

# THE ALLERGIC CHILD

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ASTHMA is one of the commonest causes of chronic handicap in childhood, is responsible for a great deal of intercurrent illness in childhood and occasionally has a fatal outcome. It is pre-eminently the concern of the generalist, either general practitioner or general paediatrician – or more commonly both working together. The different views of childhood asthma taken by various specialists remind one of the tale of the blind men examining an elephant. One feels the trunk and exclaims that it is like a rope: another the leg and likens it to a tree: a third feels the ear and says it is like a mat: while the fourth meets the side of the elephant and thinks it is like a wall. All of them are partially right and yet none has any idea of the elephant as a whole: each argues from his own standpoint and is certain that the others are wrong. Thus the allergist sees asthma in terms of identification of the offending allergen and hyposensitization: the psychiatrist as a psychosomatic manifestation: the chest physician as a problem in respiratory function: and so on. Each may be convinced that the others treat asthma inadequately and yet none has a really balanced view of the child and his family. And yet such a global approach is of great importance in a condition which is likely to improve in the course of time whatever treatment is given (Rackemann and Edwards, 1952: Barr and Logan, 1964: Smith, 1971) and in which the potentialities for imposing secondary handicap and iatrogenic complications is immense. I make no excuse therefore for presenting a general paediatrician's view of asthma in childhood which is unlikely to satisfy any of the specialists.

## THE ATOPIC INFANT

The word allergy originally meant any alteration in tissue sensitivity but its meaning has become restricted to signify only a heightened sensitivity. Anyone may become allergic if the conditions for sensitization are met but certain individuals are unusually easily sensitized. Such people are said to have the atopic constitution, although the precise nature of their difference from their non-atopic fellows is poorly understood. The atopic constitution is inherited and when both parents have a strong personal and family history of atopic disorders, the likelihood of their having an affected child is high, although the precise risk cannot be calculated because the mode of inheritance is not known. In such circumstances it is reasonable to keep the baby under close observation and to consider whether any untoward symptoms might not be allergic in nature. While acute gastrointestinal allergy may be manifest by vomiting, diarrhoea and colic in early infancy, the first indication that the child is atopic is usually the appearance of eczema at the age of a few months. This affects mainly the face, pursues an intermittent course over the next year or so, and then clears up or changes to a flexural type of eczema. While atopic eczema can be controlled with topical

corticosteroid hormones, it may erupt and die down periodically throughout the patient's life, constituting an annoyance by its itching and its unpredictable appearance, and in severe cases a significant handicap. Eczema is readily influenced by anxiety and tension, tending to subside during periods of tranquillity and to reappear suddenly when there is emotional stress.

In the first year food substances are more important than inhalants as allergens and, if there is evidence of hypersensitivity to a food, it is wise to withhold it or introduce it only in very small quantities.

#### THE ATOPIC TODDLER

About the time that the child begins to walk independently, he may begin to experience the first episodes of respiratory allergy. Whenever his upper respiratory tract is infected, he develops obstructive wheezing which may take several days to clear up. At this stage it is not easy to distinguish respiratory allergy from the obstructive type of bronchitis or bronchiolitis commonly caused by the respiratory syncytial and other viruses. A strong family history of atopic disorders, a tendency to wheeze when no acute respiratory infection is present, frequent prolonged attacks or other manifestations of allergy such as infantile eczema, all suggest that we are dealing with an atopic child rather than a non-atopic child with obstructive bronchitis. However, the clinical picture may not become clear until some months or years later, when the child begins to have typical attacks of asthma without obvious precipitating cause.

Unless there are sound reasons for doing so, it is unwise to announce the diagnosis of asthma before this stage. It may generate much anxiety in parents to whom the word conjures up a vision of long-standing disability and this may be quite unfounded, for the child may not develop asthma subsequently, even if there have been suggestive pointers in the history. Once established, the course of asthma is very variable, ranging from slight short-lived attacks which soon cease to occur to severe intractable asthma of long duration, causing disruption of the child's life. When it is clear that the child has asthma, a full explanation of the implications should be made to the parents: this takes time and will usually require to be spread over more than one session. It must be impressed upon them that their child is different only in respect of his allergy and is in every other way a normal child. An analogy can be drawn with the child who has poor eyesight, and must wear glasses, but is perfectly healthy otherwise. They should understand that he has inherited the atopic constitution, that nothing can be done about this and that it may show itself in a number of different ways. Once they fully appreciate that atopy is a part of the child's make-up, they will more readily accept that there is no quick "cure" of asthma and will not be unduly disappointed if other atopic manifestations appear later.

It can then be explained that much can be done to relieve symptoms and that there is no need to consider him as inevitably handicapped or unable to lead a reasonably normal life. It should be especially emphasized that he should not be kept off school when he has slight wheezing, that he should not be allowed to use his asthma to dodge unpleasant but necessary duties or events and that he can be allowed to do anything reasonable which is within his capacity, provided that

undue fatigue is avoided. It is remarkable how one child with sensible parents can play games outside on a cold day, often wheezing audibly but determined to take part, whereas another with lesser symptoms will be in bed surrounded by medicines and over-solicitous attendants. Parents who allow the latter situation to develop live to regret it, because the household comes to revolve round the asthma, which dictates the whole pattern of family life.

Most parents after adequate explanation will accept the reasons why they should be unusually firm with their asthmatic child. At the same time they must show proper sympathy and understanding, and must be taught to recognize when the clinical condition of the child really warrants confinement to the house and suitable therapy.

#### THE MANAGEMENT OF THE ASTHMATIC CHILD

Given sensible, co-operative parents, more than half the battle against childhood asthma is won. In addition to parent counselling, the management of asthma implies environmental control, preventive measures and symptomatic relief.

#### *General Considerations*

I have no doubt from my own experience that substantial improvement can be effected in the condition of most asthmatic children if considerable time is devoted to the task. The beneficial effects tend to be in direct proportion to the time spent, but subject to the law of diminishing returns. I am therefore less certain that it is always justifiable to devote a great deal of time to the child with asthma, when medical manpower is limited and there are many other demands on professional skills. Moreover the large numbers of asthmatic children and the likelihood that most will improve and many ultimately recover must influence the amount of time that is spent. Such considerations go far to explain why asthma in childhood is not always optimally treated. Allergists and others can legitimately say that more could often be done but whether it should be done, to the inevitable detriment of other children when resources are limited, is another matter.

The long-term objectives of the physician treating a child with asthma should be to ensure that secondary handicap is not superimposed by faulty management – particularly parental over-protection – and to counter adverse effects on growth and development, for severe asthma can significantly restrict increase in height and weight (Dawson et al., 1969). The effect of the asthma on the lungs and chest wall (McNicol et al. 1970) should be watched closely and measures instituted if there is evidence of increasing damage. The amount of time lost from school and the extent to which social activities are limited must be kept under observation and action taken if the effect on school or social life becomes excessive. Beyond these basic principles, the benefit from treatment must be measured against the cost in time and money and the accompanying discomfort and inconvenience to the patient and his family. It is sometimes difficult to take the long view, especially for the family doctor faced with an acutely distressed child and parental expectations, but I am convinced that he must do so and must try to make the parents understand the reasons.

Recently at a dance my attention was caught by a tall, handsome young couple vigorously enjoying a reel. On enquiring who they were, I realised that I had looked

after both of them during very severe asthma in early childhood. I had spent many disturbed nights with the boy, whose father was a doctor, and had had great difficulty in persuading him not to resort to corticosteroids on such occasions. However, the parents had followed my advice and had been firm with their son and even a little harsh on occasion: as a result he had grown into a tall, healthy and pleasant-mannered young man who no longer suffered from asthma. The girl I had also seen on numerous occasions with severe attacks of asthma, and I recalled many long talks with her over-anxious parents, trying to persuade them to allow her to use her natural initiative and to do what she felt capable of despite her wheezing and breathlessness. My efforts had been successful, the parents increasingly adopted a sensible non-fussing approach to their daughter, and here she was at eighteen – a delightful attractive girl free from all but the slightest symptoms. These are only two striking examples out of many similar instances and I set them in my mind against those many other children who in their teens are no longer asthmatic but have serious personality disorders as the result of mishandling in childhood. I believe that excessive medication, over-scrupulous searching for causes and attempts at hyposensitization, and the imposition of unnecessary restrictions can be far more harmful to asthmatic children than the asthma itself. This is not of course to condemn therapy or to deny that there are some cases of very serious asthma which justify the most vigorous methods of treatment, but simply to urge that in most cases there is more virtue in watchful forbearance than in over-busy interference.

#### *Environmental control*

A stable supportive family home is the best environment for the asthmatic child, enabling him to live an equable life without the anxieties and stresses imposed by family friction, excessive parental expectations or sibling rivalries. Other sources of emotional tension outside his home, especially those relating to school, should be identified and removed or reduced as much as is feasible.

A child spends half his time in his bedroom and rendering this as free as possible from allergens goes a long way to improving the environment. House dust is an irritant and also strongly allergenic, usually containing a mixture of protein materials including the mite *Dermatophagoides pteronyssinus*; inspection of the bedroom may reveal many ways in which dust can be reduced – by removing dust-collecting carpets, bedding and toys, by substituting dust-repellent material for curtains and bedcovers, and by banning animal pets from the room. While it is seldom essential to get rid of a pet animal, it is on the whole wiser for atopic children not to keep animals, for their hair or dander is widely dispersed through the house and readily causes sensitization. It is not possible to rid a house completely of dust and extracting equipment of various kinds, apart from being expensive, may defeat its purpose by harbouring allergenic moulds. The house should be sparsely furnished and regularly dusted, the child being out of the vicinity when dusting takes place.

The search for allergens starts with a careful history, when any identifiable cause will usually become apparent or at least suspicion will be aroused. Skin testing can then be undertaken to confirm the suspicion. Random skin testing is seldom

useful and, even if some sensitivity is demonstrated, it does not follow that the protein concerned is causing the symptoms. If the history suggests an agent such as a particular food, animal or plant, and skin testing confirms the suspicion, it may be possible to remove the offending substance from the environment. Failing this, an attempt can be made to hyposensitize the child by a series of injections of the appropriate antigenic extract. If there is no strong lead from history and skin-testing, non-specific or multiple hyposensitization is unlikely to be beneficial.

#### *Other preventive measures*

The early treatment of respiratory infections with antibiotics may reduce the frequency of asthmatic attacks in young children, but the value of this is limited since so many infections are caused by viruses unresponsive to antibiotics. Simple breathing and postural exercises regularly carried out at home are of some help in improving posture and preventing thoracic deformity but occasional physiotherapy is of doubtful value and any benefit conferred does not usually justify complex or inconvenient arrangements to attend a clinic.

Antihistamine drugs are of little or no value in preventing or treating asthma. The introduction of disodium cromoglycate, on the other hand, constituted a real advance in the prevention of symptoms. Regular inhalation of the powder two or three times daily reduces both the number and the severity of attacks. The mode of action is not entirely clear but it appears to interfere with the mechanism of histamine release initiated by the antigen-antibody reaction. It is important that parents should realise that cromoglycate does not relieve symptoms but is a prophylactic, and should therefore be taken regularly rather than only when symptoms are present.

#### *Drug therapy*

The large number of bronchodilator drugs available makes it advisable to use only a few and become really familiar with their effects. Ephedrine is still a useful drug to start with and may control mild asthma for some time before more potent agents are needed. Thereafter orciprenaline, salbutamol or choline theophyllinate may be used to control wheezing. Aerosols in inhalers should be used with discretion if at all and pressurised inhalers are no longer advised since it seems certain that the recent increase in sudden deaths from asthma was due to the abuse of these. In severe attacks of asthma, adrenaline may be injected subcutaneously but it should be avoided if possible in young children because there is a risk of undesirable cardiac effects. Similarly, the inhalation of a mist containing isoprenaline may affect the heart: salbutamol has much less tendency to do so and is equally effective.

In general, it is unwise to embark on corticosteroid therapy, even in severe attacks of asthma, unless it is deemed absolutely necessary. Steroid dependence soon develops and the long-term nature of asthma increases the probability of eventual overdosage and dangerous side-effects such as osteoporosis or peptic ulceration. Moreover, the prolonged use of corticosteroid hormones results in growth arrest and possible ultimate dwarfing. The intention at the beginning may be to give only short courses at low dosage but the amount and frequency inevitably escalate in response to parental pressure. The risk may be less with ACTH

but here there is the additional risk of sensitization and the need to inject the hormone is a disadvantage in children. Synthetic ACTH (tetracosactrin) or inhaled beclamethasone may not have the same objections as the more familiar hormones, but it is still too early to assess their value fully.

#### *Status asthmaticus*

When an acute attack of asthma fails to respond to ordinary therapy and persists for many hours, status asthmaticus is said to exist. Aminophylline by intravenous injection may relieve symptoms but usually it will be necessary to use parenteral hormone therapy, e.g. intravenous hydrocortisone. The presence of pneumonia is often unsuspected in status asthmaticus and if there is any indication of infection the appropriate antibiotic should be given. Treatment with expectorants or nebulized mists is only marginally helpful in most cases and any benefit tends to be offset by the disadvantages.

Hypoxia is commonly present, even when there is no cyanosis, and the need for oxygen should be judged by the  $pO_2$  of arterialised capillary blood, the aim being to prevent it dropping below 60 mm. Hg. If there is increasing retention of carbon dioxide, mechanical ventilation should not be postponed too long, for it is more likely to be effective and less liable to cause harm if it is started early. Modern methods of intermittent positive pressure ventilation by the nasotracheal route avoid the need for tracheostomy with its attendant hazards (Tunstall et al., 1968).

#### RESEARCH

The importance of asthma as a cause of acute illness and chronic disability and the relative inefficacy of treatment indicate the urgent need to find a more effective means of prevention. This implies better understanding of the atopic constitution and the asthmatic process and research is therefore essential. Four main lines of investigation appear to offer promise – the epidemiology of asthma and the characteristics of the asthmatic child: the nature of atopy and its allergic and immunological mechanisms: the metabolism and effects of the active mediators released in asthma: and the ways in which pulmonary function is disturbed. A great deal of work has been and is being done in these and other aspects of asthma: here I shall consider mainly those areas in which my colleagues and I have made some contributions.

#### *Epidemiology of asthma*

Hospital admissions for asthma have increased greatly since the earlier years of this century (Sheldon, 1958: Palm et al., 1970). Recent studies of the prevalence of asthma in the child population have shown that it is even commoner than hospital statistics suggest. Thus in the United States, surveys in Michigan and Indiana have shown prevalence rates of 4 to 5 per cent (Broder et al., 1962: Arbeiter, 1967). From Australia, Williams and McNicol (1969) reported a rate of 3.7 per cent. In the United Kingdom, surveys in the Isle of Wight (Rutter et al., 1970) and in Birmingham (Smith et al., 1971) recorded rates of 2.3 per cent: the National Child Development Study of some 16,000 children in England, Wales and Scotland found a rate of 3.1 per cent by the age of seven years (Davie et al., 1972): while our survey in Aberdeen (Dawson et al., 1969) showed that 4.8 per cent

of schoolchildren aged 10 to 15 years had asthma. Although these differences may be due to real geographical variations as well as to different definitions and techniques of case-finding, all the studies clearly indicate that asthma is a common disorder of childhood. It is also a major cause of chronic disability, causing significant handicap in about 25 children per 1,000 of the related population, and heading the list of physically handicapping conditions (Younghusband et al., 1970).

Data from the Aberdeen survey show that boys are more frequently affected than girls – a result in agreement with other studies (Smith et al., 1971; Davie et al., 1972): that over 80 per cent of asthmatic children experience their first attack before the age of five years: and that asthmatic children as a group are more intelligent than their non-asthmatic peers, despite their more frequent absences from school (Mitchell and Dawson, 1973). This survey also showed that children with severe asthma tend to come from larger families in poorer social circumstances: the greater overall prevalence of asthma in Social Class I as compared with Social Class V reported by Davie et al (1972) was not found in Aberdeen.

#### *Allergic and immunological mechanisms*

One characteristic of atopic people which has been clearly demonstrated is that they form reaginic antibodies with unusual ease. These antibodies, which have been shown to consist mainly of immunoglobulin E (Ishizaka and Ishizaka, 1970), become attached to the surface of histamine-containing cells – tissue mast cells and basophilic leucocytes. When the specific antigen interacts with two molecules of antibody, an enzyme system in the cell is activated and chemical mediators are released from the intracellular granules. These cause the mucosal swelling, secretion of tenacious mucus and spasm of bronchial muscle which are responsible for the respiratory obstruction in asthma.

The enzyme pathways in the cell have not yet been fully elucidated but may be related to the cyclic adenosine monophosphate system (cyclic AMP). Indeed Szentivanyi (1968) has suggested that the basic inherited defect of the atopic individual is deficiency of the intracellular enzyme, adenylyl cyclase, with resultant malfunction of beta-adrenergic receptors in the bronchioles. When active mediators are released, adrenergic imbalance leads to contraction of bronchial muscle. While this theory is attractive and would explain the increased sensitivity of atopic people to bronchoconstrictors such as histamine, it cannot yet be accepted as proven.

One unanswered question about childhood asthma is how symptoms are precipitated by agents which are not allergens, such as emotional stress, cold and mechanical irritation. Some workers postulate that not all asthma in childhood is atopic and that there is a distinct type of psychogenic asthma with a different mechanism of action. While there is no conclusive proof one way or the other, the balance of evidence favours the view that all childhood asthma is mediated through the same pathway. When this has been facilitated by frequent antigen-antibody reaction, it becomes highly responsive to all sorts of stimuli, including a variety of psychological and physical agents, which can then trigger the release mechanism without the need for further participation of antigen. For all practical purposes, I believe that every child with asthma should be considered as having

the atopic constitution, i.e. that all childhood asthma is extrinsic in type, regardless of the fact that it is not always possible to identify the offending allergen or demonstrate an increase in reaginic antibodies (Wood and Oliver, 1972).

#### *Metabolism of active agents*

It has been known for many years that histamine is involved in the allergic process and in 1951 Schild and his colleagues proved that it participates in the production of human asthma. Evidence that asthmatic people are unusually sensitive to histamine, that levels of histamine in whole blood vary more in asthmatic than in non-asthmatic people, and that corticosteroid hormones both relieve asthmatic symptoms and cause profound changes in numbers of histamine-containing cells and the amount of histamine in body fluids (see Code et al., 1964: Porter and Mitchell, 1972), all suggested that the study of histamine metabolism would yield the answer to the riddle of asthma. From time to time major alterations in histamine metabolism in asthma have been reported but few have withstood closer scrutiny.

The report by Rose and his associates (1950) that there was a great outpouring of histamine in the urine in asthma stimulated many studies of urinary histamine but the finding was never confirmed (Code et al., 1964). Since only about 1 per cent of extrinsic histamine is excreted in the urine unchanged, only massive alterations in histamine metabolism would be demonstrable in this way. If considerable quantities of histamine were being released in the body in acute asthma, an increase in plasma levels might be expected, but no such increase was found by Porter and Mitchell (1970), who showed that, when very sensitive methods were used, the plasma level remained consistently below 1 ng. per ml.

The catabolic pathways of histamine were elucidated by Schayer and Cooper (1956), who showed that methylation was the principle pathway in man. Subsequently great interest was aroused by the work of Kerr (1964), who reported that end-products of methylation virtually disappeared from the urine in status asthmaticus, suggesting a block somewhere in the degradation process. However, our own recent work (Thom et al., 1973) has not substantiated these results, for we have shown that children with acute asthma methylate histamine efficiently and indeed excrete rather more methyl imidazole acetic acid than do control children.

One major difference in the handling of histamine by asthmatic people is in the histamine-binding capacity of plasma protein (histaminopexy), attributed to the presence of a gamma globulin named plasmapexin I (Laborde et al., 1959). Parrot and his colleagues (1964) showed that histaminopexy is greatly reduced in acute asthma and this has been confirmed in our laboratory (Porter and Smith, 1969), although the degree of reduction was not as great as that reported by the French workers.

There is clearly much still to be learned about the role of histamine in asthma but sufficient is known to indicate that it does play an important part and that there is some fundamental difference in respect of histamine which distinguishes atopic from non-atopic people. Whether this difference is due to abnormal pro-



duction, metabolism, or tissue response is not yet clear but the evidence suggests that more than one of these is involved.

In contrast with the vast amount of research into the role of histamine in allergy, work on slow-reacting substance (SRS-A) in man has been extremely scanty, and in consequence not much more is known now than when Brocklehurst (1960) and Chakravarty (1960) first studied it. This is due at least in part to the difficulty of working with a substance which is very unstable in the laboratory and correspondingly difficult to measure. It is known that SRS-A appears with histamine in response to the antigen-antibody reaction, that its action persists much longer than that of histamine and that it causes a sustained contraction of smooth muscle (Brocklehurst, 1960; Sheard et al., 1967; Ishizaka et al., 1970). It seems reasonable therefore to suppose that released histamine initiates the bronchial changes in acute asthma and that newly formed SRS-A maintains them thereafter (Brocklehurst, 1970). It is possible, however, that newly formed histamine may also play a continuing part (Kahlson and Rosengren, 1968). There is a small amount of evidence that kinins are actively involved in human asthma. Thus Abe and his colleagues (1967) showed that the circulating level of plasma kinins is significantly increased in most patients with severe asthma. Increased kinin-like activity has also been found in the nasal secretions of patients with allergic rhinitis (Dolovich et al., 1970). Whether other substances, such as 5-hydroxytryptamine, acetyl choline, or prostaglandins play any significant part in the genesis of asthma is still uncertain (Collier, 1970) and much more work is needed before their importance can be assessed.

#### *Pulmonary Function*

The practical value of pulmonary function tests in asthmatic children has been discussed recently by Weng and his associates (1969). They concluded that measurement of the expiratory flow rate using the Wright flowmeter is the most satisfactory way of assessing the child's response to therapy. Tests on asthmatic children have shown that the degree of impairment of respiratory function as measured by such parameters as forced expiratory volume in one second ( $FEV_1$ ), peak flow rate (PFR) and maximum expiratory flow volume (MEFV) is directly related to the severity of the asthmatic symptoms (Dawson et al., 1969; Hill et al., 1972). Whereas children with chronic asthma usually have normal pulmonary resistance during symptom-free periods, infants with recurring wheezing show a persistent increase in airways resistance unresponsive to sympathomimetic drugs (Phelan and Williams, 1969). While such studies of pulmonary function are unlikely to lead directly to new preventive methods, by clarifying the mechanisms of asthma and the response to drugs they can be expected to promote that deeper understanding of the disorder which is essential if the approach to prevention is to be soundly based.

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