Asthma in Children

EDITED BY
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Natural history, assessment, treatment
and recent advances

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Preface

To be breathless is to be near death. Children with asthma often suffer unnecessarily because this fact is not fully appreciated. They lose countless hours of school work, of play and enjoyment and of sleep—largely because the care of their condition is poor.

Ignorance regarding the natural history of asthma remains deeply ingrained in the minds of many—'he will grow out of it' is an epitaph as common today as it used to be in my student days, and treatment at times assumes an almost patronising attitude. And yet if we are to offer the most effective treatment we must try to understand the causes. Our aim in this small book is to give an objective outline of asthma in children and point the way towards a more rational and better management the child of today surely deserves.

Each chapter offers a concise account of a particular aspect of asthma but, inevitably, an occasional overlap occurs. This is intentional.

I would like to thank the many people who have been concerned in bringing this book to fruition. I am especially indebted to Dr P Morton, BA, for reading the manuscript through and for helpful suggestions; to Mrs M Rushford, Librarian, Postgraduate Medical Centre, Peterborough; and Mrs E Gibbs my secretary. Lastly I thank my long suffering wife for patiently typing the many drafts, and for her forbearance, support and encouragement, without which this book could not have been completed.

I take full responsibility and apologise for any omissions and inadequacies.

Jan A Kuzemko

Preface to the second edition

We have been encouraged by the response with which the book has been received. The second edition has been thoroughly revised to keep pace with advances in the understanding and treatment of asthma in children. A new important chapter by A W Monks on exercise has been added.

The research staff of the Department of Physical Education and Sports Science at Loughborough University and the Pharmaceutical Division are thanked for their help with Chapter 9.

The editor would like to thank Mr David Dickens, of Pitman Medical for his encouragement, help and guidance.

Jan A Kuzemko

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CHAPTER 1

Definition

Jan A Kuzemko

The word asthma (Greek—breathe hard) has retained its meaning intact through the centuries, although the pathogenesis of the disease remains poorly understood. Thus, in children, asthma must still be defined in clinical and functional terms: *It is a condition of altered dynamic state of respiratory passages due to the action of diverse stimuli resulting in airways obstruction of varying degree and duration, and reversible partially or completely, spontaneously or under treatment.*

Childhood asthma is a heterogeneous disease. It is familial, meaning that it is inherited by involvement of more than one gene, and environmental factors also play an important role. Indeed, the environmental component is undoubtedly of paramount influence. Many trigger mechanisms provoking episodes of asthma are well understood, but there are others that are not. Despite this, there probably exists a common pathway to explain the clinical features of asthma.

Asthma in children presents in many clinical forms and its degree of severity can be very variable. It may occur in acute attacks, with free intervals lasting from hours to days or even years, or it may occur as a chronic state in which the child has frequent minor and major exacerbations of the disease. Consequently, it may affect lung function to a slight degree or it may develop into a serious handicap resulting in marked disturbance of the life of the child and its family. It is because of its unpredictable course that childhood asthma is poorly understood and difficult to treat, and different views are held regarding its nature and management. Moreover, objective data on asthma in children are scarce and a great deal of what is available is anecdotal, giving rise to erroneous speculation.

Since much more work has been done on asthma in adults, it is common to find data derived from adults extrapolated to children and a biased interpretation given. It is worth stressing that asthma in children occurs in a pure state and that the degenerative pulmonary diseases of

adults are absent; hence, diagnosis and management is of asthma rather than of a symptom complex (chronic bronchitis, emphysema, etc) often seen in adult practice. Further, the lungs, bronchi and bronchioles actively develop throughout childhood leading to changes in the structure and function.

It follows that a child's lungs must not be regarded as a mirror image of the adult lung. The response to treatment of the asthmatic child is often different from that of an adult and assessment of specific therapy much more accurate. Also, anyone caring for a child must always remember that he is dealing with a growing patient, as well as the asthma and the patient's family. Hence, not only is a basic objective knowledge of asthma in children essential if the doctor is to do justice to a young patient, but equally important, the interest, enthusiasm and personality of the doctor will have a beneficial effect on both the patient and the family as a whole by encouraging confidence and a better understanding of the disease.

CHAPTER 2

Incidence, Prognosis and Mortality

Jan A Kuzemko

The true incidence of asthma in children remains unknown. Since about half the adult population with asthma and hay fever develop their first symptoms during childhood, study of this subject in children is relevant to its occurrence in adults. In general, up to the age of 15 years, 2 to 3 per cent of boys have asthma and about 1 to 2 per cent of girls. Each year, in England and Wales, well over eight million children attend school and, with the probable incidence of asthma at this age at about 4 per cent, it can be assumed that 250000 to 350000 children will have symptoms of asthma. This assessment does not include pre-school children in whom the incidence of asthma is higher than in the child of 7 to 9 years. It is uncertain whether the wheeziness associated with a respiratory infection in the very young has any relationship to the development of asthma. Indeed some believe that both are part of one disease process[4]. Table 2.1 shows the incidence of asthma in children in various areas.

Table 2.1 Incidence of asthma in children in various countries

Authors	Year	Locality	Age (years)	No. of children	%
Fry[1]	1961	Kent, England	0–10	797	1·5
Graham *et al*[2]	1967	Isle of Wight			2·3
Dawson *et al*[3]		Aberdeen, Scotland	5–16	2511	4·8
Williams and McNicol[4]	1969	Australia	6–11	30000	3·7
Morrison-Smith *et al*[5]	1969–1970	Birmingham, England	5–18	20958	4·2
Varonier[6]	1970	Switzerland	5–6	4781	1·69
Rhyne[7]	1971	USA	Under 10	3939	6·9
Kuzemko[78]	1974	Peterborough, England	5–11	9045	4·9
Hamman *et al*[76]	1978	Kent, England	5–14	4704	3·8
Peckham and Butler[77]	1978	National Study in UK	11	13509	3·5

Morrison-Smith[8] studied the incidence of asthma in children at school and showed that in a period of 12 years there was an increase of about 30 per cent. He suggested that environmental factors, especially during the first two years of life, were of great importance in determining the occurrence of atopic disease and hinted that an understanding of these factors at this period of life might lead to a better control of asthma. There are no other studies to support this contention although Fireman[9] showed that the number of hospital admissions in Pittsburgh, USA showed that the number of children with asthma admitted to hospital had doubled in recent years and the severity of the disease had increased considerably during the last ten years.

Factors Related to Incidence and Pathogenesis

Family History

Many factors influence the incidence of the disease. A family history of asthma or other manifestations of hypersensitivity state are often present, varying between 50 and 75 per cent of cases[12,56,57]. The presence of the disease in the mother has much greater significance than disease in the father. Montgomery Smith[10] in the USA, showed that a child with asthma was twice as likely to have an affected mother than an affected father. This is of interest since more males have asthma than females, and fathers therefore should be affected more than mothers. Eczema is frequently related, but gastrointestinal allergy and migraine less so. The nature of genetic factors and mode of inheritance is unknown. In a large study of 7000 twin pairs from Sweden, Edford-Lubs[11] found that allergic diseases had an environmental and hereditary component and demonstrated that the environmental factor was of much greater importance than had been suggested by any previous study. This was shown by the low concordance rates in the monozygotic twin group (25.3 per cent) and the dizygotic group (16.1 per cent). The author found that the prevalent rate of allergic disease (asthma, hay fever, or eczema) in the general population was 18 per cent and 40 per cent low penetrance. A distinction between recessive, dominant and multigenic inheritance could not be established. Also, most allergic children were born in families in which neither parent was allergic (67 per cent) or only one parent (30 per cent). The risk of having an affected child from these matings varied from 0.5 to 0.29. In 3 per cent of matings in which both parents were allergic the risk rose to only 0.3. These observations are at variance with other reports[78]. In a study of 676 asthmatic children[85] it was found that there was positive family history of asthma in 59 per

cent, hay fever in 29 per cent, atopic dermatitis in 18 per cent, urticaria in 1 per cent and food allergy in a further 19 per cent.

Allergy

Any material capable of mediating an immunological reaction can initiate a hypersensitivity state. In general, the antigens (allergens) that are of importance in childhood asthma are protein extracts of some form. The common allergens are inhalants, pollens, moulds, bacteria and foods. Atopic eczema occurs at least seven times more commonly in babies fed on whole cows' milk than in breast fed babies. Moreover, Ratner and Silverman[12] reported 59 per cent of children with eczema who subsequently developed asthma and allergic rhinitis. About 5 per cent of children with hay fever will eventually develop asthma. In a seven year follow-up study of 903 college students, Hagy and Settipane[55] found that 6 per cent who developed asthma had previously had allergic rhinitis.

Allergies to food such as cows' milk and egg proteins, related as they are to the respiratory tract, are of importance in the very young child; indeed, cows' milk protein allergy may be the cause of recurrent iron deficiency anaemia, wheezy bronchitis and recurrent otitis media in later childhood[13].

Sensitivity to house dust is relatively common in children, which is to be expected if it is remembered that house dust contains much organic matter, pollens, skin scales, moulds and insects, some of which have been fully identified. The house dust mite (*Dermatophagoides pteronyssinus* and *D farinae*) is a common sensitiser in children and is associated with humid and damp conditions[14,39], and not uncommonly responsible for the nocturnal episodes of wheezing[82].

Other common allergens are cat, dog and horse dander and, occasionally, aspirin (an idiosyncrasy rather than a hypersensitivity state[40,42]) and antibiotics such as penicillin.

Any child with one form of atopic disease, whether it be hay fever, dermatitis, rhinitis or asthma, will often subsequently develop another atopic disorder from eczema to asthma. Symptoms in the particular susceptible organ can be easily reproduced by very small doses of histamine in the allergic child, but not in normal children[48]. Psychic stimuli can produce similar responses at times. It appears, therefore, that certain children have an inborn predilection to develop atopic diseases, but some as yet unproven environmental factors are also responsible for the acquisition of an atopic state.

When a child becomes sensitised to an allergen (first or initial expos-

ure) a second or further exposure to such an allergen can lead to tissue-damaging reaction. These reactions occur immediately following exposure and are due to the release of pharmacologically active substances such as histamine, slow reacting substance of anaphylaxis, heparin, platelet activity factor causing oedema, vasodilation and contraction of smooth muscles. Gell, Coombs and Lachmann[79] have described a useful classification of allergic reactions based on the immunological changes observed in the tissues following antigen exposure.

Type I. Immediate hypersensitivity, anaphylactic. Allergens react with reaginic antibody (IgE) on the surface of mast cells or basophils and cause release of vasoactive amines. The reactions occur within minutes of exposure to the allergen. *Example*: Asthma.

Type II. Cytotoxic. Allergens or haptens associated with cell surfaces react with circulating antibodies. Complement, mononuclear cells etc. are involved in tissue damage. The reactions vary in onset. *Example*: Autoimmune haemolytic anaemia.

Type III. Arthus, antigen–antibody complexes. Soluble complexes formed by combining with precipitating antibodies. C_3 component of complement and neutrophil polymorphs involved. The reactions take a few hours to develop. *Examples*: Serum sickness, ? asthma.

Type IV. Delayed, cell mediated. The reactions are mediated by sensitised lymphocytes which combine with allergens. Lymphokines are released causing inflammatory changes and infiltration of the side by lymphocytes and macrophages. The reaction takes 24 hours or longer to develop. *Example*: Contact dermatitis.

Infections

The onset of asthma is often associated with an acute respiratory tract infection. Pearson[15] studied the natural course of asthma in 625 patients. Of these, 393 attributed their first attack to a specific cause. Over 100 stated that it followed an attack of acute bronchitis, 12 after measles, 15 after whooping cough, and 54 after pneumonia or other respiratory infections. The significance of these figures is difficult to interpret because it is possible that such infections only brought out an already existing tendency to develop asthma. A number of authors have tried to demonstrate a relationship between infections and exacerbations of asthma. Viruses such as parainfluenza and respiratory syncytial virus have been reported to cause more exacerbations of asthma than other viruses[41], and 50 per cent of children eventually developed asthma[16] following an attack of respiratory syncytial virus bronchiolitis.

It is not known whether the allergic child gets more viral infections than the non-allergic. Freeman and Todd[35] showed that wheezing occurred more frequently during respiratory viral illness in the allergic child than in the non-allergic. Berkovich, Millian and Snyder[17] demonstrated that a third of their children had virus infections at the time of an attack of asthma, while others:[36,38] found concurrent viral infections during exacerbations of asthma, but not all such infections precipitated attacks. Minor and colleagues[37], in a longitudinal study of 16 asthmatic children and their siblings, found that over a six month period, children with asthma experienced more viral respiratory infections than their non-asthmatic siblings and when viral infections of an identical nature occurred both in the asthmatic child and his sibling, they took slightly longer to clear up in the asthmatic child. The viruses involved were usually rhinoviruses. Gregg and colleagues[18], in a five year study of respiratory viral infections of children in a London general practice, demonstrated that rhinoviruses were isolated more frequently than any other agent in episodes of asthma in children. He suggested that these viruses were often provocative agents in many children but other host factors were also important. He also found that rhinoviruses and enteroviruses had greater tendency to cause wheezing than other viruses, and that rhinoviruses predominated much more commonly in the child over the age of eight years. There are indications that a child who has asthma, bronchitis or pneumonia during the first five years of life is more likely to have respiratory symptoms at the age of 14 years[80,81] and possibly as an adult. If these studies are confirmed then implications for prevention are far reaching.

In summary, the relationship of infection to the development of asthma can either be explained as a hypersensitivity reaction to the infecting agent or its products, or alternatively, it is possible that infection is a non-specific precipitating agent of an extrinsic allergic cause of asthma.

Psychosomatic factors.

Graham and colleagues[2] found that children with asthma were often more emotionally disturbed and more intelligent than controls, but educational attainments were not greater and the psychiatric disturbance was as common as in any other child with a handicap. Asthma in children is not associated with any specific personality disorder[19,2.]. Some attacks of asthma are precipitated by psychological factors[58,60] but it is very rare to find asthma caused exclusively by psychological factors.

Mitchell and Dawson[20], in a detailed psychological and psychiatric assessment of 121 asthmatic children, found only two with a psychiatric disorder.

There is convincing evidence that although psychosomatic factors can be important in triggering some attacks, there must first exist a somatic substrate for bronchial hyper-reactivity or hyper-irritability before psychosomatic mechanisms can operate[21,22].

Some children with recurrent severe asthma do appear to have behaviour and emotional disturbances[63,64]. Whether these features are specific for such asthmatic children remains undetermined. Certainly, one cannot identify any definite fault in the mother-child relationship[65]. Mothers of children with asthma do not differ from mothers of children with any other chronic condition[2]. In an Australian investigation[64], it was suggested that mothers of children with very severe asthma were more anxious and put more restrictions on their children (overprotectiveness) than mothers of a control group. An investigation into the role between clinical, physiological and psychological factors in 63 children attending a hospital clinic suggested that effective approach and treatment of asthma at an early stage might prevent the subsequent development of emotional problems[84]. But such findings are surely to be expected from a disease that is life-threatening.

Nevertheless, personal interrelationships within a family setting must have an influence on the course of the child's asthma and there can be little doubt that many attacks are provoked by tensions within the household. In one study[2], emotional states (fear, excitement, anger) were responsible for about 35 per cent of attacks of asthma. Other factors that can trigger attacks may be associated with laughing, crying, coughing or hyperventilation. The exact way such factors operate in producing bronchospasm remains uncertain[66].

It is also to be remembered that the majority of published research deals with a very selective group, usually in or attending hospital, *i.e* with severe asthma; hence any conclusions reached would apply only to such a group and not to the considerably larger proportion of asthmatic children living in a community.

Educational and Social Characteristics

A number of studies have shown that the incidence of asthma in children increases with parental income[2,45]. Mitchell and Dawson[20], on the other hand, found an excess of severe asthma in children of semi- and unskilled manual workers (social classes IV and V) and these children tended to come from families of four or more children. Pinkerton and

Weaver[52], in an analysis of 206 children with asthma, found sociopathological factors in 44 per cent of those who were resident in special schools but only in 15 per cent admitted to a children's hospital. In two studies[2,22], the intelligence quotient of asthmatic children was higher than that of control groups. In an Australian study[63,64] the socioeconomic conditions of the family were found not to be significantly different in children with asthma compared with a control group. However, a study of 1190 children (6 to 11 years of age) in the United States[59] failed to show any difference between allergic and other children in regard to arithmetic, reading and intelligence tests. The allergic children were less emotionally responsive than the control groups and were found to repress conflict, which produced emotions such as aggression in a significantly higher proportion of cases.

It is possible, yet unproven, that children with asthma are more intelligent than children in the general population, but they do not appear to achieve noticeably better than their fellows in school work and life careers.

Exercise

Most children with asthma have attacks shortly after physical exertion such as free running[50] or running on a treadmill[51]. Within 3 to 10 minutes of an 8 to 10 minute period of exercise, bronchoconstriction occurs. This can be evidenced by a pulmonary lung function testing, or a frank clinical attack requiring treatment may ensue. The bronchospasm disappears during the next thirty minutes or so. The nature of this bronchoconstriction is uncertain, but it does not appear to be related to mechanical irritation (cold air, dust), hyperventilation, metabolic acidosis or hypocapnia[43,44]. It may, however, be mediated by the involvement of the parasympathetic nervous system[50,71]. Children with atopic eczema alone do not show similar findings[68].

After a very short exercise of one or two minutes duration or early during a more prolonged exercise, the majority of asthmatic and normal children develop bronchodilation[50,51] which is most likely due to excessive sympathetic activity[67]. There is some evidence that during exercise predominantly large bronchi (greater than 2 mm diameter) become obstructed[69,70] but undoubtedly the small airways also become involved during severe exercise and are responsible for the 'air hunger' many children experience.

It has been observed that the majority of children with asthma will develop bronchoconstriction if they exceed a certain threshold of exertion, usually at a heart rate of 150 or so per minute[51,72].

The exercise test forms the basis of the Bronchial Lability Index for assessing asthma, devised by R S Jones[23], and is discussed further on pages 39 to 42.

Pollution and Climate

It is not clear whether pollution and the mobility of the population because of exposure to different climatic conditions have any role to play in the development of asthma. Ribon and colleagues[24], in a statistical analysis of asthma in children and its occurrence in relation to weather and air pollution, showed an increase in the percentage of visits and admissions of children to hospital and clinics during the autumn months. In Queensland, Australia, it was shown that not only in autumn was there a rise of admissions but also in the spring. The nature of the factors concerned was undetermined[61]. No significant relationship was found in the daily air pollution averages but there was a tendency for changes in temperature to be related to changes in the number of asthma consultations. Smoke and wind direction may act as non-specific irritating factors in provoking attacks[54]. Breathing cold air alone may induce bronchospasm, possibly through the efferent cholinergic pathways in the upper airways[62]. A study of the effects of humidity in 18 children in an air-conditioned chamber failed to show any definite exacerbations[73]. A six-month study of 105 children with asthma living in the south of France demonstrated that extremes of environmental temperatures had bronchoconstrictive effects on the airways[74]. It would seem, therefore, that environmental factors may be important in exacerbation of asthma and very likely these factors operate together rather than alone.

Table 2.2 Mortality from asthma

Authors	Year	No.	Follow up (years)	Death rate %
Rackemann and Edwards[25]	1952	688	20	1
Barr and Logan[26]	1964	324	22	1
Buffum and Settipane[27]	1966	136	20	2·5
Leveque and colleagues[28]	1969	94	5	4
Vialatte and Paupe[29]	1971	231	5–14	0·45
Blair[83]	1979	237	20	1·2

Mortality

The mortality rate varies between 1 and 4 per cent, which is shown in Table 2.2. The number of deaths in England and Wales from asthma per 100000 children aged 5 to 14 is between 25 and 35 each year, excluding the years 1963 to 1966, when the annual number of deaths attributed to asthma increased[75]. Several reasons for this change in mortality have been discussed extensively elsewhere[30,46,47]. Since 1967 the death rate from asthma in Britain has declined to the pre-1960 years[75].

Prognosis

The knowledge of factors affecting prognosis remains incomplete. A review of the literature shows that two factors have been thought to be of prognostic significance, namely the age of onset and the relationship to allergy. It has been found that the majority of children develop asthma during the first two years of life and their prognosis is much worse than those children who develop asthma later in childhood[3,49]. The presence of atopic diseases such as eczema or hay fever signifies a poorer outlook[34]. Also, the more severe the symptoms in early childhood the more likely it is that asthma will continue into adulthood.

Table 2.3 Prognosis of childhood asthma

Authors	Year	Place	No.	Symptom free	Asthma % Improved	Unchanged
Rackemann & Edwards[25]	1952	Massachusetts	499	31	56	13
Ryssing & Fleusborg[31]	1963	Copenhagen	442	37	9	54
Aas[52]	1963	Oslo	174	44	17	39
Kraepelien[33]	1963	Stockholm	528	29	65	6
Leveque *et al*[28]	1969	Paris	94	31	43	22
Vialatte & Paupe[29]	1971	Paris	221	57	33	10
Barr & Logan[26]	1964	USA	336	52	No details	
Blair[53]	1979	London	237	28	24	48

Table 2.3 shows the long-term prospects for the asthmatic child; observations have been made for 5 to 20 years. Kraepelien[33,53] found that in a group of 528 asthmatic children the long-term outlook was less favourable than was generally claimed. Over a 13-year period of observations, 29 per cent of the individuals were symptom free, 70 per cent still had asthma but were considerably improved, 4·9 per cent remained