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Asthma and allergy: a worldwide problem of meanings and management?

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Experimental researches on the nature and causes of catarrhus aestivus (hay-fever, or hay-asthma)

Chapter I

§ 1. At no period in the history of medicine has the investigation of the causes of disease been carried out more assiduously than it is at the present day. Such is the magnitude of the work, however, and so great are the difficulties which are inseparable from it, that comparatively little has yet been accomplished, and it is still, practically, one of the widest and also one of the least exhausted fields of inquiry in the whole domain of science.

Introduction

With that challenge, issued in 1873, Charles Blackley began an account of his investigations into the causes of hay fever, and opened the door to the study of allergic disease (1). While much has been accomplished in the intervening 129 years, none of the common allergic diseases have been unambiguously defined, the predisposing causes remain largely unknown, and the increasing prevalence is unexplained. Arguably therefore, allergic diseases do, as then, offer plenty of opportunity for inquiry and resolution.

Blackley recognized many of the problems of allergic

disease that remain today. He recognized that constitutional, as well as environmental factors, were required to develop disease. He described hay-asthma and recognized that this form posed the greatest risk to health and could occasionally be life threatening. Perhaps most pertinent today, was his recognition that these conditions had a predilection for the educated classes, while those regularly exposed to grass and hay, were largely spared: observations that foreshadowed elements of both the hygiene hypothesis and immunological tolerance. But perhaps the most striking feature of hay fever was that it just appeared for the first time in the mid 19th century (2).

This paper will not attempt a comprehensive review of global allergic disease, but rather focus on specific aspects of the geographical and temporal variation in the prevalence of childhood asthma. Population surveys have mostly involved children, and asthma has been the outcome of most interest. At the heart of the rationale for population surveys is the search for causality, initially raising hypotheses and later estimating risk. For this, variation in exposure and in disease frequency is required and hence comparative studies by place and over time are of particular interest.

International prevalence surveys

International comparisons of asthma prevalence have

Table 1. Percent prevalence of wheezing, current asthma and fall in PEFR with exercise, in 12-year-old children (from [5])

	New Zealand	Wales	South Africa	Sweden
Wheezing ever	26.6	22.3	25.9	21.7
Wheeze last 12/12	17.9	15.2	17.8	9.2
Current asthma	11.1	9.1	8.7	2.8
> 15% fall PEFR	12.2	7.7	4.1	2.1

only recently been undertaken (3–5). Burr *et al.* compared symptoms and exercise fall in peak flow, as a marker of airway hyper-responsiveness, in 12-year-old children in Wales, New Zealand, South Africa and Sweden (5) Table 1. Asthma prevalence and a fall in Peak Expirator Flow Rate (PEFR) with exercise was higher in New Zealand than Wales, and a fall in PEFR less prevalent in South Africa and Sweden.

International Study of Asthma and Allergies in Childhood (ISAAC)

Asher and collaborators in ISAAC, used simple written and video questionnaires in the first large-scale study of asthma and allergic disease in children, to measure the prevalence of the self reported, or parentally reported, symptoms and signs of allergic disease (6). Almost 258 000 6–7 year olds, from 91 centres in 38 countries, and 464 000 13–14 year olds from 155 centres in 56 countries took part. There was a 15-fold variation in asthma symptoms between countries, with economically developed countries tending to have higher rates of asthma symptoms than less developed countries. This economic development gradient was apparent within Europe, with Western European countries tending to have higher prevalence than Eastern European countries. Very high rates were found in some, but not all, South American countries, often higher than in Spain or Portugal.

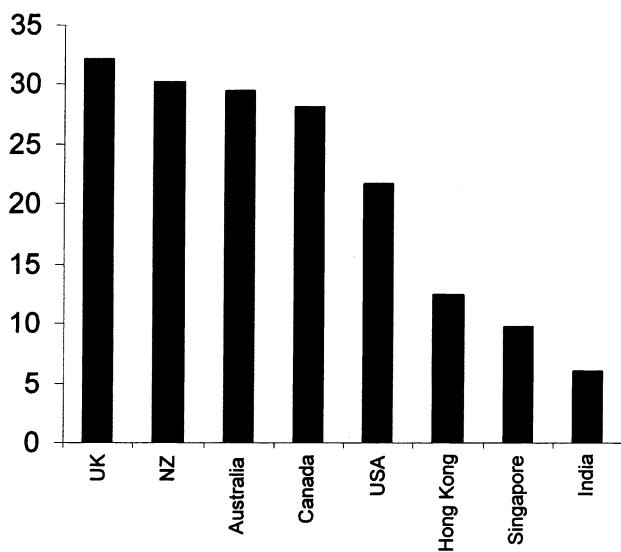


Figure 1. Percent prevalence of self-reported wheezing in the last 12 months amongst 13–14 year olds. (from [6]).

The single most striking feature of the ISAAC data, was the uniformly high rates of asthma symptoms reporting by children from the UK, and ex-UK colonies with a history of extensive in-migration of UK citizens, Fig. 1. The highest rates were seen in the UK, New Zealand, Australia and Canada with lower rates in the US and much lower rates in Hong Kong, Singapore and India. In these latter three countries, some or all of the questionnaires were delivered in English, but the respondents were predominantly indigenous, suggesting that it is not the language of enquiry that is the principal determinant of symptom reporting. Furthermore, video questionnaires showing asthma symptoms without any language component showed the same patterns of asthma prevalence, although symptom prevalence measured by the video questionnaire was invariably lower than from written questionnaires.

Within Europe, symptom prevalence in France and Germany is less than half that of the UK, and in Southern Europe a third, Figure 2. Table 2 show the prevalence ratios for asthma symptoms in the UK and former colonies, compared with Western and Eastern Europe. For 6–7 year olds, the differences between Western and Eastern European countries are small, compared to the differences between both these regions, and the UK and former colonies. For 13–14 year olds, there are greater differences between Western and Eastern Europe, but once again prevalence is considerably lower than in the UK and the former colonies.

The higher of asthma symptom prevalence amongst native English-speaking people (the same was true to a lesser extent for rhinitis and eczema) is striking. The same pattern was found for young adults in the European Community Respiratory Health Survey (7). The reasons are unexplained, but important clues to the

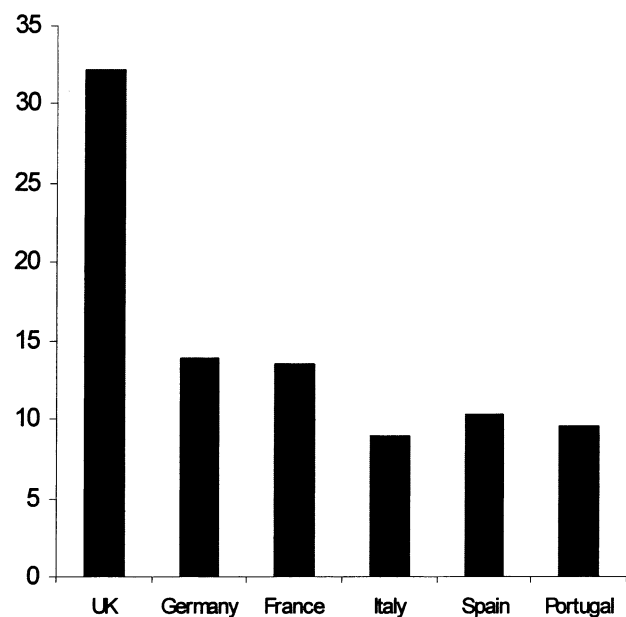


Figure 2. Percent prevalence of self reported wheezing in the last 12 months in 13–14 year olds (from [6]).

Table 2. Prevalence ratios for asthma symptoms in 13-14-year-old-children from the ISAAC study. (from [6])

	Wheeze ever	Wheeze last 12/12	Awoken by wheezing last 12 months	Wheeze limits speech last 12 months	Exercise wheezing last 12 months
6-7 years olds					
UK and ex colonies	1.00	1.00	1.00	1.00	1.00
Western Europe	0.58	0.34	0.26	0.35	0.24
Eastern Europe	0.50	0.37	0.30	0.34	0.22
13-14 years olds					
UK and ex colonies	1.00	1.00	1.00	1.00	1.00
Western Europe	0.48	0.37	0.26	0.31	0.51
Eastern Europe	0.36	0.23	0.19	0.17	0.27

causes of asthma and allergic disease might be related to these differences. ISAAC has shown for the first time, that the symptoms of asthma and allergic disease in children are truly global, symptoms were reported from every centre, with considerable inter-national variation and a predilection for English speakers. The history of the changing prevalence of asthma in English-speaking countries over time, is therefore worthy of review.

Time trends in asthma

Logan and Cushion reported in 1958 that the prevalence of asthma in England and Wales, was 1.2% for boys and 0.64% for girls aged under 15 years (8). In 1961 Morrison Smith, defining asthma as 'recurrent wheezing and dyspnoea not known to be of extrapulmonary origin', reported rates of 1.8% for 5-6 year olds and 10-11 year olds and 1.6% for 13-15 year olds in schoolchildren from Birmingham, UK (9) and confirmed higher prevalence in male subjects up to the age of 15. These rates were similar to those in Norway in 1954, 1.8% in 7 year olds (10), and in Sweden in 1954, 1.4% amongst children aged 7-14 years (11). In these early surveys there was no evidence that prevalence was higher in the UK compared to Scandinavia. But at exactly the same time, Broder *et al.* reported a prevalence of asthma of 14% in 6-9 year olds in Michigan, some nine-fold higher than in the UK or Scandinavia. Their criterion for asthma, included wheezy bronchitis, or wheezing associated with respiratory infection (12). With the exception of the Michigan survey, these studies considered what we would now regard as the severe end of the spectrum of asthma, as suggested by the definitions involving recurrent wheezing in the absence of infection. When wheezy bronchitis was considered in addition to recurrent wheezing without infection, much higher rates were also recorded in the UK.

In 1978, Peckham reported data from a national UK birth cohort of children born in 1958 (13). At the age of 7, 3% of children were reported to have a history of asthma and a further 15% were reported to have a history of one or more attacks of wheezy bronchitis, a total of 18% with a history of any wheezing. By the age

of 11, a further 4% had developed asthma or wheezy bronchitis since the age of 7 years, giving a prevalence of any recurrent wheezing illness of 22%.

In 1969 Williams and McNicol, in a landmark study, published a detailed account of the prevalence and natural history of wheezy bronchitis and asthma, in 10-year-old Melbourne school children (14). They defined three groups:

- mild wheezy bronchitis – < 5 episodes wheezing always with bronchitis or apparent respiratory infection;
- wheezy bronchitis – > 5 episodes wheezing always associated with bronchitis or apparent respiratory infection;
- asthma – wheezing children where at least one wheezing episode was not associated with bronchitis or apparent respiratory infection.

The prevalence of asthma by this definition was 3.7%, while the prevalence of wheezy bronchitis was 15.4%, giving a prevalence of any recurrent wheezing of 19.1%, although only a third of these children, or 6% of the population, experienced wheezing in the last year, Table 3. All of these wheezy children were more likely to be atopic than non wheezy children, even the mild wheezy bronchitis group were four times more likely to be atopic than non wheezers, while 80% of the 'asthmatic' children, who wheezed without infection, were atopic and their respiratory symptoms tended to be more severe. The authors considered that all of these wheezy children belonged to a single population who shared a common abnormality that was variably manifest, leading to considerable variation in symptom frequency and severity.

These studies of asthma prevalence in young children in the 1960s suggest that a history of

Table 3. The prevalence of asthma and wheezy bronchitis and the percentage of atopy in each symptom group. (from [14])

	% Prevalence	% Atopy
Non wheezers	80.9	7.5
Mild wheezy bronchitis	7.7	28.8
Wheezy bronchitis	7.7	39.6
Asthma	3.7	80.2
All wheezing	19.1	42.9
Wheezing last 12 months	6.1	–

wheezing was common; up to 20% in both the UK and Australia, the majority of wheezing occurring in association with respiratory tract infections. Only a small proportion of these children experienced frequent or severe attacks, and the more wheezing they experienced, the more likely they were to be atopic. Early studies of asthma prevalence had in fact only revealed the tip of the wheezing iceberg, by restricting cases to those with frequent wheeze in the absence of respiratory infection.

The therapeutic implication of disassociating wheezing from a diagnosis of asthma was first raised in the UK by Speight in 1978. In a series of 34 paediatric asthma referrals from general practice, a failure to make a positive diagnosis led to inappropriate management. In 1983, Speight *et al.* explored this in more detail in 7-year-old children in the UK (15). Amongst 300 7 year olds, who had wheezed since starting school, only 12% had been diagnosed as having asthma and only a third had ever received a bronchodilator, despite many of them experiencing frequent symptoms. The studies by Speight, and Williams and McNicol had a significant impact on clinical practice, especially in the UK, Australia and New Zealand, increasing the readiness to diagnose childhood wheezing as asthma, which in turn led to more rational treatment with inhaled bronchodilators rather than antibiotics (16). This change may however, have reduced the appreciation of the importance of respiratory infection as a cause of wheezing both in children with and without atopy and has meant that most studies since the early 1980s have not separated wheezing with and without respiratory infection (16). More recently this situation has been addressed with longitudinal studies exploring the etiology of childhood wheezing in relation to lung size, infection and atopy separately (17).

In 1982, Britton *et al.* examined asthma prevalence in 8–10-year-old children in Belmont, a small coastal suburb of Newcastle, New South Wales (18). The prevalence of asthma symptoms in 1982 were similar to those found by Williams and McNicol in Melbourne, 18 years earlier, as the authors noted in their report, Table 4. In the 18 years between these different surveys, both undertaken in coastal

Australia, only reported wheezing in the last 12 months had increased. The prevalence of atopy had however increased.

A decade later in 1992, the Belmont survey was repeated (19). An unprecedented increase in asthma symptoms, diagnosed asthma and asthma treatment had occurred, in fact the prevalence of symptoms had doubled, a diagnosis of asthma had increased four-fold and asthma treatment had increased three-fold, Table 5. The prevalence of atopy was unchanged. The authors also noted an increase in bronchial hyper-responsiveness (BHR) to histamine amongst atopic children, however, the nebulisers used to generate histamine aerosols were different in the later study and their increased output may have explained this increased prevalence of BHR (20).

Whatever is responsible for these dramatic and rapid increases in reported wheezing, frequency of attacks, diagnosed asthma, and increased asthma treatment, they are not related to increased sensitization to allergens. Indeed, it is striking that between the Melbourne study in 1964 and the first Belmont study in 1982, the prevalence of atopy had doubled but symptoms of asthma had changed little. Between 1982 and 1992 in Belmont, atopy was unchanged but symptoms of asthma had increased two to three-fold. Similar high rates of asthma symptom reporting have also been found more recently in Melbourne (21), and appear to be largely synchronized throughout Australia, and indeed as the ISAAC study has shown, throughout the English-speaking world (6).

In 1989 Ninan and Russell published a repeat prevalence survey from Aberdeen over 25 years from 1964 to 1989. The 1964 survey reported by Dawson (22) was repeated in 1989 but with differences in key questions and with self-completed rather than interviewer-administered questionnaires (23). The 1964 data was reanalyzed to make it more comparable with the 1989 data. The 1989 survey was repeated again in 1994 (24). After 25 years and again after only 5 years, substantial increases in both diagnosed asthma, wheezing, and attacks of shortness of breath (SOB) were apparent, Table 6. The rate of change,

Table 4. Percent prevalence of wheezing, diagnosed asthma and atopy in Melbourne children and Belmont children. (from [14,18,19])

	Melbourne 1964 7–10 year olds	Belmont 1982 8–10 year olds
Wheezing history	19.2	19.7
Wheeze last 12/12	6.1	10.4
Diagnosed asthma	11.0	9.3
Any positive skin prick tests	14.3	27.7
House dust	7.7	19.5
Rye grass	11.3	10.9

Table 5. Percent prevalence of selected symptoms, diagnoses and proportions with bronchial hyperresponsiveness in Belmont New South Wales. (from [19])

	Belmont 1982	Belmont 1992
Wheezing ever	19.7	—
Wheeze last 12 months	10.4	27.6
> 4 attacks wheezing/year	2.5	15.8
Diagnosed asthma	9.1	37.7
Any atopy	27.7	29.3
Asthma treatment ever	9.6	28.3
% atopics c BHR	18.6	47.2
% non atopics c BHR	5.4	8.4

Table 6. Percent prevalence, and annual change in wheezing, asthma, hay fever and eczema in Aberdeen schoolchildren. (from [24])

	1964 8–14 year olds	Annual change	1989 8–14 year olds	Annual change	1994 8–14 year olds
Wheeze last 3 years	10.4	0.376	19.8	1.12	25.4
Attack SOB	5.4	0.188	10.1	1.72	18.7
Diagnosed asthma	4.1	0.244	10.2	1.88	19.6
Hay Fever	3.2	0.348	11.9	0.16	12.7
Eczema	5.3	0.268	12.0	1.14	17.7

for all outcomes, except hay fever, between 1989 and 1994 is considerably greater, on an annual basis, than between 1964 and 1989.

Other comparative studies over time in the UK have revealed less dramatic changes. Anderson *et al.* compared asthma prevalence and severity in London in 7–8-year olds between 1978 and 1991 (25). They noted a 16% relative increase in reported wheezing in the last year, but a reduction in severe attacks, which they attributed to the increased use of inhaled corticosteroids. Burr *et al.* compared asthma prevalence in 12 year olds in Wales between 1973 and 1988. They reported a two-fold increase in current asthma (diagnosed and recent symptoms), and diagnosed asthma ever, and a 55% increase in wheeze in the last year, but no increase in BHR as measured by a fall in peak expiratory flow rates following a 6-min run (26).

Time trends in allergic rhinitis, atopic eczema/dermatitis syndrome (AEDS) and IgE sensitization

Rhinitis and itchy skin rashes are very common in childhood. Separating allergic causes from others in large scale surveys is particularly difficult. In the same way that the term 'asthma' has led to difficulty in respiratory health surveys so the terms 'atopy' or 'allergy' have led to problems in further characterizing rhinitis or itchy skin rashes. Recently, the European Academy of Allergology and Immunology has published a revised allergy nomenclature (27) where allergy is defined by the presence of an allergen-specific IgE sensitization. Atopic eczema/dermatitis syndrome (AEDS) is recommended in this nomenclature as the term to describe both the IgE and non-IgE subgroups often referred to as 'atopic dermatitis'.

Despite these problems of definition most comparative studies have tended to show an increase in the prevalence of both conditions over time (28, 29), but these changes have not been as consistent as for asthma. Whereas symptom questions have been validated for asthma often against BHR or a doctors diagnosis (30), questions for eczema and allergic rhinitis, suitable for large surveys have only recently been standardized and validated against a diagnosis (31, 32)].

Difficulties in measuring hay fever prevalence were

apparent from early surveys. For example, Williams and McNicol noted a prevalence of hay fever at 7 years of 5.1% increasing to 11.0% by age 10 years in Melbourne schoolchildren in 1964 (14). However, they also noted a prevalence of 29% for persistent or recurrent nasal discharge. Both these conditions were much more common amongst wheezy children and distinguishing seasonal or perennial rhinitis from rhinitis secondary to frequent colds in young children is difficult (33). There exists large differences in prevalence estimates between studies in the same city. For example, the prevalence of hay fever reported by parents of predominantly 7–8 year olds in Auckland, New Zealand, in 1985 was 30% (34). In the ISAAC study, a decade later in 1994, the parents of 6–7-year-old children in Auckland reported a prevalence of hay fever of 12.4% (35). Similar variations are apparent in other studies. For example the prevalence of hay fever in 8–9-year-old children in coastal New South Wales in 1982 was 20%, increasing to 34% by 1992 (19). In Sydney however, in 1994 in the ISAAC study amongst 6–7 year olds the prevalence was 12.2% (35). While some of this variation will be due to the small differences in age of the children and the different survey settings, these studies do not suggest a large recent increase in the prevalence of allergic rhinitis. The incidence of allergic rhinitis presenting in general practice in the UK shows no upward trend between 1981 and 1992 (36). In reviewing the changing prevalence of allergic rhinitis in the English language literature, Sly noted an increase in the UK from 12% to 23% amongst 16 year olds in two cohorts born in 1958 and 1970. In the US local surveys undertaken between 1962 and 1965 showed a prevalence between 15 and 28%, while a national survey between 1976 and 1980 gave a prevalence of 26% (37). Improved questionnaires for measuring the prevalence of allergic rhinitis in adults and children will clarify changes over time, and in particular the important associations between allergic rhinitis and asthma at different ages, and their associations with atopic sensitization (38).

For AEDS the recent prevalence rates are more consistent. Thus, in 1985 the reported prevalence of eczema in Auckland children was 27% (34), in the ISAAC study in 1994 it was 22% (39). For coastal NSW in 1982 20%, rising to 24% in 1992 (19), while in Sydney in 1994 the rate was 19% (39). Thus, while bearing in mind the problems of definition and standardization

some studies suggest an increase in both allergic rhinitis and allergic dermatitis over the last 20–30 years, but no evidence of an explosive increase as for asthma symptoms between the 1980s and the 1990s.

Few repeat random population surveys of IgE sensitization over time have been undertaken. Nakagomi reported an upward trend in specific IgE to a variety of allergens in 13–14-year-old school-children in Northern Japan (40). Skin-test reactivity to environmental allergens increased over 8 years in the Tuscon epidemiologic study, but most of this change was attributed to earlier in-migration (41). Adults in Copenhagen showed a 30% increase in atopy over an 8-year period, 1990–98, but the response rate in the second survey was lower than in the first, raising the possibility of response bias (42). Perhaps most striking is the lack of increase in the prevalence of atopy in New South Wales, when asthma symptom prevalence increased two to three-fold (19).

For children born in the 1950s and 60s, at least in the UK, Australia and the US, wheezing secondary to respiratory tract infection was common but not particularly severe, and was labelled 'wheezy bronchitis'. Only a small proportion had recurrent wheezing in the absence of infection, most of these children were atopic, and were labelled 'asthma'. In the 1970s, and increasingly since, especially in UK, Australia and New Zealand, the wheezy bronchitic children were subsumed under the label asthma when it was appreciated that their morbidity improved with the prescription of inhaled bronchodilators rather than antibiotics. For children born in the 1980s and surveyed in the 1990s, in some studies in coastal Australia and in Aberdeen, and to a lesser extent in Wales, there appears to have been an unprecedented explosive increase in asthma symptoms, diagnosed asthma and asthma treatment, largely unaccompanied by any definite increase in BHR or a large increase in atopic sensitization.

Why is asthma prevalence increasing?

Three broad patterns emerge from this review of asthma prevalence:

- A gradual rise in prevalence of asthma and atopic disease between the 1950s (when the first population surveys began) and the 1980s.
- A dramatic rise in the prevalence of asthma symptoms from the 1980s, most evident in the UK and the former UK colonies.
- Higher rates of asthma symptoms in the UK and former UK colonies compared to most other countries

The hygiene hypothesis

The gradual rise in the prevalence of atopic disease has been linked to the decline in infectious disease. In 1976 Gerrard and colleagues examined serum IgE amongst

275 individuals from 58 Metis families, descendants of Cree Indians in Northern Saskatchewan (43). They compared total IgE and the prevalence of atopic disease with 819 individuals from 176 white families living in the same region. The prevalence of eczema was seven-fold higher and asthma almost three-fold higher in the white community compared to the Metis. In contrast to this the geometric mean total IgE was three-fold higher in the Metis community compared with the white. In their concluding statement these authors spelled out what was to be termed the hygiene hypothesis a decade later.

'The prevalence of asthma, eczema and urticaria was greater in the white than in the Metis community and contrasted with the increased prevalence of helminth infestation as well as of other untreated viral and bacterial diseases in the Metis community. It is suggested that atopic disease is the price paid by some members of the white community for their relative freedom from diseases due to viruses, bacteria and helminths'.

In noting this inverse relationship between infection and atopic disease they raised, as others had previously done in rural and urban Gambia (44) and elsewhere, the paradox, that in communities exposed to more infection and helminth infestation in particular, total IgE was elevated but atopic disease infrequent.

In 1989 David Strachan noted a strong inverse relationship between household size and hay fever in cohort data in the UK (45). He first articulated and coined the term 'hygiene hypothesis' to explain these associations, suggesting that a greater exposure to infection in early childhood might arise from contact with siblings. Subsequently a number of studies have identified inverse prevalence relationships between atopy or atopic disease and specific infections (46–48). In Italy which has high rates of hepatitis A infection, a clear positive relationship has been established between the number of siblings and positive hepatitis A serology (49), providing a direct link between family size, the risk of infection and the decreased risk of atopic disease. The epidemiological associations were soon followed by a complementary immunological hypothesis (50), in which reduced infection and microbial exposure in early life would delay the switch from a Th2 to Th1 immune response in infancy (51). It is in this postnatal switch from Th2 to Th1 that infection and microbial exposure would be expected to operate, microbial exposure being a potent Th1 stimulus.

The utility of the hygiene hypothesis is that it provides a clear link between the immunology and the epidemiology of IgE-mediated disease. It might help to explain the long-term time trends, and the sudden appearance of hay fever in the mid 19th century. The profound reductions in infectious disease through improved sanitation and housing, reduced crowding,

and later, antibiotic treatment and immunization in the developed economies through the 19th and 20th centuries certainly led to an environment with rapidly diminishing risk of serious morbidity and mortality from infectious disease. The same argument would probably provide the best single explanation so far for the positive associations between atopic disease and the Western lifestyle (52). When this increased susceptibility to allergens is combined with increased exposure to common environmental allergens, and to a greater array of potential allergens, the hypothesis becomes even more compelling, as an explanation for the long-term rise in the prevalence of atopic disease.

Recent rise in asthma symptom prevalence and the English predilection

Many risk factors for the rise in asthma prevalence have been identified. While there are no universally agreed definitions, small variations in study definition may have an important effect on prevalence estimates, as has been seen by the inclusion or exclusion of children who wheeze with and without infection. The greater awareness of asthma in many communities and amongst health professionals, are likely to have increased symptom reporting and the recall of asthma symptoms (53). Increased bronchodilator prescribing for childhood wheezing following the recognition of significant undertreatment in the early 1980s will in itself have consolidated the diagnosis of asthma by health professionals and their patients. Indeed, a response to bronchodilators is part of the operational description of asthma (54). But it seems unlikely that this alone could explain all of the explosive rises in asthma symptoms seen in Australia or Aberdeen in the 1990s. It is even less likely that these later trends could be related to changes in infection or microbial exposure.

Firstly, as Strachan has emphasized, the hygiene hypothesis applies only to IgE-mediated disease (55), and asthma is only partly related to allergy, less so in infancy and early childhood than in older children or young adults. Secondly, it is difficult to conceive major changes in hygiene or infectious disease exposure for children growing up during the 1970s and 1980s, in Australia or Scotland, or that hygiene and infection should be so very different between the UK and Scandinavia, for example. Thirdly, again as Strachan has pointed out, the relationships between risk-factor exposure and a two or three-fold change in prevalence, require either very large differences in exposure to the risk factor or a very strong risk, or both (55), at least when they act alone.

A further possibility however, needs to be considered; that the increase in bronchodilator treatment from the late 1970s and early 1980s, and in particular their recommendation as regular daily treatment (56), rather

than as required to relieve symptoms, might be directly responsible for some of the recent increase in the frequency and severity of asthma symptoms in children.

During the late 1970s and 1980s New Zealand suffered an epidemic of asthma deaths (57). In 1989 we reported a case control study of medication use amongst asthmatics who had died from asthma, and asthmatics admitted to hospital with asthma but who did not die, and showed that the beta 2 agonist fenoterol, substantially increased the risk of a fatal outcome from a severe attack of asthma (58). In two further case control studies we confirmed these results (59, 60) and further confirmation was provided independently by Spitzer *et al.* in Canada (61). The warnings about fenoterol use and removal from the subsidized drug tariff in New Zealand led to a marked and sustained decline in asthma mortality (62). Following withdrawal of fenoterol, hospital admissions for asthma also declined substantially in New Zealand (63, 64) suggesting that fenoterol increased the risk of death by increasing the chronic severity of asthma. In 1990 Sears *et al.* reported that among 64 patients taking regular fenoterol for 24 weeks, asthma control was worse in 70% compared to 'as required' beta-agonist use and that this was not associated with any increase in bronchial hyper-responsiveness (65). More recently Taylor *et al.* has studied the effects of salbutamol and salmeterol on asthma control. For salbutamol, no differences in exacerbation rates were found compared to placebo, but both the duration and severity of exacerbations, as judged by prednisone requirements, were greater during treatment with regular salbutamol than with placebo plus salbutamol as required (66).

There is evidence that short-acting beta agonists have a pro-inflammatory effect increasing and activating airway eosinophils (67, 68). Evans *et al.* have shown that regular salbutamol can significantly increase airway hyper-responsiveness to hypertonic saline but not methacholine in nonasthmatic subjects with allergic rhinitis (69). This evidence suggests that short-acting beta agonists exert direct effects on the airway capable of worsening asthma. In the case of fenoterol this was sufficient to substantially increase asthma mortality and hospital admissions for asthma in New Zealand.

However, three studies have examined the effects of regular versus 'as needed' salbutamol and have failed to reveal any significant adverse effects. Some of these have been of short duration (70) and in mild asthmatics (71), but a year-long study in a more severe group of asthmatics has also failed to show obvious deleterious effects (72). A recent study comparing regular salbutamol with formoterol found a small but significant decline in FEV1 in the salbutamol-treated group, but not in the formoterol-treated group (73). These studies are generally reassuring with regard to regular salbutamol treatment in adults with asthma. However, most of the research concerning increasing asthma preva-

lence has been conducted amongst children, while the studies of adverse effects of bronchodilators have been conducted amongst adults. There have been very few studies in children that have examined the effects of asthma therapy on viral associated asthma alone.

Thus, the trend at the end of the 1970s and early 1980s towards treating all childhood wheezing with beta agonists regularly by inhalation while improving immediate symptoms, may have prolonged exacerbations, and made symptoms more frequent and severe, especially from viral-associated wheezing. Such an hypothesis would explain the recent dramatic increases in asthma symptom frequency for children growing up in the 1980s. Similarly it would explain the high prevalence in the UK, Australia and New Zealand. Inhaled beta-agonist therapy for maintenance as well as acute asthma management was most enthusiastically taken up in English-speaking countries, with the exception of the US where oral theophylline remained the bronchodilator of choice into the 1980s (74). Studies of asthma prevalence in the US have consistently shown lower rates than in the UK or Australasia (75), although the gap now appears to be narrowing. Interestingly symptom reporting was lower in US centres compared to the UK, Australia, New Zealand or Canada (see Fig. 1) in the ISAAC study. As we have seen from ISAAC, asthma symptom prevalence is much lower in France and southern Europe compared with the UK. A survey of respiratory specialists carried out in 1984 revealed that in France, Portugal and other southern European countries, the emphasis was placed on the use of oral theophyllines and desensitization therapy rather than inhaled beta-agonists as first line therapy for asthma (76).

A role for beta agonists in modifying the natural history of wheezing in early childhood remains plausible and would fit two unexplained aspects of asthma prevalence, the predilection for English-speaking countries, and the explosive recent rise in symptoms in some studies in these countries. It would also conform to the constraints discussed recently by Strachan (56), in that exposure is very common amongst wheezing children (at least in the UK and former UK colonies) and virtually absent amongst non-

wheezing children and could thus explain the two to three-fold increases in symptom prevalence without invoking an inordinately large risk. It is also conceivable that increased beta agonist treatment of young wheezy children might have contributed to the considerable increase in acute asthma admissions noted in the UK, New Zealand, and Australia, and to a lesser extent in Canada and the US (77). Anderson noted a large increase in childhood admissions for asthma in the UK between 1958 and 1985. Hospital admissions rose much more steeply after 1980 than before, in both younger and older children, with the largest increase occurring in children aged 0–4 years. In a regional analysis in the South-West Thames region he was able to show that this was not owing to a reduction in severity on admission or an increase in readmission rates but suggested an increase in the number of children experiencing severe attacks (78). If beta agonists are related to this increase in hospital admissions then the strength of the effect would have to vary inversely with age, at least in childhood. In turn this would suggest that wheezing associated with viral infections treated with beta agonists might be more likely to lead to an adverse outcome than wheezing associated with atopy.

In 1989, Wilson revisited wheezy bronchitis, and drew attention to the importance of distinguishing atopy- and infection-related wheezing, both to understand the pathophysiology and to rationalize treatment in children (16). These suggestions in relation to asthma treatment should be dusted off and revisited. The recent rise in asthma symptom prevalence and severity in children, could plausibly be a lesser reincarnation of the deleterious effects of isoprenaline and fenoterol in adults, and the recent increase in asthma prevalence in children, at least in part, might have a modifiable iatrogenic component.

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