong inverse dose-dependent association between factors associated to exposure to livestock and IgE-mediated allergies was found. In childhood, allergies against cows, pigs and chickens are uncommon. Therefore it seems unlikely that the inverse relation is due to allergen avoidance. Increased concentrations of bacterial compounds such as endotoxin and its purified derivate lipopolysaccharide have been found in stables where livestock has been kept [190(III)].

In a study in Austria, Germany and Switzerland, among farmer’s children, current wheeze and IgE sensitisation were significantly lower among children who spent time in the stables. This effect was stronger for children who spent time during the 1st year of life in the stables (odds ratio 0.36 and 0.33, respectively) than for those who spent time in the stables from 2 to 5 years of age (odds ratio 0.73 and 0.87, respectively), compared with non-farming children. Similar reductions were found with those who drank unpasteurised farm milk. Time spent in the stables and consumption of farm milk in the 1st year were independently associated with health outcome [196(III)]. Among farmers’ children who spent time in the stables in the 1st year of life, drank farm milk, and whose mother spent time in the stables while pregnant, there was only 1 case of asthma (expected 19 cases) [197(III)]. There was an indication of a multiplicative effect for asthma. These results suggest that exposure to the farming environment influences the development of asthma and IgE sensitisation [196(III)]. A protective effect of the farm environment has also been found in Finland [144(III), 198(III)], four European centres and New Zealand in the European Community Respiratory Health Survey study [199(III)], Nepal [200(III)], Crete [201(III)], Canada [202(III)], Australia [203(III)] but not in New Zealand [204(III)].

The role of the farm environment and animal contact for the development of asthma and allergies, including the above studies, has recently been reviewed [205(NC), 206(NC), 207(NC)].

Endotoxin

Endotoxin is part of the outer membrane of gram-negative bacteria, found ubiquitously in nature, being present in most indoor environments as a constituent of house dust. It has been suggested that endotoxin levels increase where animals are kept indoors and it seems noteworthy that two recent cross-sectional studies have shown a protective effect of early exposure to cats and dogs on the development of IgE sensitisation [146(III), 208(IIIC)]. However in a prospective birth cohort study in Boston a reduced risk of wheezing was shown in children whose mothers did not have asthma, but an increased risk in children whose mothers had asthma [209(IIIC)].

Endotoxin levels are likely to be particularly high in developing countries where poultry and livestock are kept in close proximity to human housing. One study from Africa has found a significantly decreased development of IgE sensitisation in children in whose homes pigs were kept [102(IIIC)]. Bacterial endotoxin is known to induce production of Th1-associated cytokines, interferon- γ and interleukin-12 and therefore has the potential to decrease allergen sensitisation. Chronic endotoxin exposure, before polarised T-cell responses are established, might be expected to protect against allergen sensitisation by continually enhancing Th1-type lymphocyte development. Reductions in allergen sensitisation and IgE-mediated disease have been found in children of farmers, children with pigs, dogs, or cats in their homes, children raised in day care from an early age, and children of large families. In a USA study of 61 infants the homes of allergen-sensitised infants contained significantly lower concentrations of house dust endotoxin than those of non-sensitised infants. Thus, indoor endotoxin exposure early in life may protect against allergen sensitisation by enhancing Th1-related immunity [210(III)].

In a comparison of farming and non-farming families in rural areas in southern Germany and Switzerland, differences in endotoxin levels were found. Endotoxin concentrations were highest in stables of farming families but were also significantly higher indoors in dust from kitchen floors and children's mattresses compared to non-farming families. Endotoxin levels were also significantly higher in mattresses and dust from kitchen floors in households where children had regular contact with farm animals through their neighbours, compared with control subjects. All farming families kept cattle and some additionally kept a few pigs, sheep, goats or horses. It is proposed that the level of environmental exposure to endotoxin and other bacterial wall components is an important protective determinant for the development of IgE-mediated diseases in childhood [211(III)].

Two more studies shed additional light on the potential role of endotoxin. In a cross-sectional study in Germany involving 740 children aged 5–10 years, there was an inverse relationship between house dust endotoxin levels and allergic sensitisation, although no relationship between endotoxin levels and allergic diseases or symptoms was noted [212(III)]. In the Boston Home Allergens and Asthma Study [213(IIIC)], a longitudinal analysis of wheezing in young children, and the independent effects of early life exposures to house dust endotoxin, allergens and pets, suggests that the timing, dose and other environmental factors may be important. In this study, the investigators found that higher levels of endotoxin were associated with increased risk of wheezing initially, but this risk rapidly decreased with time. The protective effects of cat and dog ownership were independent of the endotoxin level.

Airborne Allergens

Allergens

The concept of allergen avoidance dates back to the 17th century and clinical studies date back to the first part of the 20th century. This field has recently been thoroughly reviewed [214(NC)]. The major airborne allergens associated with the risk of asthma differ within and between communities, and may alter with climate, season, housing and hygiene. Many studies show that persistent asthma is associated with exposure to allergens that occur in the indoor environment.

The Allergens

Exposure to ‘indoor’ allergens is probably more important than exposure to outdoor allergens because most time is spent indoors, indoor exposure may be at a high level and throughout the year, and may increase with the modernisation of housing design. However, typical outdoor allergens like pollens are regularly found indoors. The increasing indoor allergens – house dust mite, pets and cockroaches – are the result of changes in the indoor environment induced by human activities including housing design, and bedding materials [215(NC)]. In many temperate and humid regions the greatest risk for asthma has been associated with allergy to house dust mites [216(NC)]. In some communities, such as Australia, with high mite exposure, the association between exposure, sensitisation and asthma is very strong. In these communities, it has been suggested that reducing the level of house dust mite allergen could be anticipated to have a significant impact on the prevalence of asthma [217(NC)]. In some dry climates the strongest risk factor is allergy to the fungus *Alternaria* spp. [218(III), 219(IIIC)]. In Tucson, Ariz., USA there is a high prevalence of allergen reactivity, believed to be due to high year-round concentrations of multiple aeroallergens including house dust mite, mould, grass and tree pollens, mesquite, *Alternaria* and cockroach mix [53(IIIC)]. In other urban communities allergy to cockroaches appears to be the dominant allergen [220(IIIC), 221(III)].

Allergy to cats and dogs appears to be important in many places [222(III)]. The major cat allergen Fel d 1 is carried by small dimension particles that readily become airborne and persist unmodified for a long time. Fel d 1 is a ubiquitous allergen, being found not only in homes where cats are kept, but also on the clothing of cat owners and in public places [215(NC)]. In a study of 6- to 12-year-old children in The Netherlands pet ownership (cats, dogs, birds and/or rodents in the home) was associated with lower prevalence of respiratory allergy and symptoms. However, past, but not current pet ownership was associated with a higher prevalence of symptoms and pet allergy. These results

suggest that selective avoidance and removal of pets leads to distortion of cross-sectional associations of pet ownership and respiratory allergy and disease among children [223(III)]. In adolescents in Norway, sensitisation to pet allergens (cat, dog and horse) was associated with increased AHR in children with asthma and allergic rhinitis. The risk of being sensitised to cat allergens was significantly reduced in those who had kept cats, compared with those who had never kept them. Keeping dogs or horses did not influence the risk of being sensitised to the respective allergens. Therefore keeping pets did not increase the risk of being sensitised to pet allergens [224(III)].

It is of interest that two recent studies have shown a protective effect of early exposure to cats and dogs on the development of IgE sensitisation [146(III), 208(IIIC)]. However, in a study in New Delhi, India, dogs and cats at home were significant risk factors associated with the symptoms of asthma in school children [225(III)].

Homes can accumulate many milligrams of mite, pet and other allergens in the dust of beds, carpets, soft furnishings, and clothing [222(III)]. However there is a poor understanding of true personal exposure in relationship to indices of allergen exposure used in most studies [214(NC)].

Responses to animal allergens may not be restricted to the animals discussed above. A study in the United Arab Emirates detected responses to rat and mouse hair [226(III)]. Another study in Buenos Aires, Argentina, identified positive specific skin tests and IgE antibodies for bat faeces among patients living in tall buildings and old houses [227(IIb)].

Pollen allergy is associated with acute hospital admissions [228(III)] but is rarely an independent risk factor for persistent asthma [229(IIIC)]. Pollen sensitivity was common among Asian immigrants in Melbourne and pollen mono-reactors had nearly a 5-fold higher (hay fever) allergic rhinoconjunctivitis risk. It was concluded that the association between prevalence of (hay fever) allergic rhinoconjunctivitis and length of stay was due to acquired sensitivity to grass pollen [57(III)].

Risk of IgE Sensitisation

Numerous studies demonstrate a relationship between risk for sensitisation and the level of exposure to allergen [214(NC)]. Some susceptible individuals become sensitised at apparently very low levels of mite, cockroach or cat allergens [230(NC)], and sensitisation is common in 'western' environments.

The relation between the incidence of sensitisation to mite and cat allergens during the first 3 years of life has been clearly demonstrated by the West German study conducted by Wahn et al. [231(IIIC)]. These authors showed that increasing exposure, both in a group of infants with atopic parents and in a group with non-atopic parents, was associated with increasing incidence of

sensitisation, and concluded that allergen intervention needs to begin in early life.

Randomised controlled trials have tested whether specific interventions are effective in reducing allergen exposure and whether this reduction leads to a reduction in sensitisation or disease. The second approach is only valid if the first is proven. Unfortunately, despite a huge amount of research, there is no simple 'allergen avoidance' intervention designed to be prescribed or evaluated [214(NC)].

Allergen Avoidance and Prevention

Tovey and Marks [214(NC)] have described how 'primary preventive strategies have been targeted at infancy because most cases of asthma arise at that time. However, there is a complex relation among the various elements involved in the evolution of allergic disease. The observed pattern of cellular, humoral, and in vivo responses may not fully reflect the effects of allergen exposure, and their relation to clinical outcomes in later life remains uncertain. A further pragmatic problem with primary prevention studies is the difficulty in clinically characterizing wheezing illness, impaired lung function, and airway hyperresponsiveness in infants'.

The first randomised controlled trial of allergen avoidance in the primary prevention of asthma took place in the Isle of Wight [232(Ib), 233(Ib), 234(Ib)]. This involved a total of 120 infants with a strong family history of allergic disease. The intervention group received an intensive food and house dust mite allergen avoidance regimen starting at birth; including breast-feeding, with mothers excluding dairy products, eggs, fish and nuts. The control group did not make any dietary modifications. The house dust mite intervention in carpets and furnishings significantly reduced allergen levels at 9 months. At 4 years of age the control group showed more positive skin prick tests and more eczema, but not asthma or rhinitis [234(Ib)]. A few further primary prevention studies have commenced in the last 3–4 years. In each of these trials, high-risk infants identified on the basis of a family history of asthma, allergy, or both are enrolled and randomised antenatally. Short-term clinical outcome data have been reported, but definitive conclusions about long-term efficacy cannot be expected for a few years. In Vancouver and Winnipeg, 493 infants have been enrolled in a study testing a multifaceted environmental intervention. The intervention includes house dust mite avoidance, avoidance of pets, maintaining a smoke-free indoor environment, and food allergen avoidance. At the 1-year follow-up, the house dust mite allergen levels were substantially reduced in beds but not floors, and there were significantly less rhinitis symptoms and a strong tendency for less asthma-like symptoms in the intervention group compared with control subjects [235(Ib)]. The Manchester (UK)

Asthma and Allergy Study, which enrolled 300 infants, uses a stringent house dust mite avoidance intervention [236(Ib)]. Very low house dust mite allergen levels have been achieved in, and maintained during pregnancy and the 1st year of life in the homes of children with atopy. At 1 year the intervention group showed some reduction in respiratory symptoms in the 1st year of life [237(Ib)]. Reporting of clinical outcomes is awaited. The Southampton (UK) trial has enrolled 200 infants. There is active house dust mite avoidance intervention. Some preliminary data on allergen reductions in a subgroup have been presented [238(IIa)]. A recent prospective, randomised placebo-controlled study on allergic pregnant women and their infants using mattress and pillow encasings only showed no difference among the children at 2 years of age in rhinitis, wheeze or sensitisation between intervention group and placebo controls [239(I)].

In commenting on primary prevention studies, Björkstén [176(NC)] wrote that 'Efforts to prevent allergy by various avoidance regimens have at best had only marginal effects. This discouraging result may be due to the complexity and demands of the intervention which result in poor compliance or simply to the fact that allergen exposure and environmental pollution are not major risk factors to be addressed in primary prevention, although they are undoubtedly so in secondary prevention'.

Secondary intervention studies are few. A study in Japan [240(Ib)] identified infants at high risk of house dust mite allergy and asthma postnatally, on the basis of early manifestations of atopy (i.e. eczema and food allergy). Children were enrolled during the 1st year of life and randomised to house dust mite prevention which resulted in a substantial reduction in house dust mite allergen levels. At the 1-year follow-up, children in the active treatment group had lower levels of IgE antibody, prevalence of positive skin prick test responses to house dust mite, and lower incidence of wheezing episodes. Follow-up is awaited.

Between 30 and 70% of children with asthma or wheezing illness in childhood enter remission during the transition to adult life [241(IIIC)]. It is not known whether any therapeutic interventions can improve the chances of remission. If allergen exposure is important in the aetiology of asthma, it seems probable that it will be involved in its persistence. This hypothesis is supported by a cohort study in Scandinavia in which children with positive skin tests to mite allergen, who became negative over a period of 24 years had a low level of mite allergens, whereas those whose skin test responses remained positive had a higher level in their environment. Furthermore, in the setting of occupational asthma, continuing exposure to the relevant occupational allergen is associated with a higher risk of persisting asthma.

There are studies that support tertiary interventions: a temporary move to a residence with low allergen exposure from one with high exposure; observations in the same residence during seasonal fluctuations of allergen, and observations within a residence during interventions to reduce exposure. People with asthma who have moved to high-altitude environments, where allergen exposure levels are very low, experience improvements in symptoms, lung function, and immunologic markers [242(NC)]. In studies from The Netherlands, variations in mite allergen levels in mattresses and carpets correlated with differences in peak flow amplitudes [243(III)] and changes in AHR [244(III), 245(III)].

Tovey and Marks [214(NC)] state that ‘Uncontrolled studies, such as those cited above, have encouraged the view that avoidance of exposure to allergens may be an effective form of treatment for asthma’. This has been extensively investigated in clinical trials. The plethora of randomised controlled clinical trials (in addition to uncontrolled trials) testing various house dust mite allergen avoidance strategies as treatment for people with asthma has been extensively reviewed recently [246(Ia), 247(Ia)]. Unfortunately, the evidence even for randomised controlled trials is seriously flawed because of a number of problems. First, very few researchers have demonstrated that they have successfully reduced allergen exposure in the intervention group, even using the crude measures of reservoir allergen concentrations. Second, some studies are probably too brief to detect changes in clinical outcomes. Finally, there is a limited range of outcome measures that have been selected for evaluation. These problems, together with the complexity and heterogeneity of the interventions, limit the utility of a simple statistical summary of the existing data as presented in the Cochrane Review [247(Ia)]. Four randomised, placebo-controlled trials have successfully achieved a difference between active and control arms of the study over a sustained period of follow-up (6 months or longer). These are the most appropriate studies to test the hypothesis that allergen avoidance, when it is achieved, is an effective treatment for asthma. In these small numbers of trials in which the intervention group experienced a sustained reduction in allergen exposure, clinical benefits have been forthcoming. Unfortunately, the range of outcome measures tested in these studies are limited, and we have little information that allows assessment of the importance of these benefits. In particular, there are no data concerning the impact of these interventions on quality of life or on rates of severe exacerbations. There are no existing data that would support an economic analysis. These deficiencies require data from further randomised controlled trials, which should only be conducted when there is a consensus among investigators about the most effective and efficient method of achieving house dust mite allergen avoidance’ [214(NC)].

Methods for Allergen Avoidance

There has been debate about the most effective approaches for allergen avoidance. For house dust mite avoidance, treatment of bedding [240(Ib)] and laundry are effective. There is less certainty about replacement of fitted carpets with smooth flooring, and cleaning of hard surfaces, and even less about vacuuming, air filtration, ionisers, and air conditioning. Acaricides are unlikely to be useful [214(NC)].

Modern building design has been thought to contribute to allergen exposure, prompting studies of alteration in building design. This approach has been successfully implemented in Denmark [248(IIa)]. However, its utility appears to be limited to climates with sufficiently low absolute humidity in winter and 'tight' houses. This approach has not been so successful in more humid climates [214(NC)].

In many communities, almost all houses and some public places [249(III)] contain detectable cat and dog allergen, although the mean level in houses without pets is manyfold lower than that found in houses with pets. However this lower level is still sufficient to cause symptoms in some individuals. Transfer of the allergen is thought to be by clothing [214(NC)].

Cockroach allergens are widely distributed in reservoir dust and are highest in kitchens [214(NC)]. Cockroach allergy, combined with high exposure, continues to be strongly associated with asthma risk in some studies of inner-city populations in the USA, and may be the most important in some communities there [220(IIIC), 221(III)]. Cockroach allergens may trigger asthma exacerbations in sensitised individuals. Methods for decreasing exposure are still not well established and aim to reduce the populations of cockroaches through control of sources of food and water plus intensive vacuum cleaning and the use of chemical agents [215(NC)], but whether this results in reduced sensitisation and disease is not known.

In arid climates *Alternaria* spp. is the dominant allergen [218(III), 219(IIIC)]. However, the extent to which exposure occurs indoors, and is therefore potentially avoidable, is unclear. Establishing the strength of the independent association of indoor fungal exposure to asthma symptoms without confounding by endotoxin or mite exposure has been difficult [250(NC)]. Avoidance methods for indoor fungi are focused on preventing the ingress of outdoor fungi into buildings, maintaining a dry indoor environment, and adopting domestic hygiene measures [214(NC)].

Despite all that has been researched and written about allergen avoidance, the recent Cochrane Review found no significant clinical benefit on tertiary prevention of asthma and recommended larger and more rigorous trials with more careful monitoring of exposure and clinical outcomes [246(Ia)].

Indoor Environment

Environmental Tobacco Smoke

Tobacco Exposure

Tobacco smoke exposure is undoubtedly an important risk factor for allergic rhinitis and asthma. However, the precise role of chemicals from smoke on IgE sensitisation is not known, and further studies are necessary. Both active smokers and non-smokers exposed to ETS have been found to be affected adversely. ETS – consisting of mainstream smoke which has been inhaled and exhaled by the primary smoker, and sidestream smoke which arises directly from a burning cigarette – contains many agents that have pathological effects on human tissues [251(IV), 252(III)].

Effect of Active Smoking on the Airways

Active smoking causes a number of immunologic and inflammatory changes in the lungs. Macrophages from smokers are numerous and larger in size, with pigmented cytoplasmic inclusions [253(III)]. Functionally, alveolar macrophages from smokers display increased motility, enhanced responsiveness to chemotactic stimulants, increased metabolic activity, increased content, and releasability of lysosomal enzymes [254(III)]. Smokers' macrophages were found spontaneously to release chemotactic factors for neutrophils [255(III)]. Changes in the local T-cell system are also observed. Although the total number of T cells in bronchoalveolar lavage (BAL) fluid is not different from non-smokers, the CD4/CD8 ratio is significantly decreased due to low CD4 and higher CD8 percentages [256(III)]. Elevated histamine and tryptase levels were observed in bronchoalveolar lavage fluid of smokers, suggesting increased mast cell degranulation [257(III)]. Furthermore, there is evidence both from clinical studies and animal models that cigarette smoke may increase the number of pulmonary neuroendocrine cells that produce bombesin-like peptides [258(IIb)]. Bombesin-like peptides stimulate mucus secretion, bronchoconstriction and the expression of various cytokines by alveolar macrophages. It is postulated that neuroendocrine cells and neuropeptides such as bombesin-like peptide may have a potential influence on airway inflammation and airway remodelling [258(IIb)].

A relation between active smoking and total serum IgE levels was demonstrated in cross-sectional studies. IgE levels were found to correlate with the number of cigarettes smoked [259(III), 260(III)] indicating a dose-response effect on immunoglobulin production control mechanisms. In addition to serum IgE, an increase in peripheral eosinophil numbers was also recorded [261(III)]. Bronchoalveolar lavage fluid of asymptomatic smokers shows increase in the

eosinophil count and eosinophil cationic protein [261(III)]. A recent explanation for the susceptibility of smokers to develop asthma is that this is gene related [262(III)].

Mechanisms of Action of Environmental Tobacco Smoke

ETS has been described to act on the airway mucosa in several different ways. The constituents of ETS have been demonstrated to have a negative effect on mucociliary function [263(III)]. It has been postulated [264(III)] but despite considerable efforts never proven, that tobacco proteins present in smoke, can, like conventional allergens, cause IgE sensitisation.

It may also be hypothesised that ETS may produce similar effects to active smoking. In children, passive smoking documented by urinary cotinine measurements seemed to stimulate a polyclonal IgE production [265(III)]. This finding was confirmed by another study also showing the same correlation with interleukin-4 levels [266(III)].

Moreover, eosinophilia was demonstrated in children exposed to tobacco smoke, similar to that demonstrated in active smokers [267(III)]. Exposure to ETS may lead to eosinophilia by stimulating the production of interleukin-4 by mast cells and lymphocytes, which then induces the expression of VCAM-1, enhancing the adherence of eosinophils to endothelial cells in the mucosa [252(III)]. Tobacco smoke was also demonstrated to enhance the production of IgE antibodies in rat models [268(IIb)].

Eosinophilia, independent of IgE sensitisation, may have a role in the pathogenesis of asthma, according to recent information on the relationship between chronic asthma and the results of longitudinal studies of eosinophils [269(III)].

Clinical Evidence

In a Japanese study investigating the effects of passive smoking on allergic rhinoconjunctivitis, 1,168 teenage students were studied for nasal disorders and degree of passive smoke exposure. Nasal allergies were documented in 81.5% of students who were heavily exposed to tobacco smoke, which was a significantly higher incidence than in mild-exposed or non-exposed students [270(III)].

Vinke et al. [252(III)] demonstrated cellular changes in the nasal mucosa of tobacco-smoke-exposed non-atopic children, i.e. children not having the atopic constitution. They found a cellular infiltrate in the nasal mucosa of ETS-exposed children similar to that found in the nasal mucosa of allergic children, including an increased number of eosinophils and IgE-positive cells.

The effects of tobacco smoke on the lower airways, however, are more complex than can be replicated in clinical studies. Children can be exposed to

tobacco smoke before or after birth. It has been difficult to demonstrate the isolated effect of intrauterine exposure, as postnatal exposure continues in many instances. Moreover, children who wheeze in early life, but will not develop asthma, have already been recruited into many studies investigating the effect of tobacco exposure in the development of asthma. The conditions which may contribute to the development of asthma in children, such as impaired lung growth, and infections like RSV bronchiolitis, are also discussed.

Prenatal Exposure

The effect of prenatal exposure on allergic sensitisation has been investigated. No correlation was found between cord blood IgE of newborns and an active smoking history of either mothers or fathers [271(III), 272(III)]. However, cord blood eosinophil counts were found to correlate with the urinary cotinine levels of mothers [273(IIa)].

Exposure to ETS during childhood, and in utero exposure to maternal smoking, are also associated with adverse effects on lung growth and development. A study was undertaken of the associations between maternal smoking during pregnancy, exposure to ETS, and pulmonary function in 3,357 school children in Southern California. Current and past exposure to household ETS and exposure to maternal smoking in utero were assessed by a self-administered questionnaire completed by parents [274(IIa)].

In utero exposure to maternal smoking was associated with reduced peak expiratory flow rate, mean mid-expiratory flow, and forced expiratory flow, but not FEV₁. In utero exposure to maternal smoking was found to be independently associated with decreased lung function in children of school age, especially for small airway flow rates [274(IIa)].

In another study, the authors assessed the effects of passive smoking on respiratory symptoms in a cohort of over 1,000 children born during 1980–1984 [275(Ib)]. The children were enrolled in the Tucson Children's Respiratory Study in Tucson, Ariz., USA, and were followed from birth to age 11 years. Information on parental smoking and on wheeze and cough in their children was obtained from parents by using questionnaires. Maternal prenatal but not postnatal smoking was associated with current wheeze (odds ratio = 2.3, 95% confidence interval 1.4–3.8) independently of a family history of asthma, socio-economic factors, and birth weight. This effect was time dependent and significant only below age 3 years. Cough was not associated with parental smoking during the 1st decade of life. This transitory effect of maternal prenatal smoking on wheezing was attributed to changes that affect the early stages of lung development [275(Ib)].

Similar to animal models, increased neuroendocrine cells and airway changes were demonstrated in the foetuses of smoker mothers [276(IIb)].

Environmental contaminants and in particular air pollutants have been suspected as possible aggravating factors for eczema. The biological plausibility for this arises from the fact that most air pollutants act as non-specific irritants as well as immunomodulators, leading to elevated levels of total serum IgE [277(III), 278(III), 279(III), 280(III)]. The exposure to maternal ETS also leads to immunological changes in children [281(III)]. Children of mothers who had smoked during pregnancy have shown elevated levels of IgE, IgA and IgG3 [282(III), 283(III)] in their cord blood, and other altered immune functions [284(III)]. The association between exposure to (air) pollutants and eczema was studied in 678 pre-school children in Bavaria/Germany [285(III)]. 12.6% of the mothers (84/666) reported that they had been smoking during the pregnancy (62, 73.2%) or lactation (22, 26.8%) of the index child. 18.1% (98/541) of the children whose mothers did not smoke had a history of eczema, whereas in 33.8% (26/77) of the children whose mothers had smoked during pregnancy or lactation eczema was reported (odds ratio 2.30, 95% confidence interval 1.32–3.12).

Additional genetic data on the effect of in utero exposure to cigarette smoke and asthma and wheeze was reported by Gilliland et al. [286(III)]. This group found that the increased risk of asthma and wheezing from in utero smoke exposure was largely limited to those children with the GST (glutathione-S-transferase) M1 null phenotype.

Postnatal Exposure

Postnatal parental smoking was shown to have an effect on lung functions in a meta-analysis [287(Ia)]. In a pooled analysis of 21 surveys of school-aged children, the percentage reduction in FEV₁ in children exposed to parental smoking, compared with those not exposed, was 1.4%. Effects were greater on mid-expiratory flow rates (5.0% reduction) and end-expiratory flow rates (4.3% reduction).

The effect of tobacco smoke on BHR and asthma, apart from lung size and lung function, was also studied. A meta-analysis identified twenty-nine relevant studies after consideration of 1,593 articles. Of 19 studies using challenge tests in children of school age, 10 (5,759 children) could be summarised as the odds ratio of having bronchial hyperreactivity in children exposed to ETS compared with those not exposed. The pooled odds ratio for maternal smoking was 1.29, with no evidence of heterogeneity between studies. However, five further studies of 3,531 children provided some evidence, but not odds ratios, and none were statistically significant. A further four studies on 5,233 children have collected data but are not yet published. In contrast, all four studies of circadian variation in peak expiratory flow found increased variation in children exposed to ETS. A clear effect of exposure to ETS on BHR in the general population

has not been established. While the meta-analysis suggests a small but real increase in BHR in school-aged children, limited evidence suggests greater variation in peak expiratory flow in children of smoking parents [288(Ia)].

In investigations of the effects of passive smoking on asthma [289(Ia)] the relationship of parental smoking to wheezing and asthma occurring after the 1st year of life was assessed by a systematic quantitative review of case-controlled and longitudinal studies, complementing earlier reviews of cross-sectional surveys and wheezing in early childhood. Maternal smoking was associated with an increased incidence of wheezing illness up to age 6 (pooled odds ratio 1.31), but less strongly thereafter (1.13). The long-term prognosis of early wheezing illness was better if the mother smoked. The pooled odds ratio for asthma prevalence from 14 case-controlled studies was 1.37 if either parent smoked. Four studies suggest that parental smoking is more strongly associated with wheezing among 'non-atopic' children. Indicators of disease severity including symptom scores, attack frequency, medication use, hospital attendance, and life-threatening bronchospasm were in general positively related to household smoke exposure. The excess incidence of wheezing in smoking households appears to be largely non-allergic 'wheezy bronchitis' with a relatively benign prognosis, but among children with established asthma, parental smoking is associated with more severe disease. It may be postulated that ETS is a co-factor provoking wheezing attacks, rather than a cause of the underlying asthmatic tendency [289(Ia)].

The literature data over the last 20 years indicates that infantile asthma, although heterogeneous, often appears following RSV bronchiolitis, especially when sufficiently severe to justify hospitalisation. The risk of developing episodes of wheezing over the following 2–3 years is higher than 50% but estimates vary according to the authors [290(III)]. Children admitted to hospital with acute bronchiolitis were found to have higher levels of nicotine metabolites in urine or serum, indicating the pathogenetic role of passive smoking in the development of bronchiolitis [291(Ib), 292(Ib)]. It may further be postulated that ETS exposure causing bronchiolitis may later lead to asthma in young children.

In a cohort study of 6,000 children that investigated the effect of maternal smoking together with socio-economic status and low birth order on the risk of allergic disease, maternal smoking was found to be an additional risk factor for wheeze primarily in low socio-economic groups [293(Ib)].

It was reported that geographical differences occur in risk factors. A cross-sectional study involving 2,594 school children from East and West Europe concluded that exposure to ETS at home was a risk factor for IgE sensitisation only in East Europe [294(Ib)]. The authors demonstrated that exposure to tobacco smoke increased the risk of animal dander sensitisation in East Europe.

This finding exemplifies the inconsistency of findings in several studies carried out in various different settings. Another study from Germany carried out on 342 children found that pre- and postnatal tobacco smoke exposure had an adjuvant effect on IgE sensitisation to food allergens [295(Ib)].

In conclusion, ETS exposure has been shown to have an effect on allergic rhinitis and asthma in experimental models, and in humans both pre- and post-natally. The presence of one smoker at home was shown to increase hospital admissions among asthmatic children by 63% [296(III)]. Similarly, the asthma severity in children whose mothers stopped smoking was found to decrease [297(Ib)].

Estimated annual excess cases of childhood illness and death attributable to parental smoking in the United States include low birth weight (46,000 cases, 2800 perinatal deaths), sudden infant death syndrome (2,000 deaths), RSV bronchiolitis (22,000 hospitalisations, 1,100 deaths), acute otitis media (3.4 million outpatient visits), otitis media with effusion (110,000 tympanotomies), asthma (1.8 million outpatient visits, 14 deaths), and fire-related injuries (10,000 outpatient visits, 590 hospitalisations, and 250 deaths). Parental smoking was found to be an important preventable cause of morbidity and mortality among American children; it results in annual direct medical expenditures of USD 4.6 billion and loss of life costs of USD 8.2 billion [298(NC)].

Involuntary smoking is the third leading preventable cause of death, and among children it causes lower respiratory infections, middle ear disease, sudden infant death syndrome and asthma. Half the world's children may be exposed to ETS, exacerbating symptoms in 20% of children with asthma. However, favourable health outcomes can be attained with reduced exposure. Among the few studies of ETS exposure reduction interventions, low-intensity advice methods appeared ineffective, and counselling parent smokers appeared successful. Direct counselling of school-aged children to avoid ETS has yet to be tested. Community norms may need to shift further in favour of protecting children and others from ETS before minimal interventions can be successful. This will require combined and ongoing efforts by the medical and public health establishments, in concert with legislation mandating tobacco-free public places and ETS-related media campaigns [299(NC)].

Unlike the other triggers of allergic diseases, tobacco smoke is a man-made, preventable disease agent. The role of all the health professionals working in the field must therefore also extend to tobacco control.

Damp and Mould

A recent review states that 'Home dampness is thought to have health consequences because it has the potential to increase the proliferation of house dust mites and moulds, both of which are allergenic. Studies that have been

conducted in children show a small increased risk of having symptoms if the home has damp or mould. The potential benefits of reducing mould in the home have not been investigated. The few studies that have investigated alterations in the home to increase ventilation or reduce damp show this intervention is expensive, requires a large commitment, and is unlikely to be successful in the long term. This implies that houses need to be specifically designed for primary prevention of features which enhance indoor allergen proliferation rather than using post hoc procedures to improve indoor climate and reduce allergen load as a secondary or tertiary preventive strategy' [300(NC)]. Primary prevention with prospective alteration in housing design needs to be prospectively studied.

In a study in The Netherlands sensitisation to dust mites and possibly mould allergen is related to living in a damp home and childhood respiratory symptoms [301(III)]. In a study in children in the USA, dampness in the home was common and a predictor of wheeze, asthma and (hay fever) seasonal allergic rhinitis [302(IIIC)]. In a population study in Israel, viable moulds were common but IgE sensitisation to moulds was a poor predictor of development of allergic symptoms. However, allergy to moulds in atopic subjects increases risk of symptomatic allergic disease [303(III)]. In a study in children in London, there was no significant difference in the degree of bronchospasm measured from children in homes with or without mould, but wheeze in the last year was associated with reported dampness and mould [304(III)]. However, simultaneous estimation of relative humidity in the bedrooms and recordings of ambient temperature and humidity showed no association with respiratory symptoms [305(III)].

Cooking Gas and Nitrogen Dioxide

Epidemiological evidence suggests that exposure to nitrogen dioxide through the use of unvented gas cookers in homes is associated with respiratory symptoms. However, the evidence from animals suggests that NO₂ may increase the susceptibility to infection by viruses and bacteria. In addition NO₂ may aggravate respiratory symptoms in the presence of co-existent infection [306(NC)]. In the European Community Respiratory Health Survey, cooking with gas was associated with airway obstruction in females in some countries [307(III)]. A study of children in Victoria, Australia, showed that NO₂ was a marginal risk factor for respiratory symptoms, with a dose-response association present. Gas stove exposure was a significant risk factor, even after controlling for personal NO₂ exposure, suggesting an additional risk. No difference was noted between atopic and non-atopic children [308(III)]. A study of asthmatics in Port Adelaide, Australia, demonstrated associations between personal NO₂ exposure, measured by lapel badges, and asthmatic symptoms, such as chest tightness, breathlessness on exertion, and day- and night-time asthma attacks in children [309(III)].

Indoor Heating

In a study in Bavaria, Germany, coal or wood heating in children's homes reduced the risk of becoming sensitised to pollen and developing hay fever, BHR and asthma [193(III)].

Formaldehyde and Other Volatile Organic Compounds

There is evidence that indoor exposure to mixtures, and single components of volatile organic compounds, can be related to asthma symptoms, but there is no evidence that increasing exposure of a population initiates asthma and allergic disease. Although gasoline is a common volatile organic compound, and can contaminate the indoor environment in motor vehicles and buildings, there is no evidence to link this to asthma [310(NC)].

Formaldehyde is one of several volatile organic compounds. Indoor sources of formaldehyde include particleboard, plywood, fibre board, panelling, urea formaldehyde foam insulation and some carpets and furniture, as well as some household chemicals. Formaldehyde is a well-known irritant of the upper respiratory tract. Other problems may include IgE sensitisation to formaldehyde, and the possibility that formaldehyde exposure increases the risk of IgE sensitisation to common aeroallergens. In a study in Australia it was shown that low-level exposure to indoor formaldehyde may increase the risk of IgE sensitisation to common aeroallergens in school children [311(III)].

Other Features of Homes

In Kenya, urban homes tend to have a higher number of windows than rural homes. Carpets are exclusively found in the urban setting. Rural homes use firewood as the major domestic fuel and rarely use gas and electricity. Urban homes use gas and electricity as the major domestic fuel. Kerosene and charcoal are used more frequently in urban than rural homes. The prevalence of asthma symptoms are higher in urban than rural localities [49(III)].

In a comparison of children in Münster and Greifswald, asthma, (hay fever) seasonal allergic rhinitis and eczema were generally higher in Münster. Indoor exposures such as wood, coal heating and feather bedding were negatively associated with symptoms, whereas exposures such as truck traffic in a residential street and active smoking were positively associated with symptoms. Wood or coal heating could partly explain the difference of allergic (rhinitis) rhinoconjunctivitis between these two cities [44(III)].

Pillows

Increased use of non-feather pillows appeared to explain a modest rise in prevalence of wheeze over a 13-year period in London [312(III)]. Synthetic

pillows contain significantly more pet allergens than feather pillows, supporting the view that tightly woven encasements surrounding feather pillows act as a barrier for allergens [313(III)].

Outdoor Air Pollution

There is no support for a positive association at a population level between air pollution and the prevalence of childhood wheezing [314(NC), 315(NC)]. In ISAAC phase One, countries with low ambient air pollution such as New Zealand were among those with the highest prevalence of asthma symptoms. In contrast, regions such as China and East Europe, which experience some of the highest levels of air pollutants such as particulate matter and sulphur dioxide, generally had low rates of asthma prevalence. Regions such as West Europe and the USA, with high degrees of air pollutants such as ozone, had intermediate levels [6(III)]. Thus there is no evidence that outdoor air pollution increases the risk for development of asthma and allergy. On the other hand many studies of outdoor air pollution show that the various components can have the potential to increase asthma exacerbations.

One of the most important issues in environmental epidemiology is accurate exposure measurement. Urban air pollution comprises several factors which may affect respiratory illness: ozone, nitrogen dioxide, sulphur dioxide, acid aerosols, and particulates [316(NC)]. However, there is no evidence for increased air pollution contributing to increased prevalence of asthma [317(NC)].

To the contrary, studies in Germany have found lower rates of asthma and allergies in the more polluted East Germany compared with the West. During 1989 to 1991 there was a lower prevalence of asthma, (hay fever) allergic rhinoconjunctivitis and symptoms of rhinitis in Leipzig in the former East Germany compared to Munich (former West Germany) [4(III), 318(NC)]. A study of children in Dresden, Germany, using the ISAAC phase Two protocol showed that benzene, NO₂ and CO were associated with increased prevalence of morning cough and bronchitis. However, IgE sensitisation, symptoms of IgE-mediated diseases, and BHR were not associated with these pollutants [319(III)]. In a study in Swiss school children there was no association between long-term exposure to air pollution and asthmatic and allergic symptoms [320(III)]. In Latin America, a high prevalence of asthma, allergic rhinoconjunctivitis and eczema was found in heavily polluted São Paulo, Brazil, with rates comparable to less polluted cities in Australia and New Zealand, indicating that urban air pollution is not always protective [39(III)].

NO₂ concentrations have risen steadily as a result of burning fossil fuels, mainly from motor vehicle engines. Studies on the effect on respiratory health have not been consistent. NO₂ alone, and in combination with SO₂, enhances the bronchoconstrictive response to inhaled house dust mite in patients with mild asthma. It is unclear if this is clinically important. There is growing evidence that increasing levels of outdoor NO₂ over recent decades may be increasing morbidity of existing asthma by increasing the permeability of the bronchial mucosa to allergens.

A cohort study of children in Japan identified increasing prevalence of bronchitis, wheeze and asthma with increasing indoor NO₂ exposure among girls, but not boys. Increased incidence of asthma was also identified among children living in areas with high outdoor NO₂ concentrations [321(IIIC)].

Ozone-induced airway inflammation may be an important contributing factor to acute exacerbations of asthma [322(Ib)]. Ozone is capable of enhancing bronchial allergen responsiveness, causing bronchoconstriction at lower allergen doses in asthmatic subjects. Subjects with allergic rhinitis, but not asthma, have also been shown to demonstrate a bronchial response to allergen after exposure to ozone [323(NC)]. Ozone may increase the appearance of respiratory symptoms, induce changes in pulmonary function and increase bronchial reactivity in healthy subjects [324(IIa)].

Motor vehicle traffic has increased greatly during the last decades and its role in the development of asthma has been considered [315(NC)]. A positive association between self-reported truck traffic in the street of residence and reported asthma symptoms in adolescents was observed in German cities [44(III), 325(III), 326(III)]. There were similar findings in The Netherlands. Diesel exhaust may have a particularly strong effect [327(III), 328(III), 329(NC)]. In vitro and in vivo studies of the effect of diesel exhaust particles have shown increased IgE production [330(NC)] and nasal hypersensitivity [331(IIb)].

In a study of children in Italy, exposure to exhaust from heavy vehicular traffic in metropolitan areas increased the occurrence of wheezing [332(III)]. In Kenya, children from the urban area were exposed more frequently to motor vehicle fumes on the way to school than rural children [49(III)]. In a study of asthmatic children in The Netherlands black smoke, particulates and ozone were associated with acute respiratory symptoms and medication use [328(III)]. A study of children less than 5 years of age in Birmingham, UK, showed an increased risk of hospitalisation for asthma for children living in areas with high traffic flow [333(III)]. A cross-sectional study of children in Munich, Germany, showed decreased pulmonary function and increased respiratory symptoms among children with high exposure to road traffic [334(III)].

Other Population Factors

Economic Factors

An ecological analysis of ISAAC phase One data from 56 countries has shown a weak positive association between GNP and symptoms of asthma, allergic rhinoconjunctivitis and eczema. An increase of USD 10,000 per capita was associated with a 3% increase in the prevalence of wheeze [335(III)].

Within countries there has not been a clear picture of the effect of socio-economic status, but this has been studied only in developed countries. In a prospective British cohort, a high socio-economic status was related to persistence of wheeze at 16 years [100(IIIC)]. In a national birth cohort study from England, Wales and Scotland, the prevalence of both reported and examined eczema increased with rising social class [336(IIIC)]. Hay fever, but not asthma showed the same social class gradient. Socio-economic status was a risk factor for 'atopic dermatitis' in children living in Berlin, Germany [337(IIIC)]. In three towns in former East Germany, there was a positive relationship between social class and lifetime prevalences of IgE-mediated diseases and IgE sensitisation [338(III)]. Higher socio-economic status is a determinant of atopy (defined as skin prick test positivity) in an Italian population [137(III)]. In Cardiff, Wales, social deprivation was not related to asthma prevalence, but was related to admission to hospital [339(III)]. In Auckland, New Zealand, there was no association between socio-economic status and asthma diagnosis, BHR or symptoms [340(III)]. In the USA some studies have demonstrated a greater burden of asthma and allergies associated with low socio-economic class.

Water Supply

Chlorine added to domestic water may be a trigger factor for exacerbation of established eczema. However, in an ecological analysis in British children, a possible association between eczema and chlorine content of the water supply was not independently significant when adjusted for confounders. These investigators found that there was a direct relationship between lifetime prevalence of eczema and water hardness which appeared attributable to calcium rather than magnesium content of the water [341(III)]. 'Water hardness may act more on existing eczema – exacerbating the disorder or prolonging its duration – than as a cause of new cases. Calcium and magnesium may act as chemical irritants or may modify the effects of other chemicals. Skin irritation and dryness caused by exposure to such chemicals may lead to mucocutaneous-barrier defects, which in turn allow invasion of antigens. Alternatively, the association may arise indirectly from the need for more soap and shampoo to obtain a lather when washing and bathing in hard water. Increased exposure to soaps or their additives may have an irritant effect on the skin, which could cause eczema in predisposed children.

The topical effect of hard water on the skin is a more likely explanation than ingestion of increased amounts of calcium or magnesium, since drinking water contributes only a small part of the total dietary intake of these cations [341(III)].

Climate

A potential role of climatic conditions in the aetiology of asthma and allergy has often been suspected. Most studies on the effects of climate have looked at short variations in the occurrence or severity of symptoms. A study in Bermuda related emergency department acute asthma visits with weather parameters [342(III)]. In a comparative study in the United Kingdom, Australia and New Zealand the prevalence of asthma and hay fever among children was greater in the warmer regions [343(III)]. In Blenheim, New Zealand, the effects of weather and aeroallergens on peak expiratory flow rate and asthma symptoms among adults was small and not enough to account for variation in asthma severity and exacerbations [344(III)]. In London, new episodes of asthma in adults during a 2-day thunderstorm were associated with a fall in air temperature and a rise in grass pollen concentration [228(III)]. A larger study in England of the effect of thunderstorms and airborne grass pollen over a 4-year period showed thunderstorm-associated rises in hospital admissions for acute asthma were amplified after a run of high pollen counts [345(III)].

A study in the United States found that the microclimate within homes may have an effect on *Dermatophagoides* mite populations [346(III)]. An inverse association between the prevalence of BHR and altitude of the study area has been observed in mountaineering expeditions in Italy and Nepal [347(IIa)].

Little is known about the effect of long-term climatic conditions on the prevalence of asthma, allergic rhinoconjunctivitis and eczema. Studies on the long-term effect of climate have been limited to comparisons of areas within countries [348(III)].

Because climate affects whole populations, ecological studies are ideally suited to examine the relationship between prevalence of diseases and climatic conditions between populations. The association between climate and asthma and allergic diseases has been studied in ISAAC Phase One using worldwide data from 146 centres [349(III)]. In West Europe (57 centres in 12 countries) the prevalence of asthma symptoms increased by 2.7% with an increase in estimated annual mean indoor relative humidity of 10%. Altitude and the annual variation of temperature and relative humidity outdoors were negatively associated with asthma symptoms. The prevalence of eczema symptoms correlated positively with latitude and negatively with mean annual outdoor temperature. No consistent picture emerged of the association between climatic conditions and prevalence of symptoms of rhinoconjunctivitis. Worldwide data showed similar trends. These findings suggest that climate may affect the prevalence of asthma and eczema in children.

Conclusion

As countries develop and change their lifestyles, environmental factors, which protect against asthma and allergic diseases, are being lost. At the same time, environmental factors, which may initiate and aggravate asthma and allergic disease, are being added.

Unfortunately efforts aimed at prevention of allergic sensitisation through avoidance of allergen exposure have been largely unsuccessful, because they are very difficult to implement, and any beneficial effects are small and not sustained.

The case for ETS in causing wheeze in infancy and aggravating asthma is well proven. A multifaceted approach is required by governments to reduce tobacco consumption and ETS exposure. This will have benefits for many diseases apart from asthma.

There is some evidence that lack of early exposure to certain infections may be enhancing the development of asthma and allergic disease, but it is difficult to make any logical recommendations for high-risk populations or for the general population.

Environments, with high exposure very early in life to non-pathogenic microbes in the diet or in the air, show an apparently remarkable protective effect. However the method of translating this into public health measures is not clear at present. Further research into probiotics is awaited with interest.

There is mounting evidence that protective factors may include a higher plant intake in the diet, and also diet with regular fresh fish intake. Breast-feeding protects against eczema and may protect against the other conditions. These factors have not been proven in evidence-based randomised blinded controlled trials, but there are biologically plausible mechanisms for their benefit. In addition there is no evidence that they would cause any harm to the population. It is not necessary to know all the precise mechanisms of potential benefit before considering dietary recommendations.

Moreover these dietary factors are important in preventing a range of other unrelated diseases, such as cardiovascular disease and cancer. Breast-feeding is also important in preventing infection, with the exception of maternal transmission of HIV, in infancy. It is important that preventive strategies are logical, simple, and it is helpful if they are relatively low cost. Messages to promote breast-feeding, avoidance of ETS, and (if further research were to provide evidence of effect) a greater plant intake in the diet, would fit these criteria. Promotion of these strategies would be relatively easy to build onto public health messages for other conditions.

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Early Immunological Influences

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Allergy is defined as a hypersensitivity reaction mediated by an immunological mechanism. Based on the major immunological mechanisms initiating the disease we can identify two major groups of allergy. IgE-associated allergy, involving people of the atopic constitution, is responsible for common disorders such as allergic asthma, rhinoconjunctivitis and the IgE-associated subgroup (referred to below as atopic eczema, AE) of eczema (*for definitions, see Introduction and Glossary*), which are predominant in children and young adults. The other group is allergic contact dermatitis, which is mediated by sensitised lymphocytes. This report describes the basic immune events underlying initial atopic sensitisation and thus the IgE-mediated allergic diseases. Once persistent allergy becomes established, treatments to modify the natural history of the disease are extremely limited. With the possible exception of aggressive immunotherapy performed over prolonged periods [1], no cure for any of the conditions has been identified, and in many cases the ‘allergic march’ from food allergy with atopic eczema through inhalant allergy with asthma and rhinoconjunctivitis proceeds inexorably. This should inevitably focus attention on the potential for prevention, but this will only be possible if there is full understanding of the immunological events leading to allergic sensitisation and subsequent expression of persistent disease.

Early sensitisation, particularly to indoor allergens, plays a very important role in the development of asthma. Early sensitisation to house dust mite (HDM) with high levels of exposure in early life is associated with an over fourfold greater risk of having continuing asthma at the age of 11 [2]. High-level exposure to indoor allergens is strongly associated with IgE sensitisation to an allergen in the first 3 years of life, as shown by data from birth cohorts in the German Multicentre Allergy Study, MAS [3]. Furthermore, asthma with

persisting symptoms and persistent bronchial hyperresponsiveness into adolescence is associated with early IgE sensitisation. Later sensitisation has much less impact on persisting symptomatology and hyperresponsiveness [4, 5]. The risk of sensitised children developing airway hyperresponsiveness doubles with every doubling exposure to HDM [5, 6]. However MAS, despite showing a relationship between degree of allergen exposure and sensitisation, and between sensitisation particularly to aeroallergens and risk of asthma, has been unable to show a direct association between allergen exposure and asthma [7]. This emphasises that there are additional factors that contribute to the development of IgE-mediated disease rather than just IgE sensitisation to an allergen. Furthermore, it is important to note that asthma can occur in the absence of atopy and clearly, therefore, in developing an understanding of the early life origins of this condition, studies will also need to consider non-immunological factors, and immunological factors unrelated to allergy.

The last decade has witnessed a major paradigm shift in relation to perception of how the allergen immune responder phenotype is determined. Previously it was widely accepted that allergy resulted primarily from genetically determined immunological 'hyperresponsiveness' amongst a small subset of the population, in whom trivial non-pathogenic antigens, called allergens, triggered potent immune responses which (for reasons unknown) were heavily dominated by IgE antibody. The most troublesome of these allergens comprised a range of proteins which were ubiquitous in both indoor and outdoor environments, some of which are present seasonally (particularly in pollens) and others (such as mite products) present continuously. Non-allergic individuals were traditionally viewed as immunologically unresponsive to these agents, as a result of the efficient operation of a series of protective mechanisms which excluded environmental allergens at mucosal surfaces, operating in tandem with other mechanisms which actively suppressed immune responses against any allergens which evaded the exclusion barriers.

More recent evidence suggests that the role of these mucosal-associated immuno-regulatory mechanisms may be restricted to control quantitative as opposed to qualitative aspects of these immune responses. Thus, it is now recognised that cognate immunity against ubiquitous environmental allergens is the norm within the human population, and it is the nature of the underlying cytokine responses within allergen-specific T-helper (Th) memory cell populations which determine clinical responder phenotype. This conclusion was initially based on T-cell cloning experiments demonstrating that allergen-specific T-helper (Th) clones from atopics secreted a pattern of cytokines equivalent to murine Th2 cells (i.e. IL-4, IL-5), compared to the reciprocal Th1 pattern (dominated by IFN- γ) in clones from non-atopics [8, 9]. Follow-up studies using more sensitive techniques in short-term bulk cultures of

unmanipulated peripheral blood mononuclear cells confirmed both the universality [10] and the reciprocal patterns of Th1 and Th2 polarisation [11] of allergen-specific T-cell immunity within the population. However, considerable debate still surrounds the specific details of this Th polarisation in atopics and non-atopics [12], and in particular there is mounting evidence that peripheral blood mononuclear cells from many atopics display a mixed Th1/Th2 (or Th0) pattern of allergen-specific cytokine secretion [13, 14]. It is additionally clear that while T cells in non-atopics typically produce the Th1 cytokine IFN- γ in response to challenge with inhalant allergens, there is no evidence that these responses progress to expression of lymphocyte-mediated hypersensitivity equivalent to that seen with terminally differentiated Th1 cells in the mouse. This infers that some form of internal negative feedback control operates within these Th1-like responses to allergens which maintains them as non-pathogenic, and one possibility is that this may involve co-production of the inhibitory cytokine IL-10 [15]. Similarly, a modified form of Th2 immunity has recently been described in which negative feedback limits the production and/or biological activity of IgE [16], and this process may again involve IL-10. Nevertheless, the presence of a significant Th2 component in the response remains the defining feature of the atopic phenotype, and the central issue in relation to the aetiology of IgE-mediated allergic disease is when/how this T-cell response pattern is programmed into long-term immunological memory.

While a number of questions relating to the sensitisation process remain to be resolved, studies have established that allergen-specific Th-cell programming is typically initiated very early in life, and in many cases consolidates into adult-equivalent Th1- or Th2-like patterns during the pre-school years. These findings provide the basis for a range of potential early intervention strategies, discussed below, for modulation of this Th-cell programming process and/or prevention of progression of early Th2 sensitisation to persistent IgE-mediated allergic disease.

Ontogeny of Allergic Responses in the Antenatal Period

There has been a commonly held misconception that the newborn baby is completely immunologically naive. However, it is clear that the capacity to mount significant immune responses is present from very early in gestation. Stem cells are present in the human yolk sac at 21 days of gestation with the first lymphocytes seen in the thymus at the end of the 9th week of gestation. B lymphocytes can be seen in a range of organs, including the lungs and gut from 14 weeks of gestation, and by 19–20 weeks circulating B cells with

surface IgM can be detected. This implies that the complete process must have occurred from antigen presentation through T-cell proliferation to B-cell stimulation and immunoglobulin production. In addition the neonate can mount an antibody response to a wide array of antigens, following specific exposure of the mother during pregnancy. Thus fetal IgM antibody responses have been demonstrated to maternal immunisation with tetanus toxoid and to congenital infections such as rubella, toxoplasmosis, cytomegalovirus and human immunodeficiency virus [17–19]. Furthermore, direct immunisation of the baboon fetus with recombinant hepatitis B surface antigen can initiate a specific fetal IgG antibody response where there is no such response detected in the mother. The resulting infants had enhanced responsiveness to hepatitis B surface antigen postnatally [20]. Thus the ability to detect antigen-specific responses at birth should no longer be considered extraordinary.

Normal pregnancy is characterised by a suppression of maternal cell-mediated responses to feto-paternal antigens, predominantly effected by a switch to a dominant humoral immune response [21]. Initially in studies of mouse feto-placental tissues and more recently in humans, it has been apparent that a range of tissues in the feto-placental unit secrete cytokines which have a profile similar to that associated with a Th2 phenotype. These cytokines shift the balance away from cell-mediated activity towards humoral immune responses. Such cytokines almost certainly also have additional properties in promoting fetal growth. It has, for instance, been shown that granulocyte macrophage colony-stimulating factor (GM-CSF) has a critical effect on surfactant homeostasis by stimulating differentiation and proliferation of the type 2 pneumocytes [22]. Implicit in the demonstration that the Th2 cytokine bias of normal pregnancy promotes a successful outcome is that a Th1 bias will be associated with pregnancy loss. There is ever increasing evidence that this is indeed the case [23]. Furthermore, a number of additional Th2 cytokines, such as IL-4 and IL-10, will have an influence on cell maturation and therefore directly and indirectly, like GM-CSF, affect lung structure and function. IL-10 is worthy of specific attention because of its immunosuppressive properties, by diminishing the production of a range of cytokines including IL-12 and consequently IFN- γ . It is possible that this cytokine contributes to the apparent immunological naivety of the newborn.

Maternally derived decidual tissue is a source of IL-1 α and IL-1 β , IL-6, GM-CSF, IL-4, IL-10 and IL-13 [24]. IL-13 immunoreactivity in the fetal placenta is exclusively generated between 16 and 27 weeks of gestation. From 27–28 weeks of gestation onwards until 34 weeks, IL-13 can be found released spontaneously from fetal mononuclear cells and from 37 weeks to term, spontaneous release ceases and production can only be induced by mitogenic stimulation of the fetal cells. Thus there must be a very subtle regulation of the

production of this and other cytokines with an interaction between the mother, the placenta and the fetus, which leads to changes in production from different tissues at different times [25]. The cytokines generated by gestation-associated tissues may be transported to the fetus either via the trophoblasts into the fetal circulation or alternatively, and perhaps more likely, via the amniotic fluid. Certainly high levels of the Th2-associated cytokines can be detected in amniotic fluid. The protein turnover in amniotic fluid occurs at a rate of 70% each day with much of this removal being via fetal swallowing [24]. Furthermore, the fetus aspirates amniotic fluid into the respiratory tract and, in addition, the highly permeable skin is exposed directly.

Fetal gut is currently best studied. There are many HLA-DR-positive cells comprised of macrophages, B cells and dendritic cells in the lymphoid follicles of rudimentary Peyer's patches from fetuses very early in the second trimester of pregnancy. Surface markers identified on these cells suggest that necessary co-stimulatory signals are available to facilitate antigen presentation in the development of an antigen-specific response [26]. Amniotic fluid also contains IgG and IgE, putatively of maternal origin, from as early as 16 weeks' gestation. IgG receptors (CD16, CD32 and CD64) and IgE receptors (CD23 and high-affinity receptor) can be detected on cells within the lamina propria of the fetal gut. There is, therefore, the potential for these immunoglobulins to produce antigen focusing in antigen-presenting cells (APCs) which might either lead to sensitisation or tolerance, depending on which immunoglobulin and which receptor is involved [27].

Thus, there is good evidence that the cellular and molecular machinery for priming fetal T cells against environmental allergens is intact. The final link in the chain is the demonstration that allergen can potentially transfer from mother to fetus, in particular there is evidence that allergen can be transported across the amnion and is detectable in amniotic fluid [28]. While a relatively low percentage of mothers in the latter study had detectable allergen in the amniotic fluid, it must be emphasised that this was based on a single sampling which in general was taken after the mothers had been in hospital and fasted for several hours. Thus there would not have been any very recent exposure either to ingestant or relevant inhalant allergens in the domestic environment. It is thus possible that if frequent sampling had been performed during exposure in a more natural environment, a considerably higher percentage may at some time have had detectable allergen, and this possibility merits more detailed investigation. Any allergen entering via this route will be swallowed by the fetus and thereby access the small bowel where mature APCs capable of presenting antigen to T cells are present from 14–16 weeks of gestation [26]. Indeed from the latter study, there was some evidence that APCs had presented antigen to T cells because the co-stimulatory molecules CD40L

and CTLA4 showed accumulation at one edge of the cell, a phenomenon known as capping, which occurs when molecules on the surface of T cells reactivate with their counter-ligands on neighbouring APCs [29].

IgE is also present in amniotic fluid proportionate to the maternal levels and may facilitate antigen presentation by a phenomenon known as antigen focusing, which will allow sensitisation to occur with very low concentrations of allergen [30]. This might in part explain the very common finding of higher early expression of an atopic phenotype in babies born to mothers who were also atopic, rather than in babies of atopic fathers [31]. There is also suggestive evidence of the presence of putative allergen in the fetal circulation, presumably derived from the maternal circulation [28, 32]. This allergen was detected in a complex with IgG and may have been transported across the placenta in this form. However, it remains to be determined whether this material is derived from native allergen, or whether in some circumstances represents cross-reacting antigens from some other source.

It remains to be seen whether the different routes of allergen exposure in the fetus have different consequences. However, one study of birch and timothy grass pollen exposure via the pregnant mother suggested that the fetus only mounted a cellular response if the pollen season occurred during the first 6 months of pregnancy. Exposure later in pregnancy appeared to result in tolerance [33]. This suggests that earlier exposure via the amniotic fluid may lead to sensitisation facilitated by the presence of IgE from the mother, whereas exposure later in pregnancy to allergen complexed with IgG may result in the development of either a more normal non-allergy-promoting immunising response or tolerance. Indeed, there is evidence that a high level of IgG antibody to allergen in cord blood is associated with less IgE-mediated symptoms for many years thereafter, with an inverse relationship between allergen-specific IgE antibodies in the older child and levels of the same allergen-specific IgG antibody at birth [34].

If, indeed, higher IgG antibodies, which are actively transported from mother to fetus in the third trimester of pregnancy, prove to be protective, then it follows that high allergen exposure, which will increase IgG antibody in the mother, will in turn confer protection. This might explain recent observations that children born into families where there is high exposure to allergen, e.g. to cats, have less subsequent sensitisation to these allergens [35]. One study of the children of mothers who had undergone rye grass allergen vaccination during pregnancy and consequently had high IgG antibody levels, compared to children born to rye-grass-allergic mothers not given immunotherapy showed fewer positive skin tests to rye grass 3–12 years later in the offspring [36]. On the other hand, attempts to induce tolerance to food allergens by giving pregnant women additional cow's milk and eggs did not have any effect on the

allergic state of their children [37]. Accordingly, other mechanisms may be involved, in particular the development of T-cell-mediated tolerance/immune deviation of responses to inhaled antigens, which readily occurs in response to high-level exposure to aeroallergens [38]. Against this background, it is clear that until these potential mechanisms are further elucidated, it would be inappropriate to make any recommendations on modification of allergen exposure during pregnancy. However, it emphasises the need for a great deal more research in this area.

It is interesting to speculate why such sophisticated immune responses should be in place early in gestation. One author has proposed that this could be to facilitate neonatal host responses to the obligate exposure it will have to maternal helminths [30]. Certainly infants born to helminth-infected mothers have specific Th-2-biased immune responses to helminth antigen and IgE antibodies [39]. In this era of low parasite infestation, it is likely that structures on IgE-sensitising allergens that have counterparts in parasite antigens lead to stimulation of the same immune response [40]. However, it is important not to over-interpret information relating to putative T-cell responses to allergens in cord blood, in the absence of definitive information on the nature of the responding cells. In particular, it has become evident from recent studies that CD4+ T cells present in neonates are predominantly 'recent thymic emigrants' whose functional characteristics differ markedly from T cells in later childhood/adulthood [41], and their relationship to T-memory cells present in the circulation at later ages remains uncertain.

Fetal Nutrition

Fetal growth and nutrition could conceivably have an impact on the ontogeny of immune responsiveness in the fetus. There have been some bizarre associations between large head circumference at birth and levels of total IgE at birth [42], childhood [43], and even adulthood [44]. Perhaps more importantly, there has been an association made between asthma, particularly severe asthma, and large head circumference at birth [42]. The hypothesis to explain these observations is that a rapid fetal growth trajectory, because of good nutrient supply in early pregnancy, programs the fetus not only to continue to grow rapidly but also to have a high nutrient demand which cannot be met in the later stages of pregnancy, leading to continuing head growth at the expense of relative poor nutrition of the body with consequent effects on immune responsiveness. The ultimate question is whether there are any particular nutrients that are important in this respect. Hitherto the focus has been on anti-oxidants, though if they have any effect at all, these micro-nutrients appear to be more

important in relation to severity of asthma rather than its prevalence [45]. It is perhaps more likely that abnormalities in fatty acid delivery are important and there are at least two studies ongoing investigating this hypothesis. This area of research would lend itself to animal studies and human observational studies, as well as interventions.

Lung Growth and Development

Abnormal nutrient delivery may also have an effect on lung growth and development. Subtle deficiencies of vitamin A can affect airway branching and lung epithelial cell differentiation [46]. There are additional effects of vitamin A depletion on surfactant protein production which in turn could affect airway host defence [47]. Collectively, these phenomena are viewed as key abnormalities in asthma. There is, therefore, a potential for aberrant nutrient delivery to have an impact not only on IgE sensitisation to allergen but also on airway development. Clearly further research is required in this area.

The health effects of parental smoking on the respiratory health of children has been extensively reviewed [48]. The difficulty is to distinguish the independent contributions of pre- and postnatal smoking [49]. However, detailed studies of lung function of offspring of smoking mothers have shown significant differences compared with those of non-smoking mothers [50, 51]. Furthermore, the infants of smoking mothers are four times more likely to have wheezing illnesses in the 1st year of life [51]. There is, however, very little evidence based on meta-analysis that maternal smoking during pregnancy has any effect on IgE sensitisation [52]. More studies are required to investigate interactions between maternal smoking, lung growth and development, risks of IgE sensitisation and subsequent allergic and non-allergic wheezing.

T-Cell Responses to Allergens during Infancy and Early Childhood

A wide range of reports from independent laboratories [reviewed in ref. 53] point to the presence of allergen-reactive T cells in cord blood, and DNA genotyping studies have confirmed that the responsive cells are of fetal as opposed to maternal origin [54], strongly suggesting that Th-cell priming is commonly initiated in fetal life. It is also clear that these early responses are characteristically dominated by Th2 cytokines [54]. However as not all adults have an IgE-mediated allergy, this implies that these early responses must be in some way modulated during postnatal life. The mechanism(s) underlying this

modulation are incompletely understood, but a picture is progressively building up of the broad details (including the kinetics) of the process based upon a series of studies examining age-dependent changes in allergen-specific *in vitro* lymphoproliferation and *in vivo* antibody production.

Employing the robust technique of antigen-induced T-cell proliferation, distinct patterns of postnatal responses to a typical dietary allergen (ovalbumin) and a typical perennial inhalant allergen (HDM) have been observed. At the population level, responses against HDM increase between infancy and childhood, whilst those against ovalbumin remain low or decline [55, 56]. The age-dependent decline in ovalbumin responses in subjects without egg allergy is associated with a reduction in the number of T-cell epitopes recognised [56, 57], a finding which is consistent with allergen-driven modulation of these responses by high zone tolerance mechanisms.

The kinetics of these processes during early postnatal life is likely to be highly variable within the population, and in particular to be influenced by such factors as family history of atopy (FHA, *viz.* degree of genetic risk for atopy), overall magnitude and degree of Th2 polarisation of individual allergen-specific responses at birth, and the intensity/frequency of allergen exposure during infancy.

The most promising approach towards elucidation of these complexities involves prospective studies on birth cohorts of children, monitored postnatally for *in vivo* and *in vitro* markers of atopy, and symptom expression. For example, a landmark Scandinavian study following cohorts of atopic and non-atopic children from infancy to 10 years [58, 59] has documented a biphasic pattern of age-associated changes in serum IgE antibody levels which includes major differences between responses to dietary and inhalant allergens. These findings [reviewed in *ref.* 60] demonstrate an initial peak of IgE antibody against dietary allergen in early infancy, followed usually by a rapid decline by age 1–2 years, which is consistent with the onset of a form of tolerance involving some form of negative regulation. The magnitude of the transient peak of IgE antibody was highest in the atopic group, consistent with the higher frequency of food allergy symptoms within such subjects. Responses to inhalants were also biphasic [58, 59], but were typically much slower to be initiated postnatally and took several years to decline, and a higher proportion became persistent (in particular those which manifested early in infancy). Comparable biphasic response patterns during infancy have also been observed employing lymphoproliferation [55, 60].

Prospective studies on allergen-specific cytokine responses during infancy and early childhood from several centres are also providing valuable insight into this process. It is now evident that initial allergen-specific Th-cell responses in infants both at low and high genetic risk of atopy display the Th2- or Th0-like

cytokine pattern [54], and there is suggestive evidence that the degree of Th2 polarisation within these responses may be higher in subjects who progress to develop IgE-mediated disease [61, 62].

In relation to the mechanism(s) involved in postnatal modulation of these cytokine responses, a prospective study tracking *in vitro* Th-cell HDM reactivity in infants at 6-month intervals up to age 2 years has demonstrated a marked divergence in response patterns between subjects with/without allergy symptoms at the outcome age [56]. Thus, in asymptomatic subjects (who were also FHA negative), allergen-specific Th2 cytokine production declined postnatally, concomitant with early up-regulation of the IFN- γ response, and this contrasted with an age-associated increase in Th2 reactivity in subjects who developed allergy by late infancy. These latter findings are consistent with successful 'low zone tolerance', also referred to as *immune deviation* [60] of fetal allergen-specific Th2-like responses towards a Th1-like pattern in subsequently asymptomatic subjects, in contrast to consolidation and postnatal expansion of the Th2 responses in those who develop disease [56]. It is pertinent to note in this regard that other cross-sectional studies in children have formally established a positive association between markers of Th2-polarised immunity in peripheral blood and the manifestation of IgE-mediated asthma/allergic symptoms [63–65].

As argued earlier [60], the operation of different regulatory mechanisms for control of potentially pathogenic Th2 responses against inhalant versus dietary allergens in humans is predictable on the basis of a comprehensive experimental animal literature, in particular studies demonstrating that the immune system 'selects' different regulatory mechanisms as a function of the level of antigenic/allergenic stimulation at mucosal surfaces [66]. Thus at the gastrointestinal mucosa, the relatively high levels of dietary allergen exposure will frequently fall within the range which preferentially stimulates 'high zone tolerance' mechanisms involving T-cell deletion and/or anergy, and any allergen-specific T cells surviving this process would be subjected to 'low zone tolerance' (immune deviation) mechanisms which are brought into play on other occasions at lower exposure levels. In contrast, inhalant allergen exposure levels at the respiratory mucosal surface would rarely attain levels sufficient to trigger high zone tolerance mechanisms, and hence control of these responses may rely solely upon immune deviation [60]. Consequently, the frequency of failure to successfully down-regulate Th2 responses to inhalants can logically be predicted to be higher than is the case for dietary allergens, and this may account for the higher frequency of inhalant allergy within the population.

It is also very clear that this failure is more frequent amongst individuals with positive FHA, suggesting that some form of immunoregulatory defect may be intrinsic within the genotype of the atopic constitution. One likely

candidate for such a defect involves the kinetics of postnatal activation of Th1 functions. As detailed above, the fetal immunological milieu is normally maintained in a partially Th2-skewed condition, and preferential up-regulation of Th1 functions during early childhood is required for development of the appropriately balanced immune responses which are required for long-term survival within the extrauterine environment. Evidence from T-cell cloning studies in FHA+/FHA− infants suggested that the capacity to produce the Th1 cytokine IFN- γ was decreased in FHA+ subjects [67], and follow-up studies from several independent laboratories have extended these observations to cord blood, linking decreased IFN- γ responses to both positive FHA and subsequent atopy development during infancy [56, 62, 68–72]. It has been hypothesised that transiently delayed postnatal maturation of Th1 function(s) in FHA+ children may compromise their capacity to efficiently generate Th1 immunity against allergens during early life, thus increasing the likelihood that the initially Th2-polarised responses to allergens which are typical of infants will become consolidated into long-term immunological memory [67, 73].

Allergen-Specific T-Cell Immunity and Expression of Allergic Disease

One of the most contentious issues in this field is the nature of the linkage between development of potentially pathogenic Th2-polarised immunity to inhalant allergens, and the subsequent expression of persistent allergic disease as exemplified by IgE-mediated, allergic asthma. On the one hand, surprisingly, overall levels of serum IgE correlate positively with risk for asthma within the population at large [74]. Conversely, up to 40% of young children are positive to one or more inhalant allergens in the skin prick test, but only 10–12% ultimately progress to expression of persistent asthma [75]; however, 90% of those with persistent asthma are usually atopic [75].

This suggests that while the atopic constitution may be a prime risk factor for development of persistent asthma, additional co-factor(s) are required for expression of full-blown disease. Immunohistopathological studies suggest that the hallmark of severe asthma is intense inflammation of the airway wall associated with the presence of activated T cells, and parallel aberration(s) in the repair response to inflammatory injury which is associated with local tissue remodelling [76]. Presumably local allergy-mediated inflammation in the airway wall must exceed a critical threshold in order to initiate these changes, and hence the most likely asthmagenic co-factors are those which would directly or indirectly exacerbate allergy-induced damage to airway tissue. These may include environmental insults such as infection and air pollutants which,

themselves, directly damage the airway wall, and the failure of one or more local immunoregulatory mechanisms which normally regulate the intensity/duration of mucosal T-cell-mediated immuno-inflammatory responses [reviewed in ref. 77].

However, the airway immunohistopathology in established asthma with eosinophil-dominated inflammation and remodeling is present even during relatively asymptomatic periods [78]. Studies of adults have shown that inflammation indices in the airways of asthmatics correlate with the degree of bronchial hyperresponsiveness [79]. It has been shown that bronchial hyperresponsiveness can develop as early as 4 weeks of age in those born to atopic parents with IgE-mediated asthma, long before there are any symptoms [80]. Furthermore, bronchial hyperresponsiveness at 4 weeks of age is a clear risk factor for asthma at 6 years of age [81]. The implication of these observations is that the airway inflammation of asthma is initiated in very early life and may be present in many subjects before full-blown disease manifests [82].

There is also some evidence that the remodeling process can occur extremely early, and the possibility must be considered that it is a phenomenon occurring in parallel with the inflammation rather than as a consequence of it [82]. Under such circumstances, it is likely that conventional pharmacotherapeutic approaches to treatment will not modify natural history even if introduced relatively early after the onset of symptoms. This might explain why long-term follow-up studies have failed to show a major influence of pharmacotherapy on outcome, although it could be argued that the relevant interventions were initiated too late. Thus the main predictor of ongoing disease with abnormal lung function and hyperresponsiveness in adult asthmatics is significant lung function abnormality and bronchial hyperresponsiveness at first presentation, with wheezing, irrespective of the use of inhaled steroids [83]. Conversely in infrequent episodic asthma, where presumably the airway immunopathology is rather different, there is no evidence of abnormality in lung function compared with non-asthmatic controls even after 28 years of follow-up, irrespective of the use of asthma therapy [84]. These observations must now focus attention on the very early life events that sow the seeds for the development of this disease and on intervention before the airway immunopathology is established.

Environmental Factors and Allergy/Asthma

A variety of lifestyle-associated factors have also been suggested to contribute towards increasing prevalence rates of allergic diseases, including diet [85], air pollution [86], increasing levels of allergens within the domestic

environment [87], use of immunomodulatory drugs in paediatrics [88], and in particular changes in public health and hygiene practices which limit exposure to infections during infancy and early childhood, the so-called 'hygiene hypothesis'.

The notion that limiting exposure of children to microbial antigens during early life may inadvertently divert the immune system towards responsiveness to non-pathogenic environmental allergens was initially raised in studies carried out in the mid-1970s which contrasted prevalence rates of allergic disease in indigenous and white communities in Canada [89]. Subsequent studies by Strachan [90] in 1989 demonstrated an inverse relationship between birth order in families and the prevalence of allergic rhinoconjunctivitis in the families. However, hitherto virtually all the studies have focused on inverse relationships between various infections or environmental exposures such as to endotoxin and the development of IgE-mediated allergy, with or without asthma [91–94]. It has been suggested that the most important normal influence on reducing IgE-mediated disease is the development of a satisfactory intestinal microbial flora [60, 95]. A recent pilot study has focused directly upon this concept via an intervention program including the use of probiotics in infants, and has reported reduced incidence of eczema over the first 2 years of life, however without concomitant effects on indices of IgE antibody sensitisation [96]. The small sample size and the early outcome age (2 years) limit the interpretation of this study, in particular conclusions relating to IgE sensitisation, and larger controlled studies with longer-term follow-ups will be required before the value of this approach can be determined.

There are additional components of an affluent community that might have an impact on the hygiene hypothesis. These include the overuse of antibiotics in early life, which has also been suggested to increase the prevalence of IgE-mediated allergy [60, 97, 98]. There has even been a suggestion that early immunisations, by reducing early infection, may also increase risks for IgE sensitisation [97]. However, these data can easily be misinterpreted to assume that immunisations, themselves, promote IgE-mediated allergic diseases and there are grave dangers in such a message receiving wide publicity. Urgent research is required to elaborate on whether these associations are genuine or not. Children brought up in families with an anthroposophic lifestyle, where there is avoidance of immunisations and indeed all medical treatments, as well as very different dietary habits, involving the use of fermented vegetables leading to different gut flora, have a much lower prevalence of IgE-mediated allergic disease [99]. Much work is required to elaborate on the effect of lifestyle on asthma induction.

The mechanisms by which microbes provide Th1-trophic stimulation to the mammalian immune system are incompletely understood, but significant

aspects of the process have been defined in recent years. These include the importance of microbial-specific molecules such as bacterial-cell-wall-derived lipopolysaccharides and its high-affinity receptor, CD14, on bone marrow cells. It is pertinent to note in this context that recent studies have identified a polymorphism in the CD14 gene manifesting as diminished serum levels of the important lipopolysaccharide carrier molecule soluble CD14, which is associated with the intensity of atopic expression in US, UK and Japanese populations [100, 101]. However these findings were not replicated in a recent study on German children [102].

Of additional interest are recent epidemiological findings suggesting that persistent exposure during childhood to an environment which is rich in airborne microbial breakdown products such as lipopolysaccharides is associated with diminished risk for subsequent IgE-mediated disease [103, 104].

It is relevant to note in this context that microbial exposure may also function as a double-edged sword in relation to the aetiology of diseases such as asthma in atopics. In particular it is evident that lower respiratory tract infections during infancy, which are of sufficient severity to cause wheeze, increase the risk for development of persistent asthma [105–107]. These effects are most marked in children who also develop sensitisation to inhalants, suggesting that inflammation resulting from viral infection may interact synergistically with that resulting from Th2-mediated allergy, to drive asthma pathogenesis in early life [108]. It is also plausible that the same genetically determined delay in postnatal maturation of Th1 function, which is an important contributor to the risk for allergic sensitisation during infancy, also increases the risk for severe respiratory infection, particularly with viruses such as the respiratory syncytial virus [109, 110].

Prevention of the Development of Persistent Allergic Disease

Potential Options for Intervention in Early Childhood

The recent findings discussed above relating to the role of events in childhood in the development of persistent allergic disease form the basis for the scheme in figure 1.

The salient elements of this model are:

(i) Initial priming of the Th-cell system against allergens occurs in the perinatal period (frequently in utero), and these early responses are intrinsically Th2 polarized.

(ii) These responses are modulated postnatally via direct allergenic stimulation from the natural environment, resulting generally in high zone

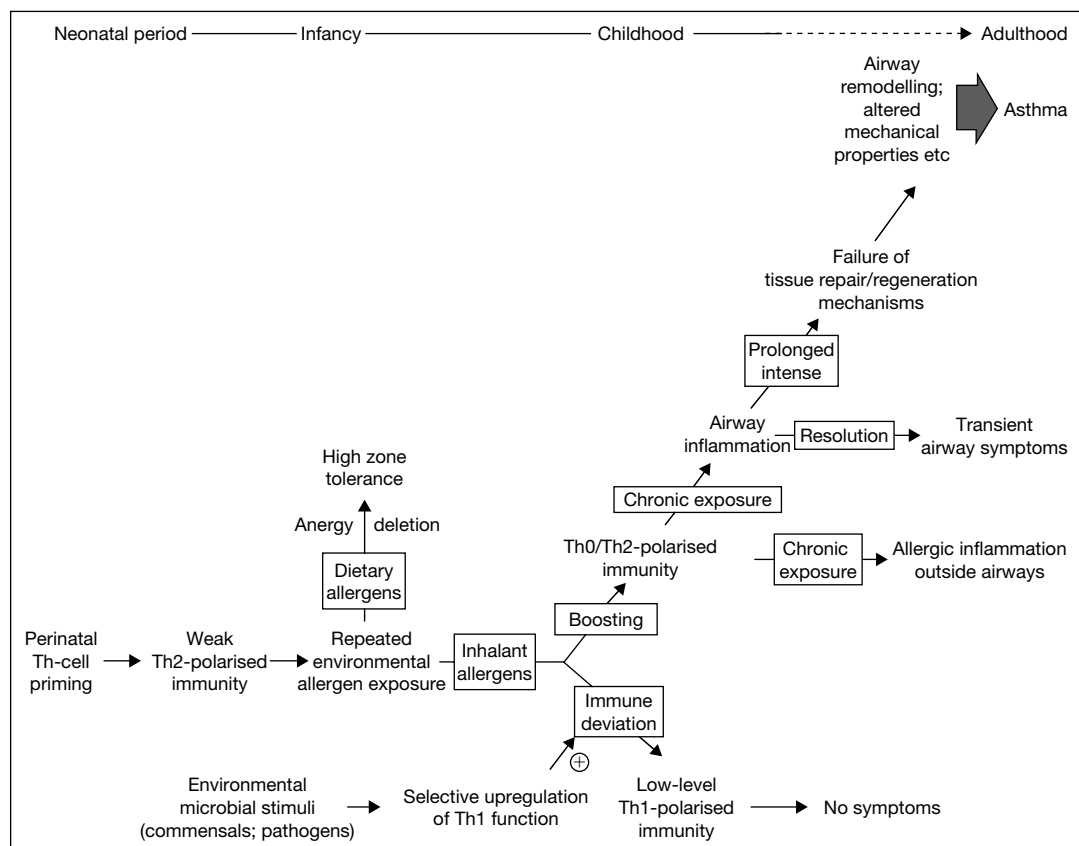


Fig. 1. Induction and expression of allergen specific T-cell immunity in early life.

tolerance induction against dietary allergens, or immune deviation of responses against inhalants towards an attenuated version of the Th1 pattern; Th2 responses in some individuals may also be modified via regulatory mechanisms which drive class switching beyond IgE, resulting in preferential production of IgG4.

(iii) The efficient operation of these regulatory processes (in particular immune deviation) requires postnatal maturation of Th1 function, which is normally stimulated by contact with microbial signals which are absent from the fetal environment [60].

(iv) The frequency of ‘failure’ in these regulatory processes, resulting in transient or long-lasting consolidation of Th2-polarised responses against allergens, is higher amongst subjects with positive FHA; the earlier that

allergen-specific T-cell sensitisation manifests, the more long-lasting are the consequences.

(v) FHA+ children appear to up-regulate Th1 function postnatally slower than their FHA- counterparts [67]; this may be associated with a blunted capacity to respond to microbial stimuli; more recent studies suggest that the 'low cytokine' phenotype characteristic of high-risk infants is already expressed during late fetal life [111].

(vi) While up to 40% of children are skin prick test positive to ≥ 1 inhalant allergen by school age, only a subset of these progress to development of long-term severe allergic disease, such as persistent IgE-mediated asthma, implying that additional co-factor(s) must be operative within this group.

This scheme provides a framework for consideration of a range of early intervention strategies, focusing in particular on FHA+ children who have the atopic constitution and thus are at high risk of development of an IgE sensitisation. The range of theoretical options includes the following concepts.

Non-Specific Immunostimulation during Infancy

This concept is based on the premise that as microbial contact during the early postnatal period provides the natural stimulus for maturation of IgE-sensitisation-antagonistic Th1 functions, enhancing the level of stimulation may accelerate the process and thus facilitate down-regulation of allergen-specific Th2 responses. Of the variety of possible approaches being contemplated, the one being most widely discussed is the use of mycobacterial vaccines in infancy. Recently published retrospective studies on Scandinavian children cast doubt on the utility of conventional BCG vaccination in this context [112, 113], although they may be partially effective in children with different genetic backgrounds [114]. Nevertheless, studies employing potentially more potent *Mycobacterium-vacciae*-based vaccines in infants are currently in progress in Europe and the results of these are eagerly anticipated. Future related possibilities may include the use of parenteral vaccines based on bacterial CpG oligonucleotides which have proven highly effective as Th1-selective adjuvants in experimental animals [115, 116], oral microbial vaccines which are currently in use for boosting mucosal immunity in human adults and children at risk of infection [117, 118], and conceivably dietary manipulation to enhance gastro-intestinal tract colonisation with known 'benign' immunostimulatory bacterial strains [119].

Immunoprophylaxis

This concept [120] envisages allergen-specific immuno-intervention in high-risk infants/young children, at a stage prior to consolidation of allergen-specific T-cell immunity into long-term immunological memory. In principle,

mixtures of allergens important in the environment of the test subjects would be administered employing protocols previously identified as 'tolerogenic' in experimental studies (e.g. passive high-dose mucosal allergen exposure) with the aim of enhancing the efficiency of the normal ongoing process of immune deviation. Multicentre trials to test this procedure in infants and pre-school children in Australia, Scandinavia, Germany and US are in the late planning stages.

Allergen Avoidance

Despite a vast enterprise over the last 3 decades to investigate the effects of allergen avoidance on subsequent prevalence of disease, there is still no consensus on whether this is of value or not. Initially, studies focused on the immediate postnatal period with very variable outcomes. It is not clear whether breast-feeding has positive immunological benefits which confer protection or whether attempts at aeroallergen avoidance are sufficiently effective to modify outcomes. In light of suggestions that allergen sensitisation may potentially occur antenatally, intervention may need to be considered at an earlier point in life. However, dose and timing of exposure during this early life period and its influences on outcomes are not really fully understood, and the impact of maternal health is a further confounding factor. In this area, more mechanistic studies are required to ensure that intervention during this life phase is safe in relation to subsequent development of specific T-cell memory.

It also remains to be seen whether modification of aeroallergen exposure postnatally will have any impact on airway disease. One study combined dietary manipulation with HDM avoidance and showed a reduced prevalence of IgE-mediated allergy in the first 2 years of life but no effect on wheezing illnesses at 4 years of age [121]. Another study has shown that environmental manipulation to reduce pre- and postnatal exposure to HDM and animal allergens has reduced the frequency of respiratory symptoms in the first year of life in infants born to atopic families [122]. Longer-term follow-up and larger studies are required, and some are in progress.

Pollutants

It is clear that environmental tobacco smoke exposure has a deleterious effect on asthma control with a 30% increase in frequency of symptoms in pre-school children exposed to such pollution [123]. Furthermore, maternal smoking has a significant effect on bronchial hyperresponsiveness and severity of symptoms in children with asthma [124].

The effect of other pollutants such as nitrogen oxides is much less clear. A meta-analysis has estimated the odds of respiratory illness as 20% higher in children from homes with a gas cooker [125]. More recent studies on very large

numbers of subjects have, however, tended to negate the previous meta-analysis [126, 127]. Indeed, a review through the Department of Health in the UK suggested that there was little or no association between a regional distribution of asthma and that of air pollution. In fact, if anything there was more asthma in non-metropolitan and presumably less-polluted areas [128]. The implications are perhaps that pollutants have, if anything, only a small effect. Nevertheless, more observational studies are required.

Early Therapeutic Interventions

While there is still debate surrounding the use of allergen vaccines in the treatment of asthma, a recent meta-analysis of published placebo-controlled, randomised studies of allergen immunotherapy in asthma demonstrated a significant reduction in asthma symptoms, medication use and a reduction in bronchial hyperresponsiveness compared to placebo [129]. In particular, one non-randomised study in 6-year-old asthmatic children demonstrated that allergen vaccines reduced the development of new allergen-specific IgE sensitisations over a 3-year period [130]. A second trial conducted in Europe known as the Preventive Allergy Treatment Study, which has suggested that 3 years of pollen allergen vaccines in children with pure seasonal allergic rhinitis has resulted in less children subsequently developing asthma than in an untreated parallel control group [131], and the results of a larger follow-up study are currently being analysed. This approach certainly merits further study. It should be noted that considerable controversy surrounds the nature of the mechanisms underlying the effects of these vaccines, with opinion divided between repolarisation of Th2 responses down the Th1 pathway, induction of T-cell anergy and/or elimination by high zone tolerance mechanisms, and induction of regulatory T cells.

Three studies have investigated the use of antihistamines in the prevention of asthma in children. Two have employed ketotifen and one has employed cetirizine. Comparing ketotifen with placebo in 121 infants with eczema, there was a significant beneficial effect in reduced prevalence of asthma over a 1 year follow-up on treatment which was observed only in those children with a raised total serum IgE level at recruitment [132]. This outcome is rather similar to the cetirizine study in over 700 infants where 18 months of treatment resulted in half the incidence of asthma over 18 months in those with an IgE sensitisation to HDM or grass pollen allergens compared with placebo [133]. However a potential weakness of conclusions based on this study lies in the different treatment effects obtained in relation to the different allergens.

A third study used ketotifen in infants with a positive family history for atopy and a raised total serum IgE, again with significantly reduced prevalence of wheezing illnesses [134]. It is clear that further studies are required with

other pharmacotherapies. The focus should be particularly on those that have an impact on the development of airway inflammation. It is possible that the increased total serum IgE values are a signal of an eosinophilic inflammation that is not necessarily allergic in origin. Indeed it is assumed that the antihistamines have effects by reducing eosinophil trafficking to the airways [135].

New-Generation 'Th2-Antagonistic' Drugs

A variety of immunomodulatory drugs selectively targeted at Th2 immunity, in particular inhibitors/antagonists of IgE, IL-4 and IL-12, are currently undergoing trials in adults in the USA and Europe. Preliminary reports [e.g. 136, 137] suggest that these agents are highly effective in neutralising their respective target molecules, but clinical effects (in persistent allergic diseases such as IgE mediated asthma) may be limited.

The model in figure 1 would predict this outcome, at least for persistent IgE-mediated asthma, given that progression of the disease to the chronic state appears to involve phenotypic changes in airway tissues which are not readily reversed. At this stage of the disease process, Th2-associated mechanisms may only constitute a subset of a wide range of environmental-related insults which are capable of triggering exacerbation of symptoms. However, it can reasonably be hypothesised that these same therapeutic agents, if used at earlier stages of the disease process in which Th2-mediated mechanisms represent the most potent trigger of airway damage, may be more effective in reducing symptoms and (more importantly) may successfully halt the progression from transient to persistent disease. Providing that adequate safety data are provided from the adult trials, follow-up studies with these drugs in a paediatric setting could be contemplated in the near future.

Use of Anti-Virals in Childhood

As noted in the discussion above, respiratory viral infections are now acknowledged as potent co-stimulants of airway inflammation in atopic children, and may be an important co-factor in driving allergic respiratory disease towards persistence. The use of recently available anti-virals in children may provide a useful prophylactic approach for reduction of the impact of these infections in asthma pathogenesis.

Conclusions

There is now a convincing body of evidence to indicate that the key immunological events which lead to the eventual development of persistent allergic disease in childhood, and potentially adulthood, occur during the first

few years of postnatal life, and perhaps in some cases in utero. While it is premature to contemplate interventions before birth, the available evidence reviewed above points to a range of ethically and scientifically justifiable approaches towards prevention of development of persistent IgE-mediated allergic disease in atopic individuals, which merit detailed investigation. The two most promising targets appear to be the initial phase of the sensitisation process underlying generation of T-cell memory to inhalant allergens, and atopy-/viral-mediated airway damage during the critical phase of rapid lung growth and differentiation during infancy.

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Prediction and Early Diagnosis

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Although predictive factors for allergic rhinitis, conjunctivitis and the IgE-associated subgroup of eczema, i.e. atopic eczema, are presented, the primary focus of this chapter is on asthma; in at least 80% of children and 50% of adults, asthma is associated with an IgE sensitisation.

The theoretical value of accurate predictive diagnosis is obvious given the enormous and increasing social and economic burden of asthma on a global scale. Studies in asthma show that the longer the time between diagnosis and treatment, the greater the impairment of final lung function, and this has tremendous implications from the point of view of public health. Improvement in early diagnosis is considered to be important to prevent lung function becoming abnormal, even though there are few data from prospective cohort studies available to support this contention.

Prediction at Birth

In order to predict a disease in a given subject it is essential to have tests with available, validated markers, which are accurate, reliable and of high predictive value.

Predictors should be separated from risk factors, indicating that a given child belongs to a group with a statistically increased risk to develop manifest disease compared to another child without this risk factor [1(II), 2(NC), 3(NC), 4(NC)].

Measures for primary prevention focus on children who can be identified by these markers before the disease process has started. An alternative option would be the application of preventive measures in children who have been

shown, compared to the general population, to have an elevated statistical risk to manifest disease. If no predictor is available and the risk for IgE-mediated allergic manifestation in general or asthma in particular is more or less evenly distributed over the whole population, measures of health education may contribute to an avoidance of certain risk factors which on a population level may lead to a decrease of morbidity.

Family History

It has been known for many years that IgE-mediated diseases run in families. The risk of neonates developing symptoms of IgE-mediated disease during the first two decades of life strongly depends on the manifestation of the disease in their parents and siblings. It has been demonstrated that at the phenotype level there is a closer association between specific symptoms like asthma or atopic eczema in the child and the same manifestation in parents or siblings than with other IgE-mediated manifestations in the family. These clinical observations suggest the presence of phenotype-specific genes [5(Ib), 6(Ib), 7(NC)].

Although the role of the family history of atopy is undoubtedly strong, the majority of children developing eczema or asthma during the first years of life are born into families without any manifestation of the atopic constitution, here referred to as atopy. Although this percentage is increasing, the majority of prospectively affected children will not be identified at birth by consideration of family history alone (fig. 1) [3(NC)].

For practical purposes, however, a family history taken by an experienced clinician is helpful in identifying children at an increased risk for developing allergic manifestations and asthma [6(Ib)].

Genetic Markers

Molecular genetic studies have been performed for various allergic diseases including asthma (see Chapter 1, Genetics). These studies were stimulated by the assumption that atopic phenotypes might become preventable once the precise recognition of genetically predisposed children was possible. Various genes supposed to predispose for atopy have since been identified. These include those that influence IgE antibody responses to particular allergens, as well as those predisposing for 'non-atopy'-related bronchial tone, or bronchial hyperresponsiveness and non-IgE mediated inflammation [7(NC), 8(Ib)].

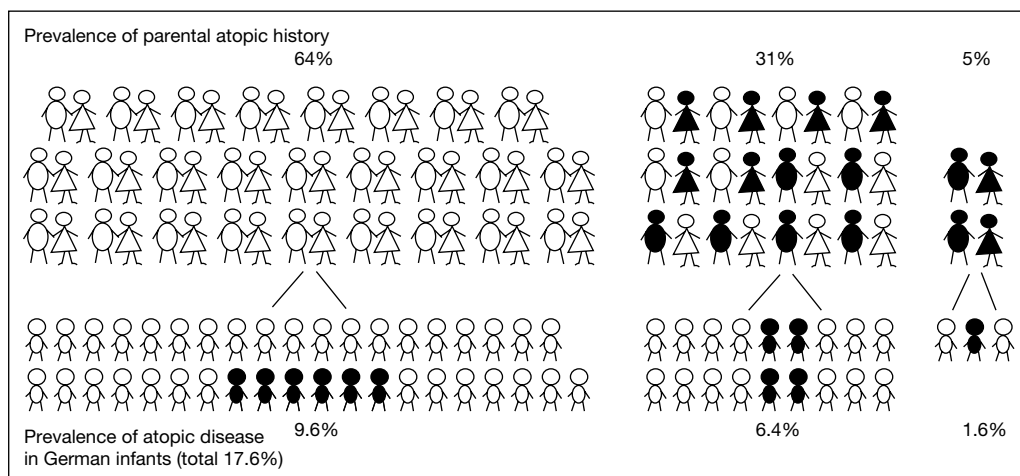


Fig. 1. Population-based prevalence of atopic disease in German infants during their first 2 years of life (manifestation plus sensitisation) according to the history of atopic disease (life-time prevalence) in their parents [20] (reproduced with permission from Blackwell Scientific Publications).

Two approaches have been adopted in order to identify genes related to disease:

(1) Positional cloning in which the entire genome is screened using a panel of polymorphic DNA markers. This tries to demonstrate a genetic linkage of a certain phenotype and genetic markers of known chromosomal localisation.

(2) Examination of candidate genes, which are already known to be involved in the pathophysiology contributing to a certain phenotype. The role of candidate genes may be assessed by defining polymorphisms within the respective genes, and testing for associations with the disease.

From the genetic studies published so far, it can be concluded that:

(1) Both asthma in general, allergic asthma and other atopic phenotypes are genetically heterogeneous disorders.

(2) Each of the atopic phenotypes is probably the result of a polygenic inheritance and a complex interaction between genes and environmental factors.

In contrast to single gene disorders in asthma and atopic phenotypes, there may be a dissociation between genotype and phenotype, where genes may increase disease susceptibility, but not necessarily lead to full-blown disease expression. Currently, whole genome screen studies are under way, focusing on different atopic sub-phenotypes including allergic asthma. These investigations will contribute to an identification of individuals at risk who might become candidates for primary prevention measures. In addition, these studies might

help in identifying individuals who may respond to certain therapeutic interventions in the future.

Immunological Markers

Whilst positive identification of genetic markers is awaited, it would be highly desirable to have immunological markers capable of identifying individuals at risk before the process of sensitisation has been induced or the disease has become manifest. The production of IgE is known to be controlled largely genetically, and therefore the measurement of IgE concentrations in cord blood was initially thought to be a useful screening test. Unfortunately, more recent studies have shown that neither the sensitivity nor specificity nor the predictive value of cord blood IgE measurements make it acceptable for use as a screening test. However, data from the German birth cohort study (the German Multicenter Atopy Study) suggest that elevated cord blood IgE concentrations are capable of predicting early sensitisation, but not airway or skin symptoms [9(Ib), 10(II), 11(Ib)].

Several groups have studied the *in vitro* response of foetal or cord blood peripheral blood mononuclear cells to allergens or mitogens with respect to later development of IgE-mediated disease. They demonstrated that foetal T cells have the capacity to respond to incubation with allergen, and that there are differences in immune responses between those infants who develop IgE-mediated disease later on and those who stay healthy. The risk of developing IgE-mediated disease is obviously associated with a reduced capacity to secrete interferon- γ after phytohemagglutinin stimulation at birth. A low Th1 cytokine production during infancy was shown to be associated with infantile atopic eczema and sensitisation to inhalant allergens at 6 years of age [12(II), 13(II), 14(II)].

From the data published so far, it appears unlikely that immunological markers obtained during the neonatal period might serve as markers of an atopic constitution and predictors for the likelihood that allergic disease will develop in the short term. Nevertheless, these observations are leading to a better understanding of the mode of immunodeviations which facilitate the manifestation of IgE-mediated disease. In some African populations prone to developing a brittle and severe form of asthma during their transition from a rural to an urbanising community, various cytokine markers have recently been shown to be helpful in targeting the subsets of these populations who seem to be more prone to the development of asthma [14(II), 15(II)]. These interesting observations require further study. Presently, since we lack confirmed markers with a high predictive value, there is no justification for neonatal screening tests including cord blood IgE measurements.

Prediction at an Early Stage of the Disease Process

Although the natural history of IgE-mediated diseases is characterised by wide individual variations, the incidence and prevalence of different atopic phenotypes, including asthma, tends to be related to the first decades of life, suggesting that IgE sensitisation obviously requires a juvenile immune system. In general, no clinical symptoms are detectable at birth. Eczema has the highest incidence during the first 3 months of life and reaches the highest prevalence during the 3rd year of life. Symptoms of the upper or lower airways related to IgE sensitisation rarely develop during the first 2 years of life and are in many cases preceded by atopic eczema. Atopic eczema should be considered a risk factor or even a prodromal state of allergic airway manifestations, particularly in children with a positive family history of allergic asthma or seasonal allergic rhinitis [2(NC)]. Episodic wheezing is frequently observed in children from infancy on. However, in the majority of cases it is transient and does not result in a chronic disease [1(NII)].

Several groups have reported presence of serum IgE antibodies to hen's egg proteins, as measured by enzyme immuno-assays, as predictors for subsequent sensitisation to aero-allergens and to the development of chronic allergic airway symptoms including asthma. These findings might become important with regard to strategies for secondary prevention, since IgE responses to hen's eggs are observed very early, generally during infancy [16(II), 17(II)].

Sensitisation to airborne allergens demonstrated by IgE antibodies in serum or positive skin test reactions in an otherwise healthy individual has been demonstrated not only to be predictive of food allergy but also of other IgE-mediated diseases like asthma and rhinoconjunctivitis.

As far as the prediction of asthma is concerned, eosinophils as well as their mediators (e.g. eosinophil cationic protein, peroxidase and protein X) have been studied in infancy in order to identify individuals who are developing chronic disease. In a Norwegian study cohort, wheezing infants had significantly higher levels of serum eosinophil cationic protein compared to controls [18(II)]. Whether concentrations of mediators from eosinophils also predict the chronic disease process remains to be shown. Studies of eosinophils in bronchial biopsies have suggested that increased numbers of eosinophils are risk factors for chronic asthma [19(II)]. So far, none of the various immunological markers has been found suitable for the prediction of atopy or asthma on an individual level.

Conclusions

In the absence of good clinical, immunological or molecular-genetic predictors for IgE-mediated sensitisation, primary prevention measures

targeted at the general population should only be introduced if they meet the following criteria:

(1) They should be of advantage to all since they will be recommended on a population level.

(2) They should be of no known harm to anyone.

(3) They should not involve unreasonable costs.

In contrast, strategies aimed at secondary prevention can be based on the early manifestation of the IgE-mediated disease or even disease preceding IgE sensitisation, which usually occurs during infancy. Potential interventions include allergen avoidance measures to induce tolerance and early immunotherapy. Data have been provided that the early administration of pharmacotherapy in infants who have already developed atopic eczema can attenuate the allergic march into asthma (see Chapter 3, Early Immunological Influences).

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Preventive Measures

Section 1: Early Interventions

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In infancy the main atopy-related symptoms are atopic eczema, gastrointestinal symptoms, and recurrent wheezing, whereas bronchial asthma and allergic rhinoconjunctivitis are the main problems later in childhood [1, 2]. Adverse reactions to foods, mainly cow's milk protein, are most common in the first years of life, whereas allergy to inhalant allergens mostly occurs later [2, 3]. Correspondingly, IgE antibodies against milk and egg are most frequent during the first 2–3 years of life, whereas IgE specific against inhalant allergens is predominant later in childhood [1, 4]. It is important to take into consideration the natural course of the disease when evaluating the results from interventional studies on the prevention of allergic diseases.

Possible Strategies in Individuals at High Risk and in the General Population

It is well documented that an atopic predisposition is associated with an increased risk of the development of allergic diseases. However, the majority of children who develop atopic, IgE-mediated disease, particularly recurrent wheezing and asthma during early childhood, do not belong to high-risk groups (at least one first-degree relative with doctor-diagnosed atopic disease) for development of atopic disease [5–8]. Thus, some preventive measures may be beneficial in the general population and supplementary measures may be beneficial and recommended only for high-risk individuals.

Methodology in Preventive Studies

When evaluating possible risk factors for the development of allergic diseases and the effect of preventive measures, several factors have to be taken into account. The study design of both non-interventional and interventional studies should be prospective, including accepted well-defined diagnostic criteria/outcome measures, a sufficient duration of follow-up, and a proper sample size for adequate statistical evaluation. Furthermore, interventional studies should include proper randomization, blinding and a control for confounders, as well as proper registration of compliance and follow-up of dropouts. Due to recall bias and selection bias, retrospective studies (case-control studies) should not be used for evaluation of predictive/risk factors. Similarly, cross-sectional studies are not suitable for the quantitative assessment of cause-effect relationships between exposure to allergens/adjuvant factors and development of allergic diseases. In general, prospective non-interventional studies can be used to generate hypotheses on the relationship between cause and effect in the development of allergic diseases. Final confirmation of a possible cause-effect relationship may, however, sometimes require demonstration of the causative mechanism and the effect of elimination/prevention of the suspected causative factors [3, 9].

Infants without a Special Risk for Allergic Disease

From prospective non-interventional studies, breast-feeding has been associated with a smaller risk of eczema and food allergy as well as a smaller risk of recurrent wheezing/asthma [10–18]. Whether breast-feeding prevents allergy remains controversial due to the lack of evidence in some studies [19–22], and because infants cannot, ethically, be randomly assigned to breast-feeding or formula feeding to enable a definitive study [3, 23]. However, common factors in studies reporting a benefit of breast-feeding are, firstly, prolonged breast-feeding (at least 4–6 months) and secondly, late solid food introduction (after 4 months). Introduction of complementary (solid) foods before 4 months of age has been associated with a greater risk of eczema in prospective non-interventional studies [24, 25]. There is no evidence of a preventive effect of a special diet during pregnancy or lactation [26–29].

As discussed in Chapter 2, several longitudinal studies have shown a significant association between parental (particularly maternal) tobacco smoking and increased wheezing and asthma in children [30–38]. This association is strongest up to 6 years of age [30, 39]. The severity and frequency of symptoms are related to the extent of exposure in the home. Passive smoking has been

associated with sensitisation to indoor allergens in some studies [40, 41], but not in others [39]. Importantly, maternal smoking during pregnancy is significantly associated with reduced respiratory function in early infancy and recurrent wheezing during infancy and early childhood [34–38].

There is evidence of a cause-effect relationship between exposure to indoor (chemical vapours, gases [42], formaldehyde and volatile organic compounds) and outdoor pollution and induction of respiratory symptoms in individuals with established disease [43–45]. However, the possible role of pollutants in the development of asthma and atopic airway disease seems less important and needs further elucidation.

Infants with a High Risk of Allergic Disease

Around 35% of neonates (high risk) have at least one parent or older sibling with previous or current doctor-diagnosed atopic disease [3, 5, 6, 46]. Several prospective studies in high-risk infants have shown a preventive effect of extensively hydrolysed formulas in combination with avoidance of cow milk proteins and solid foods for at least 4 months on the cumulative incidence of eczema and food allergy (especially cow milk allergy) until the age of 4–7 years [47–53]. Thus, a real prevention and not only a postponement of the onset of the disease has been documented. An effect of dietary allergy prevention has been demonstrated only in high-risk infants and not in other infants [19]. Clinical trials are ongoing comparing the relative preventive effects of products with highly reduced allergenicity (extensively hydrolysed) with those formulas with moderately reduced allergenicity (partially hydrolysed). Previously, some preventive effect of partially hydrolysed formulas has been reported [54–60]. Recent data indicate a greater effect with extensively hydrolysed formula [52, 53]. There is no evidence that soy formulas or other formulas based on whole proteins other than cow milk proteins are less allergenic than cow-milk-based formulas [47, 55, 61, 62]. Thus, if exclusive breast-feeding for 4–6 months is not possible in high-risk infants, a documented hypoallergenic formula and avoidance of solid foods are recommended for the first 4–6 months of life. There is no conclusive evidence for a protective effect of a maternal exclusion diet neither during pregnancy nor during lactation [23]. Likewise, there is no documentation of an effect of preventive dietary restrictions to the infant after the age of 4–6 months.

The effect of exposure to tobacco smoke and to indoor allergens seems to be most pronounced in children with atopic predisposition and in children with exposure during the first months/year of life. There seems to be a synergistic effect of several co-existing environmental factors [40]. Whilst there is no direct evidence for an increase in allergen exposure, the indirect evidence is

overwhelming. Most people with so-called 'Western life-style' spend more than 95% of their time indoors and children spend more time indoors than ever before. The indoor environment of homes (introduction of central heating, wall-to-wall carpeting, etc.) has changed over the last four decades, making it more suitable for dust mite population growth. The number of indoor pets has increased, resulting in increased community exposure. Houses have become better insulated, with lower air-exchange rates, and a consequent substantial increase in the concentration of potentially harmful substances in indoor air (e.g. allergens, air pollutants).

Airway hyperresponsiveness in children is mostly associated with airway inflammation due to IgE sensitisation [63–65]. Chronic asthma is mainly associated with sensitisation to indoor allergens (house dust mites, animal dander, cockroaches etc), which are more important than the outdoor allergens, probably because of the time spent indoors [2, 66, 67]. Several studies have demonstrated a relationship (in a dose-dependent manner) between exposure and presence of IgE antibody [68–71], as well as a clear association between presence of IgE antibody and development of asthma [65, 70–78]. However, no significant direct association between early exposure to indoor allergens and development of asthma up to the age of 7 years was found in a recent study [72]. Importantly, such an association should only be expected as regards allergic asthma. A dose-response relationship between exposure to house dust mites and development and severity of asthma has been demonstrated [74, 75]. Other longitudinal studies have shown that sensitisation to house dust mites and animal dander antedate, and are a risk factor for development of asthma in children [65, 71, 78, 79].

Data from recent cross-sectional and retrospective studies have suggested that early exposure to pets might provide an asthma-protective effect for children [70, 71]. The association between exposure to pets and the risk of asthma has been difficult to evaluate because of different study designs, and selection bias (parents of children with the atopic constitution or with asthma are more likely to remove pets from the home) may explain this controversy [70, 71]. A recent systematic review [71] concludes that exposure to pets appears to increase the risk of asthma and wheezing in children. Epidemiological studies suggest that in areas with low levels of allergens in homes, the prevalence of IgE sensitisation is low. So far, a few prospective, randomised studies on primary prevention have investigated the efficacy of the avoidance of indoor allergens (house dust mites) [80–84]. These studies have produced the first indication that a reduction in house dust mite allergen levels in homes of such infants may reduce the prevalence of sensitisation to mites and recurrent wheezing during the first years of life. Recently, a prospective study has documented that mite avoidance measures can achieve and maintain a low mite allergen environment

during pregnancy and in the first year of life in homes of infants at risk of IgE sensitisation [85], and preliminary data from the same randomised controlled study indicate a 50% reduction of airway atopic symptoms during the first year of life [86]. Thus, in homes of high-risk infants, current evidence supports measures to reduce the level of indoor allergens, such as house dust mites and pets. Furthermore, as for non-high-risk infants, exposure to tobacco smoke, damp housing conditions and indoor pollutants should be avoided.

Children with Allergic Symptoms (Secondary and Tertiary Prevention)

Specific Treatment

Avoidance

Avoiding exposure to relevant allergens is a logical way to treat allergic diseases (e.g. allergic asthma) when the offending allergen can be identified and effective avoidance is feasible. Allergen avoidance in a mountain environment improves lung function and normalises markers of allergic inflammation in children with allergic asthma [87–91]. Several controlled randomised studies have shown that allergen (especially house dust mite allergens and animal dander) avoidance measures are effective both in reducing the level of allergens and in improving disease control [80, 91–112]. Some efficacy in allergen reduction has been reported by washing, steam and vacuum cleaning procedures [113–115].

One paper has shown that allergen exposure reduces the glucocorticoid receptor binding activity in atopic asthmatics both in vivo and in vitro, with a resulting functional alteration in cellular response to glucocorticoids [116]. Thus, allergen exposure may confound the pharmacological management of the disease.

Allergy Vaccination

Allergy vaccination, also referred to as allergen-specific immunotherapy, ASIT, has been demonstrated in many studies to be an effective treatment for patients with allergic rhinoconjunctivitis. Meta-analyses show that the use of allergen vaccines can reduce asthma symptoms compared with placebo [117]. This form of therapy orchestrates an immunological switch of allergen-induced cytokine profiles from a Th2- to a Th1-like pattern [118] and is a potential early intervention strategy. Recently, allergen vaccination with subcutaneous injections has been shown to be effective in allergic asthma in randomised controlled trials with extracts of house dust mites, pollen, and animal dander

(especially cat). A significant reduction in asthma symptoms and medication, and a reduction in both non-specific as well as allergen-specific airway hyper-responsiveness has been documented [117, 119–124]. A recent study [125] suggests that 2 years of allergy vaccination with house dust mite allergen to mono-sensitised patients with persistent allergic rhinitis reduced airway responsiveness and development of asthma. The European Preventive Allergy Treatment Study [123] found that 3 years of pollen allergen vaccine treatment in children with pure seasonal allergic rhinitis resulted in significantly less children subsequently developing asthma than in an untreated parallel control group [123]. Two other prospective but not randomised studies [124, 126] and one large retrospective study [127] indicate that allergy vaccination may prevent the onset of new sensitisations in patients (children) with respiratory symptoms and mono-sensitisation.

Pharmacological Intervention in Infants/Children with Atopic Eczema

As discussed in Chapter 3, a few studies of pharmacological (e.g. ketotifen, cetirizine) intervention in young infants with atopic eczema have reported a significant reduction in development of asthma and wheezing illness [128–130].

Other Measures (Avoidance of Irritants, Especially Tobacco Smoke)

The association between parental smoking and recurrent wheezing and asthma in children is well documented, with severity and frequency of symptoms related to the extent of exposure. Avoidance of passive smoking reduces morbidity and use of medication and improves lung function in asthmatics [30, 39]. Tobacco smoke appears to be one of the most important preventable asthma inducers and triggers. Others are gases (e.g. nitrogen oxides), chemical vapours, formaldehyde and volatile organic compounds [42].

Corticosteroids and Cromones

In children with asthma the effect of prophylactic pharmaceutical treatment has been documented in several clinical trials [131]. Inhaled steroids are very efficacious in preventing exacerbations, reducing hospitalisations and even mortality. Sodium cromoglycate and nedocromil sodium have an effect in mild-to-moderate asthma, but are less efficacious than inhaled steroids [131]. None of these treatments are curative, and after cessation of prophylactic treatment symptoms usually reappear [132–135].

Leukotriene Antagonists

Leukotriene antagonists are a new class of drugs for asthma. An additional asthma-preventive effect of oral leukotriene antagonists has been documented [131, 136–140].

Theophyllines

The bronchodilation effect of theophyllines has been well known for many years, and recent data indicate an additive anti-inflammatory effect of this drug and that they can prevent exacerbations of asthma [131, 141].

New Generation 'Th2-Antagonistic' Drugs

As discussed in Chapter 3, preliminary reports on a variety of immunomodulatory drugs selectively targeted at Th2 immunity suggest that these agents are highly effective in neutralising their respective target molecules, although clinical effects in persistent allergic diseases such as IgE-mediated asthma may be limited.

Implementation of Preventive Measures

As direct evidence of the primary risk factors leading to the increase in asthma prevalence is lacking, it is necessary to test the hypothesis of changing the exposure to the risk factors for which there is a good evidence of an association with asthma. Evidence for risk factors with a direct causal role is most complete for indoor allergens (particularly house dust mites). Preventive measures have been appropriate for use in public health interventions. More focused and specialised intervention strategies may be appropriate for those at high risk, whilst general health promotion may address the needs of the general population. Genetics and environment differ in different parts of the world, and prevention measures may differ between affluent and non-affluent groups.

Primary Prevention: Evidence-Based Recommendations

Infants without a special risk for allergic diseases:

- Exclusive breast-feeding for 6 months is recommended by the WHO: if a supplement is needed, a conventional cow-milk-based formula is recommended (B)
- No special maternal diet during pregnancy or lactation (A)
- Avoidance of solid foods until 6 (4) months of age (B)
- Avoidance of exposure to tobacco smoke (also during pregnancy) (B)

Infants with a high risk for allergic diseases:

- Exclusive breast-feeding for at least 6 months: if a supplement is needed, a documented hypoallergenic formula is recommended for the first 4 months of life; after the age of 4 months, high-risk children can receive the same nutrition as non-high-risk children (A)¹
 - No special maternal diet during pregnancy or lactation (A)
 - Avoidance of solid foods until 6 (4) months of age (B)
-

Environmental measures:

- Avoidance of tobacco smoke (also during pregnancy) (B)
 - Reduce allergen exposure early in life (house dust mites, furred pets, cockroaches) (B)
 - Avoid damp housing conditions (C)
 - Avoidance of pollutants (C)
-

¹Based on allergy prevention studies, exclusive breast-feeding and avoidance of solid foods for at least 4 months seems to be effective. WHO dietary guidelines recommend exclusive breast-feeding for 6 months in general. Breast-feeding may not be recommended in cases of maternal HIV infection. Infants who are not breast-fed because their mothers are HIV positive, and who have consequently developed allergy to cow's milk, should receive a documented hypoallergenic formula.

Secondary Prevention: Evidence-Based Recommendations

Avoidance of tobacco smoke (B)

Patients who have perennial asthma, rhinitis or eczema and who are allergic to house dust mites or animal dander should try to reduce their exposure to the relevant allergens (A, B)

Recommended measures include:

- Removal of relevant pet(s)
 - Reduction of indoor relative humidity below 50% if possible
 - Encasing of mattresses with documented protective coverings
 - Washing of pillows in hot water (>55°C) regularly or encasing of pillows with documented protective coverings
 - Washing of bedding in hot water (>55°C) regularly (every 1–2 weeks)
 - Removal of carpets in bedroom
-

Tertiary Prevention: Evidence-Based Recommendations

Infants with cow milk allergy should avoid cow milk proteins; if a supplement is needed, use a documented hypoallergenic formula (in children ≥ 1 –2 years soy milk may be used as a substitute) (A)

Patients with asthma, rhinoconjunctivitis or eczema who are allergic to indoor allergens such as dust mites, cockroaches and animal danders should eliminate or reduce the exposure to improve symptom control and prevent exacerbations (A, B)

Aim pharmacotherapy primarily towards the underlying inflammatory process (A)

Avoid strictly acetyl salicylic acid or other non-steroidal anti-inflammatory drugs (NSAIDs) in patients who are sensitive to them (C)

Early treatment of common co-morbidities to prevent asthma (D)

Rhinitis, Rhinosinusitis

Epidemiological studies demonstrate that rhinitis and asthma frequently co-exist in the same patients, supporting the concept that rhinitis and asthma

are local symptoms of a single airway disease, which affects both the upper and/or lower airway. Treatment of rhinitis and of rhinosinusitis (chronic sinusitis), which is a common complication of allergic rhinitis, leads to effective control of the upper airway disease, and also improves asthma [142].

Aspirin Triad

The constellation of nasal polyps, chronic rhinosinusitis (chronic sinusitis), asthma and aspirin hypersensitivity/intolerance constitutes the ‘aspirin triad’ or Samter syndrome. Rhinitis is often the first symptom of the syndrome, appearing on average at age 30 years, characterised by rhinorrhea, nasal blockage, and anosmia. Asthma and aspirin hypersensitivity usually develop subsequently. The basic mechanisms underlying sensitivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) involve inhibition of cyclo-oxygenase by these drugs with subsequent release of cysteinyl leukotrienes [143]. Alternative therapy to NSAID must be recommended for these patients, as the ingestion of any NSAID can lead to life-threatening asthma.

Gastro-Oesophageal Reflux Disease

Asthma and gastro-oesophageal reflux disease (GORD) commonly co-exist, with GORD occurring in 45–85% of patients with asthma [144]. A Cochrane Review on asthma and GORD in adults and children [145] concluded that asthmatics with GORD, not recruited specifically on the basis of reflux-associated respiratory symptoms, did not improve following treatment. Clinical experience demonstrates that in selected patients treatment of GORD can improve asthma, and health professionals should consider this association.

Further Research Recommendations

The results from randomised prospective studies of primary prevention of asthma and allergies are awaited from the UK, The Netherlands, Canada, Australia, Denmark and Finland.

Adequately powered, randomised, controlled studies to investigate the potential benefit of low-allergen domestic environments in patients with allergic disease are needed. Such studies should also address compliance, cost-effectiveness and be of adequate length (e.g. 12 months) and tailored for different socio-economic groups and age groups.

A large-scale trial of the widespread applicability of mite allergen avoidance and the effect on patient symptoms, exacerbation rates, use of medication and overall health costs (one such study is currently being carried out in the UK).

The possible role of human milk constituents (e.g. n3/n6 fatty acids, levels of α -linolenic acid, cytokines) in long-term prospective studies.

Prospective studies on the possible role of dietary factors in the development of asthma and allergy (e.g. salt intake, antioxidants, n3/n6 fatty acids).

Prospective studies on the possible role of vaccinations, intestinal microbial flora and probiotics on the development of asthma and allergy.

The role of outdoor and indoor pollutants on the development of asthma and allergy in long-term prospective studies.

The role of viral and bacterial infections (e.g. hepatitis A, measles, tuberculosis) on the development of asthma and allergy. Although viral respiratory infections frequently trigger acute exacerbations of asthma, the relationship between such infections and asthma is not clear. There is some evidence supporting two different but not mutually exclusive hypotheses: 'predisposed children are susceptible to asthma and respiratory tract infections' or 'severe respiratory tract infections cause development of asthma'.

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Preventive Measures

Section 2: Occupational Allergies and Asthma

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Occupational Asthma

Occupational asthma is a disease characterised by variable airflow limitation and/or airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace. Occupations where dusts, gases or vapours are inhaled have the potential to cause upper and lower respiratory tract disease, or to exacerbate existing respiratory disease. There are several ways in which occupational exposures can provoke or cause asthma.

Exacerbation of Existing Asthma

Asthma may be exacerbated by work involving exercise or exposure to cold, dusts, or irritants, to which hyperresponsive airways react. For example, people with asthma react with airway narrowing to sulphur dioxide at concentrations below the recommended occupational standards [1]. Such individuals have a prior history of asthma, no latent interval of symptom-free exposure, and symptoms are improved by avoiding heavy exposure to the provoking agent, and by appropriate drug therapy.

Heavy Exposures and Irritant-Induced Asthma

Heavy exposure to irritants in industrial accidents causes pulmonary oedema and airway mucosal damage [2], leading to prolonged bronchial

hyperresponsiveness [3]. This irritant-induced asthma is termed ‘reactive airways dysfunction syndrome’ [4] and may represent the severe end of the spectrum of irritant responses.

Pharmacologically Active Agents

Pharmacologically active substances may provoke airway narrowing by pharmacological means, giving rise to a form of irritant response(s).

Sensitisation

Occupational exposures can cause IgE and non-IgE-mediated sensitisation, which in a proportion of those affected results in asthma. The symptoms and physiological findings are the same whichever mechanism underlies the disease. Clinically there is a latent interval of weeks to years, and patients may have no prior history of asthma, unless they are already hypersensitive to another allergen. Following sensitisation there may be responsiveness at extremely low levels of exposure, and potentially fatal attacks of asthma can occur after exposures that are orders of magnitude below those which irritate. The clinical picture in sensitised individuals is different from irritant-induced asthma, where, although there is non-specific airway hyperresponsiveness to a range of airway irritants, patients do not have extreme and specific sensitivity to low concentrations of the causal agent.

The pattern of response is not specific to a particular agent. For example, the acid anhydrides, a group of low-molecular-weight agents, can cause IgE-mediated asthma, stimulate IgG and other antibody production, exacerbate pre-existing asthma, and cause direct toxicity to the airways and lung parenchyma, if inhaled in sufficient concentration [6].

Morbidity and Co-Morbidities

Occupational asthma is an important source of adult-onset asthma in the community: Once switched on, asthma does not, generally, go away. Although asthma improves after elimination or reduction of exposure to occupational sensitisers, studies report persistent symptoms in up to 100% of patients [7–13]. The chronic asthma remaining after cessation of exposure is usually of mild-to-moderate severity. Early diagnosis and early removal from exposure are good prognostic factors [7, 12]. Patients who remain in exposure may remain stable

with medication, respiratory protective equipment, and modifications to work practices, or may deteriorate despite such measures [9]. Bronchodilator treatment at the same time as allergen exposure is known to suppress the immediate asthmatic response, allow exposure to a greater dose of allergen, and increase the size of the late asthmatic response [14].

Many patients with occupational asthma, particularly to high-molecular-weight substances of biological origin, also experience rhinitis (often preceding the asthma), and conjunctivitis [15]. Depending upon the sensitising agent, occupational asthma can be associated with urticaria or anaphylaxis.

Induction and Provocation of Asthma

The exposure-response relationship for the induction of sensitisation must be understood before legal occupational exposure standards are promulgated. This requires good prospective epidemiological studies because cross-sectional studies may be misleading. The exposures which provoke asthma in a sensitised individual may be orders of magnitude lower than those recommended as occupational standards [16]. Many believe that short periods of high exposure could be more important than the equivalent dose accumulated at a lower exposure over a long time. It is possible that the exposure characteristics during a time 'window' shortly after the first exposure are the major determinant of occupational asthma. The latent interval between the first exposure to a sensitising agent and the development of asthma is short for most agents, and most cases develop in the 1st or 2nd year of exposure [18, 19].

Prevention of Sensitiser-Induced Asthma

Primary prevention aims to prevent occupational exposure and other determinants of occupational asthma. Elimination of the sensitising agent is the most secure way of preventing exposure. If this is not practicable, reduction in exposure is combined with reducing the numbers of people exposed.

A general description of the assessment and control of environmental exposure [27], with special reference to allergenic agents, lists 16 control methods:

- (1) Elimination: complete removal of the allergen from the work process, e.g. cessation of a research programme using rats
- (2) Substitution: replacement of potent allergen by a less potent allergen, e.g. replacement of male rats as research animals by female rats
- (3) Isolation: complete enclosure of the allergen, e.g. handling complex platinum salts in glove boxes

- (4) Enclosure: separation of the allergen so that few people are exposed, e.g. segregated storage of trimellitic anhydride in a warehouse
- (5) Ventilation: general room ventilation and local exhaust ventilation to reduce the air concentration of an allergen
- (6) Process change: changing the way a product is made in order to reduce exposure to allergen
- (7) Product change: changing the product manufactured in a workplace
- (8) Housekeeping: attention to general cleaning and tidiness, e.g. removing spilt flour in a bakery
- (9) Dust suppression: other ways of suppressing dust, e.g. using *Bacillus subtilis* enzyme in a granular, rather than a powder, form
- (10) Maintenance: maintaining machines and ventilation so that they operate optimally
- (11) Sanitation: attention to handwashing, for example
- (12) Work practices: good work practices to minimise dust or aerosol generation
- (13) Personal protective devices: e.g. masks, gloves, protective clothing
- (14) Waste disposal practices: e.g. bagging of dust or animal waste
- (15) Administrative controls: rules about who may enter a particular area, or what personal protective devices must be worn
- (16) Medical controls: e.g. operating a policy of excluding job applicants with a past history of laboratory animal allergy from work with animals

The following determinants are indirectly related to primary prevention, as they are a prerequisite to implementation of the above controls:

- (1) Education: e.g. training workers in the operation of equipment, or the use of masks
- (2) Labelling and warning systems: so that workers can avoid areas containing allergen
- (3) Environmental monitoring: e.g. air sampling for allergen concentration, or for a surrogate measure such as total inhalable dust, when studies have shown this to be correlated with aeroallergen
- (4) Management programs: strategic programs to improve health and safety in a company or workplace

Control of other known determinants, such as atopy and smoking, may be considered as a secondary measure.

Atopy, defined either by a positive skin prick test or presence of IgE antibodies in serum to common environmental allergens, may be used as a criterion for increased risk of development of occupational allergy. Exclusion of workers with a positive skin prick test can, however, mean denying employment to approximately one third of job applicants, only a proportion of whom would develop occupational asthma [17]. More stringent criteria for IgE sensitisation

might be useful. However, as the association of occupational asthma with atopy is not absolute, this does not eliminate the problem.

Smoking has been shown to be a risk factor for the development of IgE antibody against occupational agents [18, 20–22] although not necessarily for asthma. Smoking potentiates experimental sensitisation of animals [23]. This adjuvant effect has also been suggested for irritant gases, such as ozone and sulphur dioxide [24–26]. Thus, programs for reducing smoking may have the additional benefit of reducing IgE sensitisation, and that control of respiratory irritants may have the same effect, but this is yet to be tested.

Secondary Prevention

Detection is essential for secondary prevention; there is a better long-term prognosis if exposure is ceased promptly upon development of asthma. Monitoring the workforce to detect new cases of respiratory symptoms, which may be asthma, is a legal requirement in many countries. It is essential that employers have policies for investigating the individual and the workplace whenever a suspected case develops. The data can also be used to assess the efficacy of primary prevention measures. Skin prick tests and serum IgE antibody measurements may be used to confirm sensitisation by agents used in the workplace. Spirometry [28] is an insensitive technique for detecting asthma, but peak flow records over several weeks are both sensitive and specific for occupational asthma [29]. It may be necessary to refer cases to a specialist center for further diagnostic tests, such as inhalation challenge tests. Programmes to detect early sensitisation (by skin prick test or IgE antibody measurement) in atopic workers in high-risk environments – e.g. enzymes, flours, latex or animal laboratories – could prevent the development of clinical symptoms.

Tertiary Prevention

Treatment is prompt removal from exposure. Preservation of income is an important problem in many countries, and a disincentive for patients to comply with this advice. Appropriate pharmacotherapy is needed for residual symptoms, which may persist for many years, and often permanently.

Occupational Skin Diseases

In 1988, skin diseases accounted for approximately 24% of reported occupational diseases in the United States, and represent the most frequent

occupational diseases in most industrialised countries [30, 31]. In Germany, more than 18,000 cases occur each year [32]. The highest frequencies are reported from manufacturing and agriculture, and many cases are unrecognised or never reported. Most of this morbidity is preventable by improving working conditions. The most common form of occupational skin disease is irritant contact dermatitis, usually affecting hands and forearms. Symptoms vary from mild redness to severe blistering or necrosis. Individual and environmental factors as well as the properties of the irritating substance contribute to the multifactorial aetiopathogenesis. Persons with an atopic constitution develop irritant contact dermatitis more often. An irritant is a substance that damages the skin by direct action through a non-immune mechanism. The presence of irritated skin facilitates allergic sensitisation by further contact to substances. Examples of common occupational irritants are soaps and detergents, acids and alkalies, metal salts, organic solvents, fabrics and plants. Repeated and prolonged contact with water facilitates entry of irritants and sensitisers and damages the skin barrier.

Allergic contact dermatitis can develop in the working environment. As a prerequisite for allergen avoidance at the workplace, the exact allergen must be identified by patch testing, but in many cases return to the workplace may be impossible. Examples of occupational contact allergens are nickel salts, potassium dichromate or paraphenylene diamine.

Apart from eczematous skin disease, contact urticaria, infections, and skin disease elicited by physical causes are frequently observed, and occupational skin cancer caused by physical or chemical causes also occurs.

The detailed history and examination of the patient's skin is necessary for the diagnosis of occupational skin disease, in most cases followed by patch testing. Further investigations and visits to the workplace may be necessary. Observation of symptoms after returning the patient to the same workplace is important. Evaluation has the following objectives:

- (1) Determination of the type and location of the dermatosis
- (2) In cases of non-occupational origin, determination of whether the work aggravates the condition
- (3) Establishment of a definitive relationship between skin condition and occupation
- (4) Identification of etiologic agent(s)/patch testing
- (5) Evaluation of predisposing and contributory factors (e.g. atopy, wet work)

This is followed by treatment, rehabilitation, and control or elimination of the eliciting substances from the workplace.

In Europe, many occupational substances known as contact allergens are available for routine patch testing. The patch test is not only used to reveal the cause of dermatitis, but also to rule out allergic contact dermatitis in many cases. Guidelines for patch testing of unstandardised materials have also been

published. Patch testing should be performed with standardised methods and materials to avoid false-positive or irritant reactions. In addition, the clinical relevance of a positive patch test reaction is often questionable with regard to the patient's workplace.

Once the specific causes of the disease are identified, the most important aspect of treatment of occupational skin disease is to avoid contact. Dermatological treatment of acute disease is very similar to that of disease of non-occupational background. Skin protection (gloves, barrier cream, emollients and avoidance of irritative factors) is as important as allergen avoidance. Due to the legal implications of occupational skin disease, a thorough and detailed documentation of all medical investigations is important [30–36].

Natural Rubber Latex Allergy

Natural rubber is derived from the cytosol, or latex, of the rubber tree (*Hevea brasiliensis*). So-called dipped rubber products, e.g. rubber gloves, condoms and balloons, are responsible for most of the allergic reactions to latex [37]. Latex is especially an occupational allergen, and atopic health care workers using rubber gloves are a special risk group. Allergy to latex can also cause symptoms in patients undergoing surgical procedures, and in the general population due to presence of latex in clothing, barrier contraceptives, household products and toys.

The most common manifestation of latex allergy is contact urticaria involving the hands. Symptoms are IgE mediated and are caused by natural rubber proteins. Latex products may also evoke allergic contact dermatitis, a lymphocyte-mediated hypersensitivity. The dermatitis appears 1–2 days after contact and is usually caused by low-molecular-weight components like thiuram compounds contained in the rubber product. Inhalation of latex allergen (e.g. attached to cornstarch particles from powdered gloves) can cause rhinitis and asthma in a latex-sensitised person. In rare cases latex has caused severe systemic reactions and anaphylaxis. Prevalence of latex allergy in the general population is under 1%, but in health care workers it may be as high as 3–12%. Recognition of latex allergy has led to the introduction of low-allergen and synthetic latex products. Better products and improved education of health care workers are probably decreasing the risk of sensitisation to latex [38].

Recommendations

National regulatory or advisory bodies should publish guidance on the general principles of prevention of occupational asthma and skin disease.

Table 1. Major allergens and occupational risk factors

Major allergen group	Occupational risk
Acrylates	Adhesive handlers
Amines	Cable joiners, chemists, cleaners, fur dyers, lacquer and shellac handlers, photographers, ski manufacturers, welders, spray painters
Anhydrides	Handlers of plastics and epoxy resins
Animal proteins	Animal handlers, veterinarians
Cereal grains	Bakers, millers
Chloramine-T	Cleaners and caretakers/janitors
Drugs and medicines	Health care professionals, laboratory workers, pharmaceutical industry workers
Dyes	Food industry workers, hairdressers, textile workers
Enzymes	Baskers, manufacturers/users of detergents, pharmaceutical workers
Fluxes	Electronic workers, solderers
Formaldehyde, glutaraldehyde	Health care workers
Insects	Bait handlers/fish feeders, bee keepers, food industry workers, greenhouse workers, grain handlers, laboratory workers, sewer workers, silk workers
Isocyanates	Insulation installers, plastics, foam and rubber industry workers, spray painters
Latex	Health care professionals, food handlers
Metals	Grinders, platers, polishers, refiners, solderers, turners, welders
Micro-organisms, moulds, bacteria	Bakers, cleaners, farmers, carpenters, humidifier engineers, laboratory workers, refuse/garbage collection workers
Persulfates	Hairdressers
Plants	Agricultural workers, florists, food industry workers, herbalists, vine growers
Seafood and shellfish products	Pearl (nacre) industry workers, seafood processing workers
Vegetable gums	Carpet manufacturers, food industry workers, pharmaceutical workers, printers
Wood dusts	Cabinet makers, carpenters, forestry workers, sawmill workers

Surveillance should be extended, or established, to collect information on clinical diagnoses of occupational disease, and should include the relative frequency of sensitiser-induced disease, irritant-induced disease, and work-exacerbated disease.

Several hundred agents are known to cause occupational asthma (table 1) and several thousand are known to cause contact dermatitis by inducing specific sensitisation. These agents should be collated into regularly updated lists to indicate the materials, processes, and workplace areas that are potential risk factors for the development of disease. This would help identify the occupational groups at risk, particularly of asthma, who should be offered health-screening programs, and would form the basis for standards in product labelling and exposure control strategies.

Prospective epidemiological studies of exposure-response relations should be carried out. These should include studies on the effect of modifying variables, such as personal smoking and family history of asthma. Additional studies on the time course of sensitisation would be of value.

A short respiratory symptom questionnaire should be agreed globally, to form the basis for workplace monitoring for asthma, and to provide epidemiological information.

Pilot prevention projects in industry should be encouraged, with evaluative research to assess their efficiency and effectiveness.

Occupational References

Authors' note: It is difficult to categorise many of these references according to the WHO categories of evidence, because these categories of evidence-based medicine are designed to classify therapeutic (or, conceivably, preventive) interventions. Therefore, the study by Sheppard et al. [1], for example, which was a well-designed physiological experimental study, counts as 'not codable', which presents the wrong impression of the strength of the study. There have been very few randomised interventions in the prevention of occupational disease – governments proceed by obtaining consensus and promulgating legally enforceable guidelines.

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Allergy and Asthma Education

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This chapter will discuss the role of the medical professional in providing education about allergic diseases. It will review the role of patient education in helping to prevent and ameliorate the symptoms of IgE-mediated disease, and in emphasising the importance of early recognition and treatment of symptoms in IgE-sensitised individuals. In this context, education represents a secondary or tertiary prevention strategy. There is little evidence-based information available on the content, support materials and equipment which should form the basis of educational programs, and so examples are provided from programmes currently in use. The chapter concludes with recommendations for the creation of a network of allergy and asthma promoting countries to disseminate proven educational programmes and materials.

Most of the published data about the effective strategies for educating physicians, other healthcare professionals, family members or patients with allergic diseases are about asthma, and less information is available about other allergic conditions such as rhinitis, eczema, insect allergy, anaphylaxis and food allergy.

Asthma is associated with allergy in 50–80% of patients depending on the age group. Whilst the lessons learned in asthma may be extrapolated to the development of educational programs on allergic diseases in general, there is an urgent need to continue to develop education for specific allergic conditions.

Appropriate education depends on the degree of knowledge of the physician who cares for the patient, and is primarily responsible for educating the patient and/or family members about allergic diseases and/or asthma. Nurses,

pharmacists, dieticians, emergency room physicians, and other healthcare professionals, as well as teachers and charitable lay organisations, all participate in this endeavour.

Although educational programs can lead to better patient outcomes and probably more cost-effective medication, data to support increased cost-effectiveness through education of the patient by medical professionals are lacking for allergic conditions other than asthma. There are however good studies on guided self-management which do indicate that patient education programmes are cost-effective both in children and in adults [1].

Asthma Education

Educational topics for the patient, and the patient's parents or carers, about appropriate actions for the control of allergy and asthma include:

(1) Understanding the pathogenesis of asthma and associated problems that often precede or are associated with asthma, such as allergic rhinitis, sinusitis, and gastro-oesophageal reflux.

(2) Understanding the different asthma medications and their mode of action: controllers and relievers.

(3) The importance of taking medications correctly for long-term control.

(4) Identifying and controlling factors that exacerbate an individual's asthma.

(5) Monitoring peak flows and/or symptoms.

(6) Following a written individualised action plan to avoid or treat exacerbations and knowing when to contact the physician about worsening asthma.

There is general agreement that there are four key components to asthma care: *assessment and monitoring; pharmacotherapy; control of environmental factors which exacerbate asthma*, and *patient education* [2(NC)].

Patient education is the primary responsibility of the physician who orchestrates patient care. Therefore, physician education about allergy and asthma and how to educate the asthmatic patient is sentinel to optimal asthma outcomes. A primary method of educating physicians about management of asthma is by formulating guidelines for care, however, it remains unknown to what extent guidelines have achieved this purpose. Some studies demonstrate no improvement, while others demonstrate improvement in some parameters and not others [3(IIIb), 4(IIa), 5(Ib), 6(IIa), 7(IIa)]. There is evidence that guideline-driven care is effective in changing the process and outcome of care provided by professionals allied to medicine [8(Ia)].

A Cochrane Review was conducted of eight randomised controlled, or controlled clinical trials of asthma education, provided by nurses or researchers,

involving 1,407 children who attended emergency departments for asthma, with or without hospitalisation over the previous 12 months. This revealed no firm evidence that these programs decrease subsequent emergency department visits, hospitalisations, or unscheduled physician visits [9(Ia)]. Likewise, asthma education limited only to provision of information did not improve health outcomes in patients with asthma [10(Ia)].

However, another review of twenty-five trials of adults >16 years of age with asthma was conducted. This concluded that training patients with asthma in self-management, involving self-monitoring by either peak expiratory flow or symptoms, coupled with regular medical reviews and, in particular, a written action plan which enabled people to adjust their medications, was more effective than other forms of asthma self-management [11(Ia)]. Other educational endeavours such as face-to-face education, group education, or home-based video education of parents of children with asthma increased parental knowledge, and decreased disease-associated anxiety in children and asthma morbidity scores. Interactive face-to-face settings were most effective in decreasing asthma severity [12(Ib)]. Another study demonstrated that educational intervention that emphasises self-management is most effective at improving patient outcomes [13(Ib)].

In conclusion, physician education is key to ideal patient outcomes [14(Ib)]. A specific integrated curriculum that includes education about allergic diseases, including asthma and related problems, is necessary in medical schools and post-graduate training programs. This is important for paediatricians and for general practitioners, in particular, because multiple organ systems are involved, and education in medical schools is primarily organ based. A concerted effort is also necessary to educate physicians who are in practice. Educational outreach visits, defined as a personal visit by a trained person or educator to a healthcare professional in his/her own setting, appears to be most effective in changing healthcare professional behaviour, especially in the prescribing of appropriate medications [15(Ia)]. Likewise, the physician needs to be aware that patient education, primarily orchestrated by the physician, is most effective in an intimate face-to-face environment in which patients are instructed in self-management, have regular medical reviews, and are given a written action plan [11(Ia), 12(Ib), 13(Ib)].

Asthma Education in Children

This section includes a general summary of the current status of childhood asthma education, and theoretical and practical suggestions for the development of new education programs and the promotion of asthma prevention

measures. Programs in the following subjects are discussed: *the burden of asthma; why asthma is underdiagnosed and undertreated; the effectiveness of patient education programs; the importance of the physician-patient partnership, and the cost-effectiveness of patient education programs and what an education program should include.*

Burden of Asthma in Childhood

Asthma is the most common chronic childhood illness [16–18] with an incidence of 10–15% in the paediatric population [19]. It is a source of suffering to both children and their families [20]. Though asthma is one of the most treatable and understood chronic conditions of childhood, it continues to increase in both prevalence and morbidity [16, 21–29]. While hospitalisation rates have diminished for most childhood conditions, they have increased for asthma [21]. The death rate from asthma, albeit relatively low in children, is also reported in some studies to be rising [30–32].

Children with asthma are major consumers of health services [33]. An average of 6.4% of the annual income of middle class families, and 10% of the income of low-income families, is spent for the management of childhood asthma in the USA [34]. Children with asthma miss school more frequently [35], make more visits to emergency departments and physician's offices [36], and spend more time in the hospital than healthy children [37]. Asthma has been linked to poor school performance [38, 39], especially among children of low socio-economic status [40]. Children with asthma also have problems related to poor psychological adjustment [41], low self-image [9(Ia)], and disruption of family life [32, 37]. The failure to diagnose asthma and the subsequent lack of adequate treatment [42] may cause morbidity later in adult life [43].

Why Is Asthma Underdiagnosed and Undertreated in Childhood?

The reasons for the increase in the morbidity and mortality from asthma are both physician and patient related. Many doctors and other healthcare professionals do not have sufficient updated information about the underlying mechanisms, how to diagnose the disease [44], and the new asthma drugs available [45]. Only a small proportion of practicing paediatricians and medical personnel have an adequate understanding of the changing concept of asthma management [46, 47] leading to underdiagnosis and undertreatment [29, 42, 43, 48–51]. Many doctors also lack the skills to correctly operate the new inhalers and spacers [52], leading to poor patient skills and compliance [53]. Physicians tend to overestimate patient compliance [54–56], and may fear assessment of compliance as a reflection of their own clinical skills [54].

In the absence of a patient education process, individuals are often unaware that they have asthma and that it is possible to live a normal life with

this disease [53, 57]. They remain unprotected from exposure to allergens, ignore warning signs of an impending asthma attack, incorrectly evaluate the severity of the disease, and either fail to take prescribed medications [44, 53, 54], or do so incorrectly [53]. There is a tendency for parents to underestimate the severity of their child's asthma [55] and of individual asthma attacks, even when fatal [58]. These factors are important in the planning of health education programs. A small proportion of adult patients with asthma accounts for a disproportionate number of acute health service events. Factors relating to severity, lack of a written asthma action plan, and poor self-management were related to the acute use of health resources by this at-risk group [59].

Effectiveness of Patient Education Programmes for Children

Since 1977, at least 11 asthma education programs for children have been developed and evaluated in the United States [60, 61]. National programmes have also been introduced in Canada [62], New Zealand [63], England [64], and Australia [65, 66]. The majority have resulted in a significant decrease in morbidity and use of health care services, including a reduction in the number of visits to the emergency department [67–76] and the primary care physician [59, 67–78], especially in the low-income population [59, 76], as well as a reduction in the number of hospitalisations and hospitalisation days [68–72, 75, 76]. Education programs have decreased the number of asthma attacks [68, 69], reduced the severity of asthma symptoms [70] and wheezing [79, 80], decreased the number of wheezing episodes [68], and improved lung function [81]. They also increase patient knowledge about asthma [70, 72, 78, 81, 83], improve self-management skills [76, 81, 85–88], induce more consistent use of preventive medications [89], and better control of asthma symptoms [90]. They also improve skills in peak flow meter and inhaler use [70, 82, 91], lead to better school attendance [68, 69, 80, 81] and school performance [69, 80, 81, 87], yield psychological benefits for patients and parents [93], and upgrade the quality of life [81, 82, 93]. However, a few educational programs have shown no beneficial effect on asthma morbidity [82, 87, 94, 95] or school performance [74, 75, 92, 96, 97]. According to a study performed in a low-income population, education programs increase the ability of the health care staff to identify children with asthma and to provide them with state-of-the art care [98]. Several authors have concluded that patient education with reinforcement of self-management skills may be the answer to better control of asthma [25, 90, 98, 99].

Importance of the Physician-Patient Partnership

Several panels of asthma specialists have established new standards of asthma care [100–104]. Their guidelines and recommendations call for

physicians to be more knowledgeable about asthma, utilise objective measures, such as peak expiratory flow rate or spirometry, establish preventive measures, educate patients, and create a partnership with patients through improved communication [100–104].

Physician education has been disease oriented rather than patient oriented. However, the need for a partnership between the physician or health professional and the patient and his/her family is increasingly recognised [95–109]. The patient needs to play a role in the management process; he/she wants to be informed and to be a decision-maker [105–107]. The physician should have thorough discussions with patients who have superstitions, misconceptions, fears of addiction, fears about taking medications, and bias against medications [109].

Educational dialogue based on open communication between the clinician and patient is necessary for a successful partnership in asthma care. The process should begin at the time of diagnosis and should be integrated into every step of medical care.

Cost-Effectiveness of Asthma Education

There is increasing evidence that comprehensive patient education programmes are cost-effective both in children and in adults [1b, 50, 52, 71, 72, 76]. The resulting increase in drug use, observed in some studies [96–98], especially in low-income populations [98, 87], and the increase in the number of physician visits [98] are outweighed by the reduction in emergency visits and hospitalisations [76]. Cost-benefit analysis of one such programme indicated that the savings in health services utilisation offset the costs by 2 to 1, or about USD 225 per affected child per year [72]. Another education program yielded a USD 180 saving per child per year [72]. In a large study of low-income families, the ratio of overall benefits to costs was only 0.6 to 1. However, when only the subgroup of individuals with previous hospitalisations was considered, a saving of USD 11.22 was noted for every USD spent to deliver health care [76]. An educational program conducted by a specially trained nurse in the emergency department led to a saving of USD 87,000 through a 79% decrease in emergency visits and an 86% decrease in hospitalisations [52]. In Germany an education program yielded savings of 5.8 million marks per year (USD 2.6 million), by an average decrease per patient of 3.8 visits to the emergency department, 5.2 hospitalisation days, 8.2 working days and 20 visits to the primary physician [50]. Educational programs are usually more effective when offered to asthmatic patients with high morbidity [110]. Intensive programs were found to improve the forced expiratory volume in 1 s, peak expiratory flow, non-specific bronchial hyperresponsiveness, and health-related quality of life [111].

Contents of an Educational Programme

Asthma education programs should improve self-management skills for both the prevention and treatment of asthma and to help families in decision-making while encouraging them to work closely with the physician [112]. Simple information programs are ineffective in improving self-management or reducing asthma morbidity [95–113]. Medical education based on abstract knowledge may not be sufficient to change long-held habits, beliefs, attitudes, and concepts [113–115]. The most effective programmes seem to be those that integrate asthma care with behavioural theories [112, 116, 117].

Serious management errors are common in patients admitted to a hospital with acute severe asthma, and most of these errors are related to patient self-management behaviour. Most acute severe attacks would be preventable if physicians could induce a change in their patients' behaviour [118]. The better the patients and their families are informed and actively involved, the more successful is their collaboration with the physician. Self-management programmes, when coupled with regular health practitioner reviews, have improved health outcomes [119].

Asthma education programmes should dispel the myths about asthma and improve patients' preventive measures and use of asthma medications. The programme should teach patients to recognise triggers of asthma, the signs and symptoms of attacks and of worsening of asthma and other side-effects. It should teach the correct administration of prescribed medications (use of inhalers and spacers), normalise social activities, improve communication with the physician and other health care professionals, and apply asthma co-management skills [80, 87, 100, 120–122]. In addition, physical training and techniques for relaxation can contribute positively [123]. Each programme must be modified to suit the specific cultural, religious, educational, psychological, and economic factors, as well as the health beliefs and attitudes of individual populations and cultures. They should be addressed to children and their families and school personnel and be accompanied by the education of the relevant medical professionals who interface with patients, not only specialist physicians and paediatricians, but also medical students, residents, and family physicians, as well as nurses, physiotherapists, pharmacists, and other ancillary medical personnel.

Gaps in the current understanding of patients, professionals, and the public need to be identified and areas of future research need to be defined [124]. Advanced technologies, such as videotapes [125], computer games [126, 127], interactive computer programmes [128], and mass media campaigns [66], should be made part of the learning process. To improve cost-effectiveness, a standardised approach to the economic evaluation of asthma outcomes should be developed, and studies should include long-term follow-ups as well as evaluation of patients from different socio-economic classes and with different

asthma severity [85]. The evaluation of education programmes needs to be controlled and outcome variables must be defined [129].

Example of an Asthma Education Programme

An effective education programme should include the following.

Basic Facts about Asthma. Patient's knowledge is improved. The anatomy of the lungs and bronchi and the manner in which inflammation can lead to airway hyperreactivity and bronchoconstriction should be explained in easy-to-understand terms. The link between allergic inflammation and bronchoconstriction should be clarified. Patients may be instructed to use two basic types of medications: bronchodilatory (relievers) and anti-inflammatory (controllers) medications. Charts and airway models can clarify the programme.

Change of Negative Attitudes. Misconceptions are corrected, for example, that the use of an inhaler denotes severe disease or could lead to addiction. Patients should be encouraged to take their medication at the appropriate times, prior to exercise, or before expected exposure to allergens.

Improvement in Management Skills. Patients and families should be shown the various types of medications and devices, and the patients should be tested to determine their preferences and ability to use them correctly. The appropriate selection of devices for specific patients cannot be overemphasised. Once the device is selected, patients and families must learn how to use them correctly. On repeat visits, patient ability and competence is checked and re-checked. Peak flow measurement with home monitoring is generally prescribed for those with moderate-to-severe asthma. Self-management is made as simple as possible.

Preventive Measures. Patients are taught to avoid triggers of attacks such as house dust mites, pets, cockroaches, cigarette smoke, and air pollutants.

Recognition of the Early Signs of an Attack. Patients are taught to take proper action, such as to increase asthma medication.

Asthma education sessions may be held individually or in groups. Both arrangements have advantages and disadvantages. Individual programmes are laborious for health personnel but effective, whereas group sessions utilise fewer resources and create a support group, but are not tailored to an individual patient's needs. Each patient's cultural, religious, educational, psychological, and economic environment needs to be taken into account, as well as health beliefs and attitudes. Advanced technologies could be employed as a part of the learning process.

Rhinitis Education

An 8-fold increase in allergic rhinitis occurred in the USA over a 45-year period, from 3.3 to 25% of the population [130]; an increase of over 30-fold

occurred in Switzerland in 50 years, from 0.26 to 10% [131], and a 3-fold increase occurred in Thailand in less than 10 years, from 18 to 45% [132]. It has been estimated that direct and indirect costs of allergic rhinitis in the USA amounted to USD 5.9 billion in 1996 [133]. Although once considered a trivial disease, allergic rhinitis severely affects the quality of life to an even greater degree than does asthma [134].

Guidelines for the treatment of allergic rhinitis are not as readily available as those for asthma. In 1994, an International Consensus Statement on the diagnosis and management of rhinitis was published [135] which was followed by a similar consensus statement on the treatment of allergic rhinitis [136], and the World Health Organisation document 'Allergic Rhinitis and Its Impact on Asthma' was published in 2001 [137]. Treatment recommendations in these documents include allergen avoidance, pharmacologic therapy and allergen immunotherapy, but unlike the asthma guidelines such as the Global Initiative for Asthma [138] and the US National Heart Lung & Blood Institute Expert Panel-2 Report [139], the importance of education, self-monitoring and a written management plan for disease control is not described.

The reasons for not including or only briefly mentioning this subject may include: (1) a misconception that symptoms of allergic rhinitis are trivial and can be easily alleviated with the use of oral antihistamines and/or intranasal corticosteroids; (2) an underestimation of the effect of allergic rhinitis on the quality of life, and (3) a lack of controlled trials of education in allergic rhinitis.

A Medline search utilising the key words 'allergic rhinitis', 'education' and 'compliance' yielded only two pertinent references on patient training in the treatment of allergic rhinitis. A single-group cohort of subjects with allergic rhinitis, managed with aqueous beclomethasone intranasal spray, was studied [140(Ib)]. Subjects were given comprehensive information about optimal therapy of allergic rhinitis prior to the initiation of the study. Over 80% of the study subjects reported very good symptom control and were satisfied with their management.

Three groups of allergic rhinitis patients with mild asthma, who were treated with mometasone nasal spray, were compared [141(Ib)]. The group who received 1 h of instruction on the clinical and pathologic aspects of seasonal allergic rhinitis demonstrated a significant decrease in respiratory symptoms (cough, wheeze and chest tightness). They required less albuterol and showed a tendency to need fewer antihistamine tablets, when compared to those who used intranasal corticosteroids and only followed the manufacturer's instruction sheet on how to use the intranasal spray. These two studies indicate that education in allergic rhinitis is important for the patient, physicians and other health-care professionals.

Contents of an Allergic Rhinitis Education Programme

The main objectives of an educational programme for patients with allergic rhinitis are to: (1) develop good communication between patients and their physician and to improve patient compliance; (2) to dispel myths, for example, 'hay fever cannot be treated', or 'allergic rhinitis is really not a disease', and (3) to decrease reliance on unproven treatments such as the use of air purifiers, and alternative medicines.

Educational programmes are included in a European Academy of Allergology and Clinical Immunology document on the impact of allergic rhinitis on quality of life and other airway diseases [142 (IIb)], and consist of the following.

Basic Information on How Allergic Rhinitis Develops (Allergens, IgE, Mast Cells, Mediators and Their Actions, Relating to Symptoms of Allergic Rhinitis). Simple instruction pamphlets with basic drawings can make teaching simple and easy to follow. Information regarding allergens and their avoidance, such as house dust (domestic) mites and their sources, and the allergenicity of the mite faecal pellets, can be explained to patients. Education should ideally be provided at the time that the results of skin testing are discussed to emphasise the importance of relevant allergens.

Appropriate Avoidance Measures. Simple and proven measures of avoidance should be discussed. A long list of recommendations can result in non-compliance. For example, to avoid domestic mite allergens, instructions can be made abbreviated to discuss two major impact measures, i.e. washing bedding in water for 20 min at temperatures above 56°C, and encasing beddings with allergen-impermeable covers. Following the usual clinic-based educational efforts, one study [143(III)] reported that only 17% of patients used mattress covers. Another group [144(Ib)] reported similar findings, but also found that adherence could be increased to 27% with repetitive clinic-based education and to 39% with a computer-based education programme.

Medications. Medications used for treatment should be explained to the patient. Instruction of how to correctly use intranasal corticosteroids should be given [145]. Intranasal steroids provide better control when used regularly than on an 'as needed' basis. Such explanations increase compliance. The mode of action of antihistamines and nasal decongestants on nasal symptoms should be clarified. The side-effects and safety of long-term use of the newer antihistamines and intranasal steroids should be explained.

Non-Pharmacologic Therapy. Non-pharmacologic therapy such as the use of intranasal saline washes should be demonstrated, particularly for those with tenacious and purulent nasal secretions, severe swelling of the turbinates, sinusitis, and for patients unable to access or afford pharmacotherapy.

Related Conditions. Related conditions often coexist with allergic rhinitis such as sinusitis, asthma and eczema. A large number of patients present with

more than one condition, making educational endeavours a lengthy process. The concepts may be difficult for patients and their families to understand, therefore a written action plan is recommended. Attention should be paid to all the associated or interrelated conditions that affect the patient. Neglecting the treatment of one condition could lead to failed treatment of an associated condition.

Compliance is enhanced when: (1) *the daily doses of therapy are minimised*; (2) *doses are incorporated into the patient's routine schedules, e.g. at mealtimes, before retiring, upon arising*; (3) *instruction is given by the physician: it engenders trust and increases compliance*; (4) *a written action plan is provided*; (5) *instructions are repeated at follow-up visits*, and (6) *there is a well-designed chart to increase compliance with medications that incorporate a simple symptom score sheet (numerical or graphical)*.

Education in Eczema

Burden and Triggers of Eczema

Eczema is caused by environmental influences affecting genetically predisposed individuals [146(III), 147(III)]. It is the most frequent inflammatory skin disease in childhood. Prevalence estimates for eczema ranged between 1.1 and 3.1% in the early literature, however, in newer studies these figures reach 25% based upon questionnaires, and 12.9% based upon dermatological examinations. There is evidence that the IgE-associated subgroup of eczema, atopic eczema, has increased in frequency over the past decades.

The genetic predisposition is a strong risk factor for eczema. If one parent has a positive history of eczema the risk for the offspring is estimated to be between odds ratio 3.4 (95% confidence interval 2.6–4.4) [148(IIa)] and odds ratio 6.2 (95% confidence interval 3.3–11.5) [146(III)]. Usually eczema develops early in life. A study of 1,200 hospital cases suggests that the disease is present in 57% before the age of 1 year and in 87% before the age of 6 years [149(IIb)]. Not all patients are affected by eczema throughout their life; upon re-examination 13–25 years after the first examination, 44–83% still had eczema [146(III), 147(III), 150(III), 151(IIb)].

Seasonal exacerbations of eczema occur in 56–92% of patients [146(III), 147(III), 152(IIb), 153(IIb), 154(IIa)], and many improve during the summer, probably because of more favourable climatic conditions, including UV light. However, some patients experience an exacerbation of symptoms under UV light or pollen exposure [154(IIa)].

Several factors make eczema an excellent target for successful education and prevention programmes. There is good evidence that during childhood more girls than boys suffer from eczema (2.6 in favour of girls) [155(IIb),

156(IIb), 157(Ib), 158(IIa), 159(III)] and gender has also been identified as an independent risk factor [160(III)]. Parameters of socio-economic status are also important for the manifestation of this disease. Studies from Great Britain and Germany have found a positive association between higher social class and higher level of parental education and eczema [160(III)]. Food [161(III), 162(III)], aeroallergens [154(IIa), 163(IIb), 164(IIb)], and psychological factors [165(III)] play a role in the expression of this disease.

Education and Prevention Programmes

Because of the increased incidence, costs, and the promising results of intervention studies for eczema, several countries have developed, implemented and evaluated educational programmes [166(IIb), 167(IIb), 168(IIb), 169(III), 170(III), 171(III)]. The Ministry of Health in Germany initiated an interdisciplinary approach to education for children with eczema after an expert report was issued on causes, therapy, prevention and needed research [172(III)]. An interdisciplinary consensus was established to implement a national prevention programme based on the already existing educational programmes for asthma [173(IIa)]. It is currently being evaluated [168(IIb)]. Two regional prevention programmes, including mothers with high-risk babies and affected adults, have already shown efficacy with respect to the patient's knowledge of their disease, disease occurrence, and clinical outcomes (severity, quality of life) and cost-effectiveness of care [174(IIb)].

Example of an Eczema Education Programme

The main contents of an eczema programme should include [167(IIb), 168(IIb), 169(III), 170(III), 171(III), 172(III)] basic information on: *definition; genetics; etiology; pathophysiology of eczema; identification and avoidance of individual provocation factors; skin care; specific treatment options; discussion of complementary therapies, and diagnosis and treatment of food allergies and adequate nutrition in children.*

Behaviour-oriented psychological intervention is focused on: *interrupting the itching-scratching cycle; training of alternative habits to scratching; discrimination and control of scratching stimuli, and relaxation techniques.*

The training aims to reduce negative effects of the disease on social behaviour by helping the patient to develop improved coping strategies for stress and illness-specific problems. A typical programme would be six sessions of 2 h each, which should enable the patient (or the parents) to play an active and competent role in the management of the disease.

Allergic Contact Dermatitis

Occupational skin diseases – mostly allergic contact dermatitis – represent the most frequent occupational diseases in most industrialised countries

[175(IIb),176(III)]. For the individuals affected, education concentrates on avoidance of irritants and allergens, skin care, and skin protection measures as the basis of prevention.

Severe Reactions, Allergic Anaphylaxis

Medical professionals should play an important role in the education of parents, teachers, fellow students, and school administrators, as to how to provide a safe environment for children who develop anaphylaxis to foods or insect stings. Such a programme should include the development of an individual management protocol for each child [177(III)]. Management strategies that can be employed include: *requiring the affected student to carry an epinephrine auto-injector and to know how and when to use it; requiring the affected student to carry an emergency pager; creating a no-food area of the playground; knowing how to avoid attracting stinging insects, and identifying a supervisor to carry a telephone for emergencies* [178(III)].

In the work environment, the affected individual's employer and co-workers should be alert to risk factors for the development of anaphylaxis, and avoidance measures taken to prevent occupational exposures, e.g. non-powdered latex gloves should be used instead of powdered gloves to reduce airborne latex exposure [179(III)].

Websites and contact details of national charities and support groups for patients suffering anaphylaxis and food hypersensitivities can be accessed via the World Allergy Organisation's website on www.worldallergy.org.

International Coalition for Allergy and Asthma Prevention

There is a critical need to establish an international effort to combine the benefits of the existing asthma education programmes and make them available in all countries.

It is proposed that the World Health Organisation and the World Allergy Organisation should co-ordinate an International Coalition for Allergy and Asthma Prevention, Education and Research to act as a global communication network to support national and regional organisations, and to function as follows:

- (1) Collect all effective programmes into a database to be made available to all countries.
- (2) Establish an annual Convention on Allergy and Asthma Prevention, Education and Research for medical professionals from participating countries.
- (3) Establish an International Allergy and Asthma Prevention-Education Promotion Fund, supported by public and private funding.
- (4) Determine criteria to distribute funds as:
 - (i) Seed money to initiate programme activities.
 - (ii) Match funds to supplement the available funding.

(5) Determine the criteria for membership of the International Coalition as an Allergy and Asthma Preventing/Promoting Country. Such criteria could include:

(i) Establishing a national interdisciplinary coalition on allergy and asthma prevention and education promotion, with representatives from all medical specialties.

(ii) The use of international evaluation methods, e.g. those included in the International Study for Asthma and Allergy in Childhood, for comparing longitudinal studies in various populations.

(iii) The commitment of government and private funds for allergy and asthma prevention.

(iv) The introduction of national guidelines and educational activities for physicians and other healthcare professionals and patients, which have been shown to improve treatment outcomes [180(III)]. Establishing an organisation for patient support to include all social and ethnic groups.

(v) Publicising allergy and asthma prevention by recognising ‘World Allergy Awareness Day’, and ‘International Allergy and Asthma Day Hotline’.

(vi) Cooperating with governmental offices that promote environmental control and reduction of pollution.

(vii) Publishing an annual national report on the state of allergy and asthma care and prevention.

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The Costs of Allergy and Asthma and the Potential Benefit of Prevention Strategies

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The Costs of Illness

Asthma and other allergic diseases represent chronic conditions that result in great social and economic impact on the affected persons and their families, health care systems, and society as a whole. In North America the estimated total costs of asthma vary from a low of USD 433.5 million in Canada to a high of USD 12.7 billion annually in the United States [1]. At the start of the 1990s, the annual cost of asthma was estimated at USD 400 million in Finland [2]. In Australia, children lose approximately one million school days each year due to asthma [3]. Childhood asthma also impacts on families. Families with children who have asthma report that this illness influences a range of decisions concerning holidays, pets, furnishings, carpets, lifestyle, and household spending [4–6]. Other allergic diseases account for substantial economic burden as well. For example, in 1996, in the US there were an estimated 36 million physician visits, more than 39 million prescriptions for allergic rhinitis [7], and an estimated 65% of persons seeking non-prescription medications to relieve their symptoms [8]. In the UK, treatments for asthma and other allergic disorders have been estimated to account for 10% of primary care prescribing costs in the National Health Services, and costs for managing allergic problems are estimated at GBP >1 billion per annum [9].

Worldwide, there is considerable interest in the economic impact of asthma – as evidenced by numerous cost-of-illness studies [10–18]. These

studies are difficult to compare because of differences in definitions of costs, sources of unit costs, differing time periods and exchange rates. Yet, mindful of these difficulties, the Global Initiative for Asthma conducted a review of six asthma cost-of-illness studies [19]. That review of asthma costs in developed countries suggested an average annual societal burden ranging from USD 326 to 1,315 per afflicted person. Approximately 40–50% of the total asthma costs were attributed to direct medical expenditures. There are also several studies of asthma costs in lesser-developed countries [19–21]; however, they are limited to small, select population samples. While these studies play an important role in local policy, they are of limited value for purposes of international comparison.

Two studies provide evidence that the costs of asthma are increasing. A study of the trends of asthma costs in the US between 1985 and 1994 demonstrated increased total costs, with medication costs replacing hospital costs as the largest component of direct medical expenditures [22]. A study of trends of asthma costs in Sweden between 1980 and 1991 suggests a nearly 37% increase in total asthma costs, with a 41.1% increase in direct medical expenditures and a 34.2% increase in indirect costs [23]. In Finland, a national asthma program was launched in 1994 and evaluated in 2000. It was estimated that the total costs per patient had decreased by 10–20% even though the costs of medication had increased substantially [24].

While an international literature exists for the economic impact of asthma, the literature describing the costs of illness for other allergic diseases is rather modest. The direct costs of hay fever in the US were estimated to be more than USD 1 billion in 1990 [25]. More recently, data from the US National Medical Expenditures Survey was used to estimate the costs of allergic rhinitis; 1996 costs projected to 2003 dollars resulted in an estimate of USD 4.4 billion annually in direct medical costs [26]. The use of diagnostic testing and immunotherapy may also represent significant economics costs [27], and there is evidence to suggest that the costs are substantially higher when allergic rhinitis is concomitant with asthma [28]. Using a population-based asthma cohort, one study found that yearly medical charges were on average 46% higher for persons with asthma and concomitant allergic rhinitis than for persons with asthma alone [29]. A study of more than 500 persons in Germany found the average annual cost of seasonal allergic rhinitis to be EUR 1,089 per child/adolescent and EUR 1,543 per adult [30].

It has been proposed that indirect costs in terms of loss of work productivity are also an important component cost of allergic rhinitis [31]. The 2003 estimates of US indirect costs for allergic rhinitis vary widely from USD 1.2 to >7 billion annually [26]. In one study of US workers with asthma or allergic rhinitis, nearly 20% reported some type of work-related impairment based

on a 4-week period, due to their condition [32]. Another US-population-based study found that the most significant productivity losses resulted not from absenteeism but from reduced at-work productivity associated with the use of sedating over-the-counter antihistamines [33]. While these indirect costs are most likely substantial, attempts at measurement have often been hampered by sub-optimal study designs [33, 34].

There is almost no information on the societal costs of rhinitis outside the US. One study reported on the costs of rhinitis in Japan. In this study, the 1994 total costs (both direct medical expenditures, including over-the-counter medications, and indirect costs) were estimated at USD 1.15 billion, with an average annual expenditure of USD 118 per affected patient [35].

To date, information on the economic impact of allergy and asthma for many countries with sizable populations, such as India, Indonesia, and China, is unavailable. However, based on epidemiological studies of asthma and allergy within such countries, it is likely that these conditions may account for substantial social and economic burden in these countries as well. One recent study from India provides such an example. Based on a sample of children with mild-to-moderate persistent asthma attending a pulmonary clinic, it was found that nearly two thirds of children had some restriction placed on their play activities because of asthma. The median monthly expenditure on these children's medication was 333 Rupees – about one third of the monthly per capita income [36].

Building Strategies for a Health Economic Benefit of Prevention of Asthma and Allergies

With substantive social and economic burden related to asthma and other allergic diseases, it is essential to explore ways by which care for such individuals may be most effectively managed. Economic analyses are conducted under a framework in which the decision-maker operates within a limited resource environment. Decisions to spend more on one program will necessarily mean spending less on other programs. As a result, economic analyses almost always involve a comparison between alternative therapies in order to ascertain which therapy offers the best health value in improvement in health per dollar expended. Clinical evidence, more commonly, compares a new therapy with placebo care, even when placebo care (i.e. no care) is not the standard of practice in the community.

Various health economic analysis strategies are available to assist in exploring the value of allergy and asthma preventions. Of the various strategies, cost-effectiveness analysis is becoming the leading method.

Cost-effectiveness analysis can be defined as a set of related methods to assess and quantify the costs and clinical consequences of medical care treatments in order to estimate the ‘economic value’ of the intervention in relation to alternative treatments. A cost-effectiveness analysis of competing medical [37, 38] guidelines for designing and reporting cost-effectiveness analyses – including methods for incorporating evidence on costs and effects – are now available, and should be read by those who are interested in conducting or critically appraising these types of studies [39]. The results presented in cost-effectiveness analysis papers are derived from a simple equation that integrates estimates of total costs and clinical outcomes. This simple equation has been described as depicting a value of the intervention for money. That is, the cost-effectiveness of a new intervention in a defined population of patients represents the added total costs required to achieve an incremental improvement in outcome when compared to currently accepted treatment. If the added cost/clinical benefit ratio is acceptable to decision-makers, then it is said to have value.

While there is a growing body of literature which explores the cost-effectiveness of asthma control strategies [40, 41], no health economic studies based on the efficacy of prevention strategies for allergy and asthma are currently available. It is expected that strategies for reductions in allergen load at home, work, and in the environment would be prime candidates for such analyses. A recent US Institute of Medicine Report [42] suggested that targeting reductions in smoking exposure and environmental exposure to house dust mites may be important, leading to effective reduction in the social and economic burden of asthma and allergies through prevention.

While there appear to be no published reports on the health economic impact of prevention strategies on allergies and asthma, two reports examined the issues that would define such strategies [43, 44]. As more evidence emerges demonstrating the efficacy of prevention strategies for asthma and allergic diseases, questions will certainly arise as to the value of applying these strategies. It is within the context of such studies of clinical efficacy that the issues of health economic evaluation emerge. Clear questions concerning such health economic analyses will have to be addressed, such as:

Who is the primary audience for such an analysis (i.e. individuals, health care providers, or society)?

Who would be the target population for the intervention (e.g. high risk for allergy, or asthma)?

What would be the time horizon for evaluation, both in terms of clinical endpoints, but also in terms of those paying for the intervention?

What would be the primary endpoints (e.g. time to onset or illness, or averted cases)?

What type of economic analysis is most appropriate (e.g. cost-effectiveness analysis or alternatives such as the Basic Assessment Scheme for Intervention Costs and Consequences [45])?

Without empirically based health economic evaluations to guide an understanding of allergy and asthma prevention strategies, it would seem that the next major step will rest on building valid, reliable, and dynamic health economic models derived from the larger body of literature based on the tertiary control of asthma and allergic rhinitis.

The literature is relatively conclusive that the use of inhaled corticosteroids for moderate persistent asthma is cost-effective when compared to β -agonist alone for persons with mild or moderate persistent asthma. There is only limited information on the cost-effectiveness of early intervention with controller therapy in persons with mild intermittent asthma [46]. There appears to be a favourable economic benefit to targeted and sustained asthma education directed at self-management for selected sub-groups of patients [47, 48]. Evidence about the cost-effectiveness of disease management programmes may, with further study, provide new comprehensive intervention strategies that can add value to the current clinical care of persons with asthma. Beyond these modest conclusions, the best value for other tertiary prevention strategies remains unknown.

There is at least one published analysis related to asthma based on a policy model. This model examined the relative clinical and economic impact of as-needed relievers (e.g. short-acting β -agonists) versus inhaled corticosteroid therapy in adults with a forced expiratory volume in 1 s $\geq 60\%$ of predicted normal [49]. That model estimated that over a 10-year period, use of inhaled corticosteroids increased the costs, and improved clinical outcomes, at a cost of USD 7.50 per symptom-free day gained. Such a health policy model that focuses on primary prevention, rather than secondary control, might help guide economic and policy decisions for asthma prevention.

Policy Implications for Programmes Targeting at the Prevention of Allergy and Asthma

Disease prevention is an easily understood and well-accepted strategy among public health programmes worldwide. However, both public and private health care policy makers need evidence that prevention strategies are effective and provide value to their populations within the constraints of their local health care finances. Such financial resources are limited and shared across public health concerns including prevention of the spread of infectious diseases, other chronic illnesses (e.g. diabetes, hypertension), disability such as blindness, and health maintenance (e.g. nutrition or oral hygiene programmes).

With intense competition for financial resources for prevention programs, it will be necessary for studies in asthma and allergy prevention to examine ways by which newly designed prevention strategies will demonstrate clear value, firstly in comparison to alternative strategies that aim towards secondary or tertiary control of allergy and asthma. However, a second hurdle will be to provide direct comparison of the value of newly emerging prevention strategies for allergies and asthma with other common prevention programs.

Therefore, an important step in understanding the need for allergy and asthma prevention strategies should be focused on building a policy interest for these health conditions. This might be best accomplished via demonstrating the community-specific burden of these diseases. From such studies of local burden, a credible justification can begin to be established for potential re-allocation of local health care resources. In that way any additional costs and benefits of introducing new strategies for prevention of asthma and allergy can be considered not only in regard to cultural appropriateness, but also in light of the existing resources of each community.

Conclusions

Asthma and other allergic diseases represent health conditions from which millions suffer physical impairments, reductions in quality of life, and economic impact. It is very conceivable that early prevention will lead to more effective use of health care resources. Opportunities exist for using our understanding of the health economic impact from these diseases to construct health economic models that will guide how to maximize the value of newly emerging prevention strategies.

There is a great need for health economic studies of various prevention strategies. While waiting for the funding and implementation of health economic evaluations in this area, health economic modeling represents the most useful immediate strategy to explore the potential of prevention on reducing the economic and social burden from these diseases. At the same time, population-specific studies of allergy and asthma disease burden can lay an important foundation for understanding the potential impact of such programme development.

Recommendations

A better and more recent understanding of cost of asthma and rhinitis is needed from lesser-developed countries.

Further studies are needed to understand the health economic impact, including direct and indirect costs of having concurrent asthma with rhinitis.

Health economic evaluations, examining early secondary prevention of asthma, should be conducted alongside all new randomized controlled trials in this area.

More studies of the health economic impact comparing environmental control in comparison with medication management in secondary and tertiary treatment are needed.

More advanced models of the health economic impact of asthma combined with rhinitis may improve our understanding of the resources available to reduce morbidity for these conditions.

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Summary and Guidelines

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This chapter summarises the key messages of the preceding chapters to provide an overview of the current knowledge base on the prevention of allergy and allergic asthma. Our present knowledge suggests that good progress has been made in our understanding of the underlying principles of prevention of allergy and allergic asthma, and that some prevention strategies can be effective in preventing symptoms or reducing their severity. Major questions remain regarding the prevention of IgE sensitisation, and whether exposure to allergens can be protective or pathogenic, depending upon the time course of allergen exposure in relation to immunological maturity. Much work remains to be done before further firm recommendations can be made.

Recommendations are made for research strategies which may help progress the important areas of primary, secondary and tertiary prevention and thus improve patient care.

Genetics

Current Knowledge

Individuals with a family history of atopy have an increased risk of developing IgE sensitisation.

Atopic constitution represents a high risk for the development of allergic diseases such as allergic asthma, allergic rhinoconjunctivitis and atopic eczema.

The contribution of genetic factors to the development of IgE sensitisation and to the family history of an IgE-mediated disease is between 70–80%. The risk of developing asthma, rhinitis or eczema in general is related to a family history of the respective disease.

Further Actions Required

Identification of genetic variants that predispose to allergic disease may result in several outcomes.

Early identification of susceptible individuals would allow them to be targeted at early age to prevent IgE sensitisation, and for avoidance of allergen exposure. Genetic screening in early life may become useful in preventing allergic disease.

Identification of environmental factors that interact with susceptibility genes to trigger allergic disease and the periods of life in which this occurs may give opportunities to environmental modification.

Understanding susceptibility factors will help to find new drugs to treat and prevent allergic diseases. Genetic variants influence response to therapy, and their identification will improve the efficacy of therapeutic measures.

Environmental Influences

Current Knowledge

Cigarette smoking in pregnancy deteriorates fetal lung development and increases the risk of wheezing in infancy.

Environmental tobacco smoke causes wheeze in infants and aggravates asthma. All children benefit through avoidance of environmental tobacco smoke.

Avoidance of allergen exposure has only been partially successful in the prevention of IgE sensitisation. Avoidance is difficult to implement, benefits are small and long-term effects doubtful.

Infants at high allergy risk (allergic disease in atopic parents or siblings) may benefit through avoidance of pets and dust mites during the 1st year of life.

Some early respiratory infections, e.g. pertussis and bronchiolitis caused by respiratory syncytial virus, as well as some forms of gastro-enteritis may enhance the development of allergic diseases and asthma.

Relative lack of early microbial exposure particularly early in life, may enhance the development of allergic diseases, but further research is needed in this field.

Further Actions Required

Study priorities in allergy-related environmental issues are:

Exploration of the environmental factors associated with residence in locations with high versus low prevalence of allergy.

Effect of modulating the diet of pregnant and breast-feeding mothers – including increased intake of vegetables, fruit, cereals, nuts, starches and fish.

Effect of allergen avoidance in primary and secondary prevention, and in the treatment of allergic diseases (tertiary prevention).

Effect of indoor air as well as ambient air pollutants (e.g. NO_x, ozone, fine particulates) in the development of allergic diseases and their aggravation.

Early Immunological Influences

Current Knowledge

Allergen-specific T-helper lymphocyte programming begins early in life and consolidates into the adult pattern during pre-school years. This programming is directly driven by dietary and inhalant allergens that are ubiquitous in the environment.

Early exposure to high levels of dietary or inhalant allergens usually results in high zone tolerance, which protects against IgE sensitisation. Postnatal development of allergen-specific responses is modulated by Th1 function, which develops through the contact with microbial signals being absent from the fetal environment.

Early exposure to low levels of inhalant allergens in the absence of sufficient microbial exposure may trigger low zone tolerance resulting in either weak Th1-like immunity, or Th2-polarised responses. This may increase the risk for IgE sensitisation.

Further Actions Required

Study priorities are:

Safe interventions strategies for infants at high allergy risk. As allergic manifestations are also increasingly common in children without family history of allergy, there is a need for 'easy to implement guidelines' for all infants. Allergic diseases are difficult to modify once established.

Role of nutritional factors in infants' immune function and lung development.

Possibilities to induce postnatal high zone tolerance by administering high doses of allergens.

Inhibition of Th2 function during the early stages of allergy development by new antagonists (against IgE, IL-4 and IL-12 for example) alone or in combination with allergen-specific immunotherapy.

Effect of anti-viral agents to treat bronchiolitis induced by respiratory syncytial virus and to prevent asthma in young children at high risk.

Predictive and Early Diagnosis

Current Knowledge

Family history, taken by an experienced clinician, is the most reliable predictor of development of allergy and asthma in infants. If both parents

have allergic asthma, allergic rhinoconjunctivitis, or atopic eczema, the child has a fourfold risk to develop allergies compared with a child whose parents do not have allergies. If only one parent has allergic disease, the risk is twofold.

Early signs of an allergic disease, especially atopic eczema, and presence of IgE antibodies to inhalant allergens are important risk factors for later respiratory allergy. IgE antibodies in infant serum to basic food proteins, e.g. hen's egg, may predict the so-called allergic march.

Current immunological markers obtained during the neonatal period are not specific or sensitive enough to predict allergic disease. High IgE concentration in cord blood or infant serum is specific for subsequent allergic disease but has a low sensitivity, and measuring total IgE is not recommended for screening.

Further Actions Required

Mechanisms of initial IgE sensitisation should be explored to develop markers necessary for early prediction.

Preventive measures

Guidelines

Primary Prevention

Avoid smoking and exposure to environmental tobacco smoke, particularly during pregnancy and early childhood (B). Tobacco smoke should be also removed from work places (B).

Avoid damp housing conditions (C), and reduce indoor air pollutants (C).

Breast-feed exclusively until 4–6 months (B¹). No special diet for the lactating mother (A).

Reduce exposure to inhalant allergens in young children at high risk (house dust mites, cockroaches, furred pets) (B).

Eliminate sensitizing and highly irritating agents in occupational environments (C). If this is not possible, implement measures to prevent employee exposure.

¹Based on allergy prevention studies, exclusive breast-feeding and avoidance of solid foods at least 4 months seems to be effective. WHO dietary guidelines recommend exclusive breast-feeding for 6 months in general. Infants who are not breast-fed because their mothers are HIV positive, and who have consequently developed allergy to cow's milk, should receive hypoallergenic formula, if available, to improve symptom control (B).

Secondary Prevention

Treat atopic eczema in infants and children to try to prevent respiratory allergy (D).

Treat upper airway disease (rhinoconjunctivitis) to reduce the risk of development of asthma (D).

In young children already sensitised to house dust mites, pets or cockroaches, exposure should be reduced to prevent onset of allergic disease (B).

Remove employees from occupational exposure, if they have developed symptoms caused by occupational allergic sensitisation (C).

Tertiary Prevention

Infants with cow milk allergy should avoid cow milk proteins; if a supplement is needed, use hypoallergenic formula, if available/affordable, to improve symptom control (B).

Patients with asthma, rhinoconjunctivitis or eczema who are allergic to indoor allergens such as house dust mites, cockroaches and animal danders should eliminate or reduce the exposure to improve symptom control and prevent exacerbations (A–B).

Aim pharmacotherapy primarily towards the underlying inflammatory process (A).

Avoid strictly acetylsalicylic acid or other non-steroidal anti-inflammatory drugs in patients who have been diagnosed to be sensitive to them (C).

Further Actions Required

Study priorities are:

Detection of potent allergens in marketed ready-made foods (also hidden allergens). Declaration of the food allergen content should be improved.

Effect of human milk, and the role of milk constituents (e.g. n3/n6 fatty acids, α -linolenic acid and cytokines) in the development of sensitisation and clinical manifestations of allergy.

Effect of dietary factors in the development of allergy and asthma, e.g. salt intake, antioxidants and n3/n6 fatty acids.

Effect of intestinal microbial flora, antibiotics, pro- and pre-biotics, and microbial vaccinations in the development of sensitisation and clinical manifestations of allergy.

Effect of low-allergen domestic environments in sensitised children and in patients with allergic diseases. Environmental measures should be studied in terms of clinical benefit, feasibility, compliance, costs, and the interventions should be of adequate length, e.g. 12 months.

Effect of house dust mite avoidance on allergic symptoms, exacerbation rates, need for medication and health costs.

Role of indoor air and ambient air pollutants in the development of sensitisation and clinical manifestations of allergy.

Further Actions for Occupational Allergies

Risks of occupational allergy should be monitored and epidemiological information collected by a globally agreed questionnaire.

High risk for allergy environments should be identified (e.g. enzymes, flours, latex and animals). In atopic employees who work in these environments, detection of sensitisation by skin prick tests or IgE antibody measurements could prevent the development of clinical allergy.

General principles of prevention of occupational asthma, rhinoconjunctivitis and dermatitis (e.g. hand eczema or contact dermatitis) should be published by national regulatory and advisory bodies.

Education

Guidelines

Patient education regarding precipitants of allergic symptoms, asthma, and anaphylaxis is essential. Guided self-management to prevent, assess and treat symptoms is the key to optimising disease control (A).

School policies on asthma and anaphylaxis management are essential (D).

Further Actions Required

Initiation of an International Coalition for Allergy and Asthma Prevention. The aims are:

To collect effective programs into a database for all countries.

To establish an annual convention on allergy and asthma prevention, education and applied research for medical professionals from participating countries.

To establish an International Allergy and Asthma Prevention & Education Promotion Fund, supported by public and private funding.

To determine criteria to distribute funds as:

- to seed money to initiate programme activities, and
- to match funds to supplement the available funding.

To determine the criteria for membership of the International Coalition as an Allergy and Asthma Preventing & Education Promoting Country.

Costs of Allergies and Asthma

Guideline

When considering any intervention for prevention or treatment, take into account not only the evidence showing the beneficial effect of a certain product or measure but also the costs. Use the most cost-effective product or measure.

Further Actions Required

Study priorities are:

Health economical impact of asthma, rhinitis and eczema and the conditions together, especially in terms of indirect costs.

Societal costs of allergy and asthma in developing countries, and the development of these costs.

Health economic evaluations in all controlled studies exploring early treatment of allergic disease, especially asthma.

Health economic impact of measures taken to control environmental exposure compared with medication management in prevention and treatment of allergies and asthma.

Development of more advanced models to study the economic impact of allergic diseases on health.

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Appendix 1: Patient Information Sheets: Pull-Out Sheets of Practical Allergen Avoidance Advice

House Dust Mite Allergen Reduction

Aims to reduce the amount of mite allergens in the home

Major Strategies (WHO Strength of Recommendation A)

- Wash bedding regularly (every 1–2 weeks) at 55–60°C, if possible, to kill mites (washing with cold water removes 90% of mite allergens; washing at 55–60°C kills mites but does not denature mite allergens)
- Wash pillows and duvets in hot water 55–60°C, and encase pillows and mattresses with documented protective coverings
- Latin-American Network of Human Genetics Sufficient ventilation of dwellings to decrease humidity; aim to reduce indoor relative humidity to below 50% and avoid damp housing conditions

Additional Strategies

- Use a good quality vacuum cleaner (if possible one fitted with HEPA filter)
 - Use a damp duster when dusting and cleaning surfaces
 - Replace wall-to-wall carpets with linoleum or wooden floors which can be wiped clean
 - Remove/reduce curtains and soft furnishings in the bedroom
 - Replace fabric-covered seating with leather or vinyl
 - Remove soft toys from the bedroom; wash them at 55–60°C or freeze them (in a kitchen deep-freezer) to kill house dust mites
 - Do not allow pets in the bedroom
 - House dust mites are transparent and have no natural protection against sunlight; exposure of mattresses, rugs and carpets to direct strong sunlight (for more than 3 h) kills mites and can be used in appropriate regions.
 - A hammock, easily washable and susceptible to air and sun drying, is used in many areas of the world
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Pollen Avoidance

Provides mechanical barriers to pollen contact

- Keep windows closed at peak pollen times, e.g. in the evening when airborne pollens descend to lower altitudes
 - Wear glasses or sunglasses to prevent pollens entering the eyes
 - Consider wearing a mask over the nose and mouth to prevent inhalation of pollens at peak time
 - Do not cut grass yourself
 - Keep windows closed when the grass has been mown
 - Use air-conditioning if possible
 - Install car pollen filters if possible
-

Pet Allergen Avoidance

Reduces the amount of pet allergen indoors

- If possible, find another home for the pet, and do not bring new animals into the home
 - Exclude pets from bedrooms and if possible keep pets outdoors
 - Vacuum carpets, mattresses and upholstery regularly, if a power source and equipment are available
 - Change clothes before going to school/work if you have attended your horse/cat/dog
-

Cockroach Allergen Avoidance

Removes the cockroaches, eliminates the places and conditions in which they can live, and removes allergens

- Eradicate cockroaches with appropriate insecticides
 - Seal cracks in floors and ceilings
 - Remove sources of food
 - Control dampness
 - Scrub floors with water and detergent to remove allergens
 - Bedding, curtains and clothing can be contaminated and must be washed
-

Mould Allergen Avoidance

Prevents mould from growing, and mould spores from becoming airborne during mould removal

Indoors

- Use dehumidifiers in the home if relative humidity is constantly high (above 50%)
- Ensure heating, ventilation or air-conditioning systems are properly maintained
- Use 5% ammonia solution to remove mould from bathrooms and other contaminated surfaces
- Replace carpets with hard flooring; replace wallpaper with paint
- Repair indoor water damage immediately

Outdoors

- Avoid cutting grass in late summer when mould spores are present in decaying vegetation
-

Severe Reactions, Allergic Anaphylaxis

Aims to prevent contact with the allergens that induce anaphylaxis in susceptible individuals, and to provide strategies for dealing with episodes of allergic anaphylaxis

- Carry an epinephrine auto-injector and know how and when to use it; always have a spare auto-injector available
- Carry an emergency pager or mobile telephone to call assistance
- Carry/wear MedicAlert information
- When travelling abroad, carry an anaphylaxis-alert card in the language of the country being visited, detailing food, drug, and insect allergies
- Avoid stinging insects, and learn how not to attract them:
 - do not wear perfumes or bright colours
 - do not pick ripe fruits, and avoid refuse bins and compost heaps which attract insects
 - keep car windows closed when driving
- Avoid allergenic ingredients in ready-made food by learning how to interpret ingredient lists
- If eating out check with the chef that allergenic foods/oils are not used in dishes; explain the significance of avoiding allergenic ingredients

In the school environment

- Ensure that parents, teachers, fellow students, and school administrators are aware of the necessity to provide a safe environment for children at risk for anaphylaxis to foods or insect stings
- Create a no-food area of the school playground
- Identify a supervisor to carry a telephone for emergencies

In the occupational environment

- Avoid contact with airborne or contact allergens; for example, airborne latex can be avoided by co-workers using powder-free latex gloves
-

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Appendix 2: Content of Educational Programs in Allergy and Allergic Asthma

Allergic Asthma and Allergic Rhinitis

Appropriate actions for guided self-management include

- 1 Developing good communication between patient and physician to improve patient compliance
 - 2 Promoting understanding about the basic facts, causes and triggers of allergic asthma/allergic rhinitis
 - 3 Identifying and controlling factors that aggravate asthma/rhinitis symptoms and provoke exacerbations
 - 4 Following a written action plan to avoid or handle exacerbations
 - 5 Emphasizing the importance of proper drug use and correct use of spacers and inhalers for long-term control
 - 6 Monitoring symptoms and peak flow values in persistent asthma and adjusting medication accordingly
 - 7 Educating to decrease reliance on unproven treatments
-

Eczema

Educational programs in eczema should include

- 1 Information about the nature, heredity, causes and triggers of eczema
 - 2 Identification and avoidance of individual provocation factors, skin care and treatment options, including complementary therapies
 - 3 Discussion of diagnosis and treatment of food allergies and adequate nutrition in childhood behaviour-oriented psychological intervention to interrupt the itching-scratching cycle
 - 4 Training to improve stress-management and reduce the negative social effects of illness-specific problems
-

Severe Reactions, Allergic Anaphylaxis

Each patient should have an individual management protocol to include

- 1 Carrying an epinephrine auto-injector and knowing how and when to use it; always have a spare auto-injector available
- 2 Carrying an emergency pager
- 3 Carrying/wearing MedicAlert information
- 4 Avoiding stinging insects, learning how not to attract them
- 5 Avoiding allergenic ingredients in ready-made food

In the school environment

- 6 Education of parents, teachers, fellow students, and school administrators is necessary to provide a safe environment for children at risk for anaphylaxis to foods or insect stings
- 7 Creating a no-food area of the school playground
- 8 Identifying a supervisor to carry a telephone for emergencies

In the occupational environment

- 9 Health and safety measures should be introduced to prevent exposure of affected workers to airborne or contact allergens
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