

ASTHMA



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ASTHMA



Office of Health Economics

162 Regent Street London W1R 6DD

No. 57 in a series of papers on current health problems published by the Office of Health Economics. Copies are available at 35p. For previous papers see page 48.

© October 1976, Office of Health Economics.

Printed in England by White Crescent Press Ltd, Luton

ISSN 0473 8837 57

Office of Health Economics

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Asthma, a term derived from the Greek meaning to pant, was first clearly described by Aretaeus, a physician who practised in the second and third centuries of the Christian era. Many descriptions of the disorder appeared subsequently but they were often brief and inadequate and their value was limited still further by confused theories of causation and complicated methods of treatment (Major 1953). Traditionally much emphasis was placed upon the aetiological role of emotion although there were exceptions: Cardan, in 1552, hinted at the possible hazard of feather pillows for asthmatics and van Helmont (1577–1644) recorded cases that appeared to have been provoked by dust, the eating of fish and changes in the weather. The development of more sophisticated techniques of medical science during the nineteenth century led to a greater understanding of the respiratory system and in the early years of the present century Richet (1902) and von Pirquet (1906), by defining more precisely immunological reactions, started a more scientific approach based on laboratory and animal experiments.

Bronchial asthma is characterised by periodic attacks of breathlessness caused by obstruction of the airways which is variable in degree and largely reversible, either spontaneously or as a result of treatment. In common with several other well known conditions, such as epilepsy, asthma is not strictly a disease itself but a term used to describe a set of symptoms which result from the action of a number of incompletely understood mechanisms. The common factor is the hyperreactive nature of the airways which respond to a wide variety of chemical, physical and emotional stimuli.¹

The process of breathing consists of a muscular effort which enlarges the chest in all dimensions causing the lungs to fill with air. These muscles then relax and the expulsion of air depends largely on the elasticity of the lungs. In asthma contraction of bronchial smooth muscle constricts the airways, although not necessarily always at the same level, and the passive nature of normal 'breathing out' means that there is little the patient can do to assist the removal of air from the lungs. The effort of breathing in the presence of this physical restriction usually produces a wheeze of variable audibility which may be accompanied by an irritating cough.

1 A discussion of some of the factors which may provoke an asthmatic attack through either an allergic or non-allergic mechanism is presented in Appendices 1 and 2.

The classical asthmatic attack is relatively sudden in onset. However, there are considerable variations in the frequency, duration and severity of symptoms and this has important implications regarding the indiscriminate diagnostic labelling of people who experience breathing difficulties of this nature. Some individuals suffer 'attacks' once or twice a year, lasting for a very short period of time, whilst others are in a state of chronic respiratory distress and develop recurrent severe exacerbations which may persist for several weeks.

Similarly the extent and permanence of the changes inflicted on the respiratory system are extremely variable. During remission the lungs may be clinically normal in cases of mild and infrequent asthma. At the other extreme respiratory obstruction may be readily detected even when a patient superficially appears to be symptom free. In addition to bronchial smooth muscle contraction, pathological investigations of patients dying in *status asthmaticus* frequently provide evidence of diminished elasticity of the lungs, swelling of the mucous membrane and excessive production of mucus. The significance of the latter two features in mild asthma varies considerably between patients.

This paper examines the nature and prevalence of bronchial asthma, at least in so far as it is possible to ascertain the latter given the lack of a generally accepted definition of the complaint and the problems of diagnosis at the extremes of age. It discusses the level of asthma mortality – which is low in relation to the overall morbidity generated by the condition – and the sudden, medicine-related increase in the number of deaths experienced during the 1960s. Consideration is also given to the recent advances in the treatment of asthmatic symptoms and the suppression of allergic reactions. Finally an attempt is made to calculate the costs of asthma in terms of both the expenditure incurred by the National Health Service and the social burdens imposed by the disorder.

The occurrence of asthma

The Second National Survey of Morbidity in General Practice indicated that approximately 500,000 individuals in England and Wales consulted a doctor at least once for asthma in 1970-71 (Figure 1). This compares with a figure of 380,000 suggested by the First National Study undertaken in 1955. Although the problems of defining the condition must be taken into account this increase can probably be explained by improvements in reporting and identification and by an increased willingness on the part of patients to visit their doctor now that effective therapy on prescription is available. There is little evidence to suggest that the incidence of asthma has increased over time.

The number of individuals treated in hospital (discharges and deaths) provides an alternative indication of the extent of asthma.² In 1972, the Hospital Inpatient Enquiry estimated that 33,400 cases were seen in hospital compared to 18,200 in 1958 although it should be noted that these estimates include readmissions and so the true number of individuals receiving hospital care will be somewhat smaller.³ Part of the explanation for this increase may be found in the growing awareness of the lethal potential of severe asthma attacks. However, a fully reliable interpretation of this trend would require knowledge in such areas as the severity of symptoms at the time of admission and the proportions of GP and self-referrals.

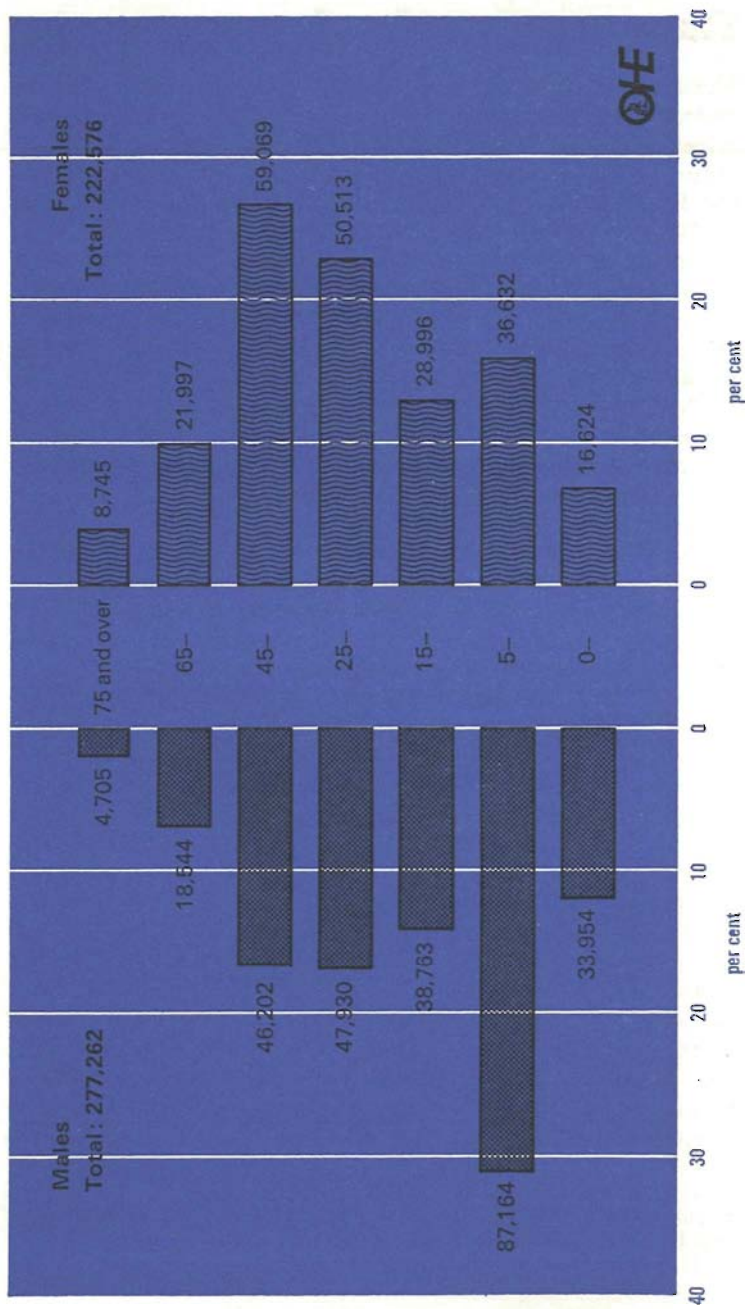
An age and sex breakdown of those receiving hospital inpatient treatment in 1972 (Table 1) shows that the ratio of 1.7 male patients to one female patient in the 0 to 14 age group is reversed in old age (65 years and older). This particular characteristic of asthma has also been identified in a number of community prevalence surveys.

The preceding statistics can be reconciled quite readily with the frequently quoted figure of about one million asthmatics in Britain. The latter includes many people who do not consider it necessary to consult a doctor because they experience mild asthmatic symptoms only infrequently. It also comprises those who may be classified under some other related diagnosis. Estimates of the numbers of people affected by asthma would be raised still further by taking into account those individuals who

² Hospitalised cases represent, of course, the more severe extremes of the condition and variations in the numbers seen in hospital over a period of time may be partly explained by changes in inpatient admission policies.

³ It has been estimated that at any one point in time approximately 15 per cent of hospital cases may be accounted for by readmitted patients (Anderson 1976).

Figure 1 *Number of individuals consulting (at least once) for asthma, 1970-71, England and Wales, by sex and age group*



Source: OPCS, 1974

Table 1 *Estimated total discharges and deaths of patients with asthma by age and sex, England and Wales, 1972*

<i>Age Group</i>	<i>0-4</i>	<i>5-14</i>	<i>15-19</i>	<i>20-24</i>	<i>25-34</i>	<i>35-44</i>	<i>45-64</i>	<i>65-74</i>	<i>75+</i>	<i>Total</i>
Males	2,824	4,241	526	591	1,090	1,159	3,887	1,213	430	15,961
Females	1,460	2,631	945	1,342	1,525	1,847	5,025	1,836	827	17,438
Total	4,284	6,872	1,471	1,933	2,615	3,006	8,912	3,049	1,257	33,399

Source Hospital Inpatient Enquiry, 1972

have experienced asthmatic symptoms at some stage in their lives but who no longer appear to be susceptible.

The availability of data on the incidence of bronchial asthma has been severely limited by the problems involved in defining and determining the date of onset of the condition. By contrast, however, numerous studies of prevalence⁴ have been undertaken but have produced widely divergent findings. Discrepancies have stemmed primarily from the use of varying definitions of the condition: some workers, for example, consider that asthma and wheezing bronchitis are unrelated disorders whilst others believe the latter to be a variant of the former. There has also been very little uniformity in sample selection, methods of examination, assessment or follow up and many studies have relied heavily on the subjective recall of patients and relatives as a source of information. Furthermore, the plethora of terms used to describe apparently different clinical entities (extrinsic, intrinsic, infective and psychogenic) has tended to confuse rather than clarify perception of the disorder (McNicol and Williams 1973). Discrepancies in survey findings can frequently be explained, therefore, in terms of varying methods of study rather than in genuine population differences.

Asthma in children

The selection of surveys of childhood asthma shown in Table 2 indicates the wide range of prevalence figures that has been established. But there has been more agreement in three particular areas. First, the majority of children develop symptoms before the age of five years (Gordis 1973). Second, significantly more boys than girls experience symptoms during early childhood but this difference disappears towards adolescence. A satisfactory explanation for this observation has yet to be found.⁵ Finally, many children lose their 'asthma' as they get older. This is probably attributable, in part at least, to larger airways which reduce the significance of obstructions.

An extensive survey of asthma and wheezy bronchitis (Williams and McNicol 1969) amongst 7-year-old Melbourne school-children (followed-up until the age of 10 years) identified a very broad spectrum of the condition. Children experiencing frequent

4 Unfortunately it is not always clear whether the studies are dealing with prevalence on a specific date, during a certain period or with prevalence of history of asthma.

5 It has been suggested, for example, that asthma in young girls may be much milder and may, therefore, go unrecorded. Alternatively, atopy among females may assume a different form than asthma. An explanation in terms of hormonal differences does not appear to be plausible.

Table 2 *Surveys of childhood asthma*

<i>Authors and year of report</i>	<i>Population investigated</i>	<i>Prevalence of asthma</i>
1 Kraepelin 1954*	Stockholm school children aged between 7 and 14	1.4 per cent
2 Peltonen <i>et al</i> 1955*	Children in a rural and urban community in Western Finland	0.85 per cent
3 Frandsen 1958*	Copenhagen schoolchildren aged between 6 and 17	0.8 per cent
4 Wilson 1958	Oxford school children	1.63 per cent Boy/Girl ratio = 2:1
5 Morrison Smith 1961	Birmingham school children aged 5-6, 10-11 and 13-15	Overall prevalence 1.76 per cent Boys: 2.31 per cent Girls: 1.17 per cent
6 Broder 1962*	Tecumseh (Michigan) children aged 6-19	11.7 per cent
7 Gibson 1966*	Primary school children in Tasmania	7.9 per cent
8 Arbeiter 1967*	Munster (Indiana) school children aged 5-15	4.9 per cent
9 Graham <i>et al</i> 1967	9, 10 and 11 year olds living on the Isle of Wight	2.3 per cent
10 Dawson <i>et al</i> 1969	Children attending primary schools in 1962 and still resident in Aberdeen in 1964	4.8 per cent Boy/Girl ratio = 2.2:1
11 Nathanson <i>et al</i> 1970	3,079 white children, aged 6-11 in the State of Maryland	Overall prevalence 7.1 per cent Boys: 8.6 per cent Girls: 5.5 per cent
12 Burr <i>et al</i> 1974	Catchment area of several schools in Cardiff area. Children with 12th birthday occurring between September 1972 and August 1973	Overall prevalence 4.2 per cent Boys: 5.6 per cent Girls: 2.7 per cent

Note For detailed reference of those investigations marked * see Gordis 1973.

Table 3 Social class distribution of asthma

Social Group	Survey 1 Percentage of sample in each social group		Survey 2 Prevalence of asthma by social group (%)		Survey 3 Percentage of sample in each social group by severity of asthma				
	Controls (%)	Asthmatics (%)	Boys	Girls	Mild	Moderate	Severe	Total	Population
I and II	15.7	39.7	6.9	3.6	40	18	10	26	31
III Non-manual	15.7	13.7	4.9	2.5	34	55	40	44	39
III Manual	43.6	35.6			26	27	50	30	30
IV and V	23.0	10.9	3.8	1.8					

Survey 1 Source Graham et al 1967

Survey 2 Source Hamman et al 1975

Survey 3 Source Dawson et al 1969

episodes of asthma from early life were found to have a prevalence of 3.7 per cent whereas those who had not had more than five episodes of wheezing and none after the age of 8 years had a prevalence of 7.7 per cent. The same children were then studied until the age of 14 years (McNicol and Williams 1973) and the following observations were made: persistent asthma usually begins before 3 years of age whereas mild asthma has a later onset and frequently disappears before 10 years; this latter group embraces three-quarters of children with the condition; the ratio of boys to girls increases as the asthma becomes more severe.

A survey of asthma amongst Kent schoolchildren aged 5-14 years found a prevalence rate of 3.8 per cent and a two-fold excess of boys - facts which correlate well with other studies undertaken in Britain (Hamman *et al* 1975). The association between asthma and certain other conditions was also examined. Thirty per cent of children who had asthma were found to have had eczema compared to only 3.7 per cent of children without a history of the former disorder. The occurrence of asthma and bronchitis together in the same patient was common but there was no evidence that either condition predisposed individuals to the subsequent development of the other.

Discrepancies between urban and rural occurrence of asthma were not found even though several American studies have considered industrial air pollution to be an important factor. Hamman and his colleagues suggest that either environmental causes are of little importance in relation to prevalence or that urban factors (pollution) and rural factors (pollen, fungus) balance each other out.

Clinical impressions that asthma has a relatively high prevalence amongst the upper social classes have been supported by a number of surveys but the reasons for these findings, which have to be interpreted with caution because of possible sample bias and the mobility between social groups over time, are still not clear (Table 3). It has been hypothesised that the explanation might lie in an increased exposure to important allergens resulting from the more varied diets and greater geographic mobility of social groups I and II. Nathanson *et al* (1970) suggested that stress and expectations in these groups may have some significance. The occurrence of the house dust mite and social class variations in the reporting of illness have also been considered. The picture is further confused, however, by contradictory observations such as the excess of severely asthmatic children found among the semi-skilled and unskilled manual classes in Aberdeen (Dawson *et al* 1969).

Asthma in adults

Community prevalence surveys of asthma among adults are very much fewer in number than childhood investigations but are subject to similar methodological limitations. However, information has been obtained from studies carried out in a number of general practices although the location and social characteristics of the latter may influence the results to some degree.

A prevalence of 1.8 per cent was observed in a semi-rural Surrey practice (Manners 1974). Although relatively small numbers were involved the male/female ratio over the age range 0-19 was found to be 1.6:1 which fell to 1:1 between the ages of 20 and 59 years. After that females dominate and it is noted that women carry the classic features of asthma into old age much more than men. A past or present history of both hay fever and chronic perennial rhinitis was recorded in about one third of asthmatics, the former alone in 26 per cent and the latter alone in 14 per cent. Results similar to these were obtained from an industrial practice (Hamilton and Bendkowski 1954) which had an asthma prevalence rate of 1.7 per cent.

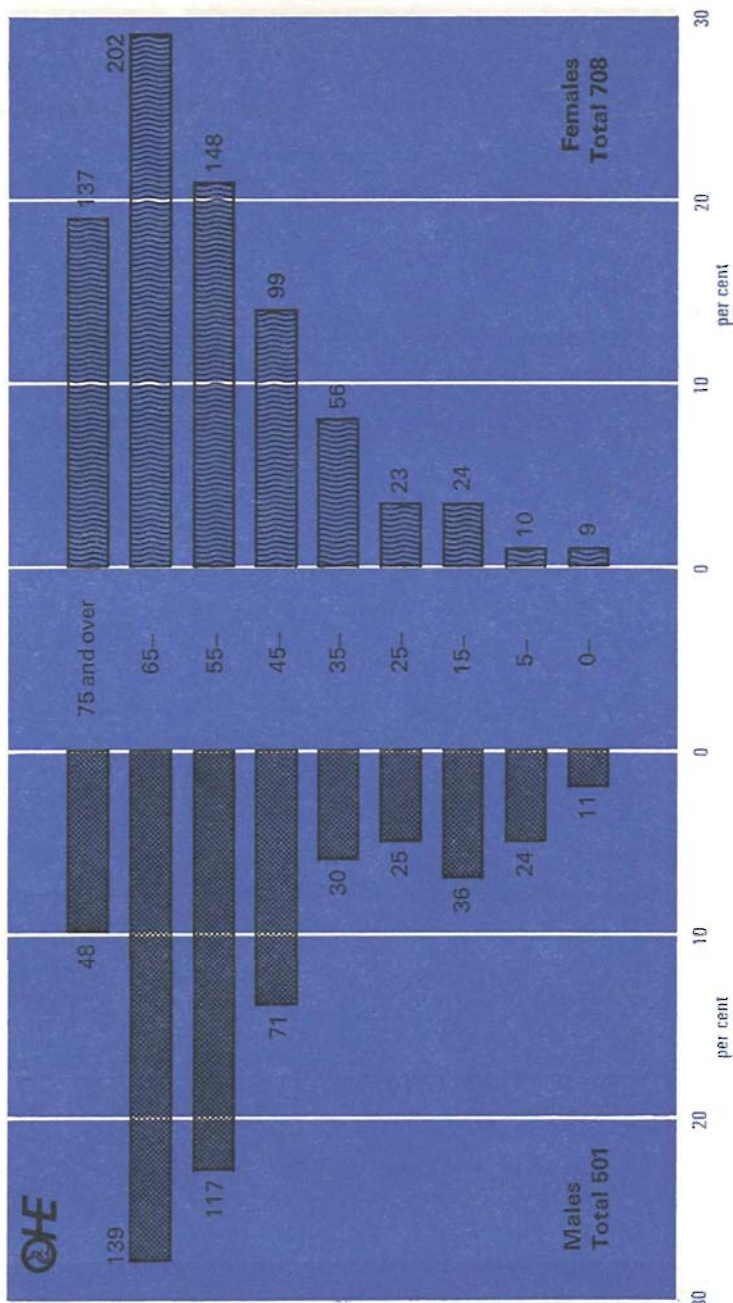
A survey in a south London practice showed an incidence rate of 2.5 per cent over a 15-year period and an annual prevalence rate of 1.2 per cent, implying that, in any one year, not all asthmatics experience troubles which are considered to require the attention of a doctor (Fry 1965). The study also found that there was a relative preponderance of asthmatics in social classes 1 and 11 and that only one sufferer in 10 developed the onset of symptoms after the age of 40 years.

Mortality

Against the high prevalence of asthma, the mortality associated with the condition is relatively low and exhibits few distinguishing characteristics. Thus in 1973 asthma accounted for 0.2 per cent of all deaths in England and Wales, claiming 501 male and 708 female lives (Figure 2). This is equivalent to crude rates of 21 and 28 per million population respectively. More than 65 per cent of these deaths occurred after the age of 55 years. The statistics also show that variations in mortality between types of location (Table 4) or by season⁶ (Figure 3) are negligible, although it is

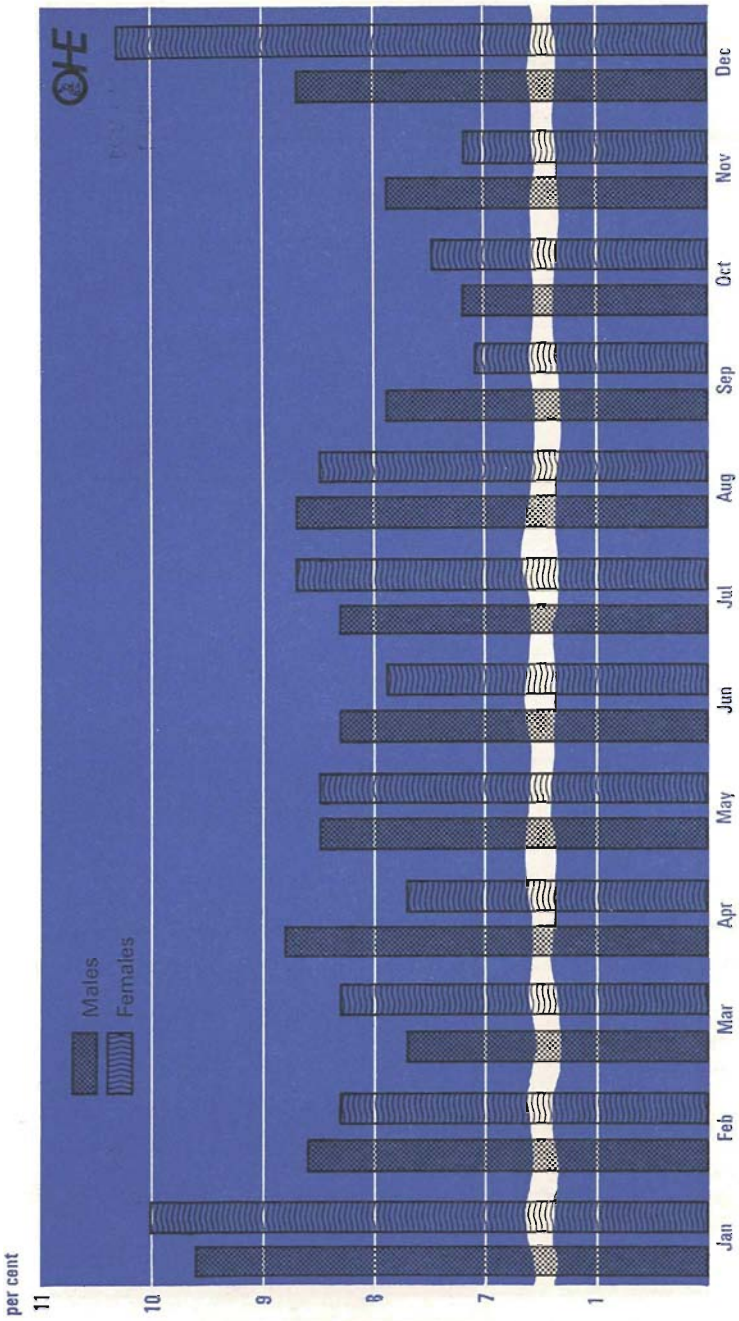
⁶ It is worth noting that although overall mortality appears to be at its lowest level during autumn a number of studies have indicated that morbidity is at a peak at this time of the year. The reasons for the latter observation are not clear - it may, for example, be related to an increasing number of respiratory infections during this season or to psychological factors associated with the beginning of a new school year (Gordis 1973).

Figure 2 Deaths attributable to asthma, 1973, England and Wales, by sex and age group



Source Registrar General's Statistical Review of England and Wales, Part 1, Medical Tables, 1973

Figure 3 Mortality from asthma: percentage of total male and female deaths in each month of the year, based on the average number of monthly deaths over the period 1968-73, England and Wales



Source Registrar General, Medical Tables, various years

Table 4 *Asthma mortality by location, England and Wales, 1973*

<i>Location</i>	<i>Males</i>		<i>Females</i>	
	<i>No of deaths</i>	<i>Rate per million pop</i>	<i>No of deaths</i>	<i>Rate per million pop</i>
Conurbations	180	24	207	25
Urban areas outside conurbations with population of 100,000 and over	66	21	108	32
Urban areas with population 50,000-100,000	52	22	64	25
Urban areas with population less than 50,000	93	17	186	32
Rural areas	109	20	138	25
Total	500	21	703	28

Source Registrar General, Medical Tables, 1973

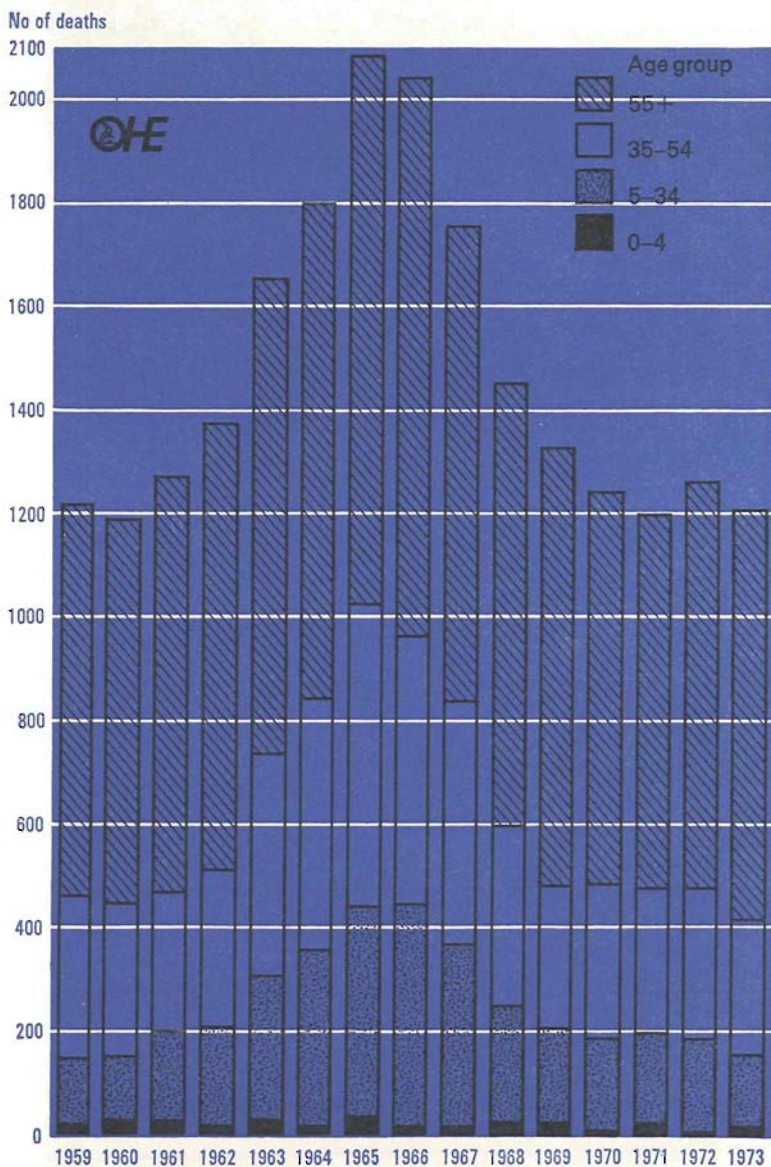
possible that more distinct patterns may be discerned in an analysis by different age groups.

With the exception of what has been termed the epidemic of the early and mid-1960s the mortality attributable to asthma has probably remained fairly constant for nearly a century (Inman 1973). However, trends over time have to be interpreted with caution because the condition has undergone several classification changes in the last two decades. A major revision in 1958, for example, resulted in the exclusion of the diagnosis 'bronchitis with asthma' and this produced an apparent reduction in the total number of recorded asthma deaths and eliminated the excess mortality among males. Revisions such as these reflect, in part, changes in the clinical concept of the disorder and further re-classifications may be expected as diagnostic precision and knowledge of causation improve.

The 1960s

Between 1961 and 1967 England and Wales experienced a sudden increase in the number of asthma fatalities (Figure 4). It was most marked among those aged between 5 and 34 years and by 1966 the condition accounted for 3.4 per cent of all deaths in this age group, contrasting with 1 per cent in 1959 and 1960. More specifically, those aged between 10 and 14 years were the most affected: by 1966 there had been a seven-fold increase in

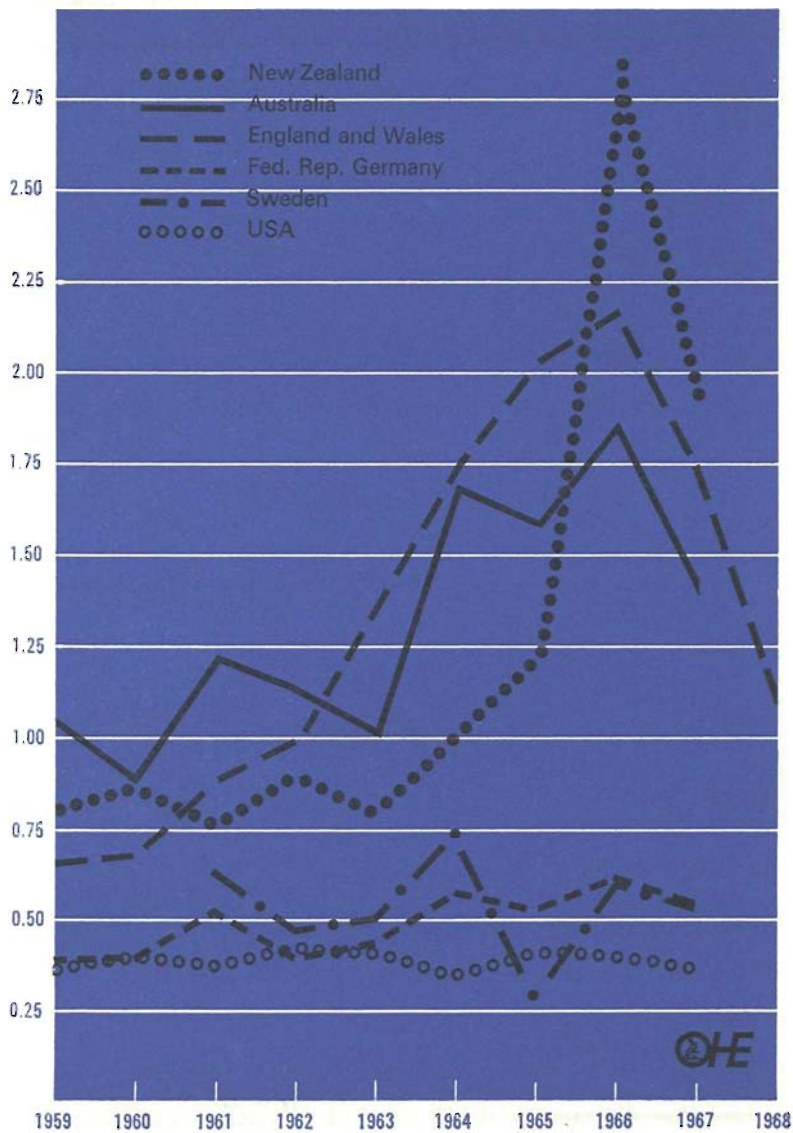
Figure 4 Mortality from asthma, by age group, England and Wales, 1959-73



Source Registrar General, Medical Tables, various years

Figure 5 Mortality from asthma at ages 5 to 34 years in selected countries, 1959-68

Death rate per 100,000 persons



Source Fraser and Doll, 1971

mortality and asthma had become the fourth most common cause of death in this age group. Similar events were experienced in only a few other countries, notably New Zealand⁷ (Figure 5).

It has been estimated that between 1961 and 1967 there was, at all ages, a total of more than 3,500 deaths from asthma in excess of the number that would have been expected on the basis of the experience of the two 'pre-epidemic' years 1959 and 1960 (Inman and Adelstein 1969). Investigations showed that a high proportion of the fatalities had not been anticipated.⁸ Speizer *et al* (1968), for example, found that death was sudden and unexpected in 81 per cent of a sample of patients aged 5 to 34 years dying between October 1966 and March 1967. In 77 per cent of these cases death occurred outside hospital.

The search for the explanation of this phenomenon identified a correlated growth in the use of pressurised aerosol bronchodilators (Figure 6) which became increasingly popular with the recognition of their effectiveness in the relief of asthmatic symptoms.⁹ It is estimated that a total of 11 million aerosol cannisters were sold in England and Wales between 1961 and 1967 and of these 87 per cent were products containing the bronchodilator drug isoprenaline which is non-selective between the beta receptors in the airways and those in the heart (Inman and Adelstein 1969).

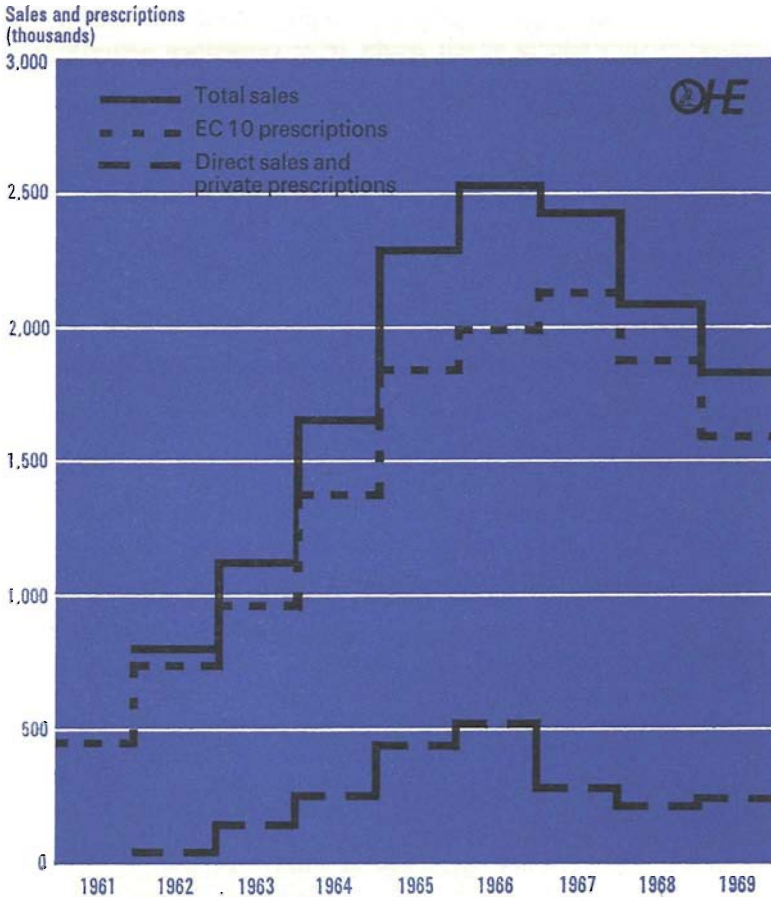
The first published suggestion that pressurised aerosols might be dangerous appeared in the correspondence section of the *Lancet* in 1965 (Greenberg). Following the publication of further letters in the medical journals, the interest generated in the lay press and the distribution by the Committee on Safety of Drugs (now Medicines) in 1967 of a warning letter to all practitioners there was a decrease in mortality. A decline also occurred in the sales of aerosols although this was not as pronounced, proportionately, as the fall in the number of deaths. Indeed, when the latter had reached near-normal levels, aerosol sales were still at their 1964 level, a year in which mortality was three times greater than expected.

7 Incomplete knowledge of aerosol sales and international variations in diagnostic practice (which influences both the type and efficacy of medications used) have made it difficult to explain satisfactorily the spectrum of events experienced by different countries.

8 The principal danger to life in severe asthma is plugging of the bronchioles with mucus and exudate. This state takes time to develop and may reach an advanced stage without producing remarkable symptoms. Thereafter, even a small increase in occlusion of the airways can prove rapidly fatal, hence the unexpectedness of many of the deaths.

9 Circumstantial evidence also appeared to support the implied association in that a number of individuals were found dead with empty aerosol containers near at hand.

Figure 6 *Estimated number of aerosol canisters distributed in England and Wales, 1961-69 (thousands)*



Source DHSS, 1973

Note The above data refer to sales of isoprenaline, orciprenaline, isoetharine, and adrenaline.

Possible explanations

Read (1968) and Gandevia (1968) postulated that spontaneous changes in the natural history of asthma may have been responsible for the raised level of mortality. However, this would involve unrealistically accepting as coincidences, first, the relationship between the increased fatalities and the growth in the use of

aerosol bronchodilators, and second, the association between the reversal of the trend and the publicity about the potential hazards of this form of medication.

There is no evidence of changes in diagnostic habits or death certification procedures which might have caused an artificial increase in mortality (Speizer *et al* 1968a). Many hypothetical explanations have therefore been proposed, but it is often difficult to establish their true significance because of the inability to test them in a meaningful way.

Much attention has focused on the possibility that the beta adrenergic stimulant drugs (principally isoprenaline) contained in the aerosols may have caused the development of fatal cardiac arrhythmias when acting in the presence of hypoxia. In support of this hypothesis it has been claimed that countries which experienced epidemics were mainly those in which strong or 'forte' preparations of isoprenaline were sold (Stolley 1972). But this correlation is not perfect and Inman and Adelstein (1969) failed to demonstrate any selective effect of publications or warnings on the sales of strong preparations relative to those of normal strength. Indeed, the explanation as a whole is unsatisfactory for a number of reasons. First, Speizer *et al* (1968) observed that nearly all patients coming to autopsy (97 per cent) showed changes in the lungs consistent with severe asthma. Second, Paterson *et al* (1968) demonstrated that chronic heavy usage of those drugs often results in resistance to their cardiac stimulating effects. Finally, the largest rise in the death rate occurred among younger asthmatics in whom arrhythmias are very rarely produced by the drugs in question.

Suggestions that the number of deaths may have risen as a result of fluoro-carbon propellants being absorbed in toxic amounts¹⁰ or because of occasionally defective valve mechanisms allowing excess doses of the drugs to enter the lungs have been discounted. Similarly, considerable doubt has been cast upon the once popular hypothesis that the introduction of disodium cromoglycate (a prophylactic drug) and salbutamol (a selective bronchodilator with reduced cardiac stimulation) played an important part in the reduction of the mortality figures. Inman has pointed out that neither of these new therapeutic measures achieved a substantial proportion of total sales until 1969 - two

10 There is very little information to indicate the threshold for fluoro-carbon sensitisation of the human heart to exercise or adrenaline provoked arrhythmia but it seems unlikely to have been responsible for many of the deaths because toxic blood levels can only be reached in situations of gross overdosage (Dollery 1973).

years after the peak of the epidemic, by which time the death rate had almost returned to 'normal'.

In recent years there has been a movement towards the opinion that the experience of the 1960s can be explained in terms of the way in which the bronchodilator aerosols were used (or abused) rather than in the toxic potential of the drugs which they contained. The availability¹¹ of such effective agents in a rapidly acting form may have lulled both doctors and patients into a false sense of security. Failure of the medication to provide the expected relief, either through the development of drug tolerance or, more likely, because of a deterioration in the patient's condition requiring alternative therapy, was sometimes met simply by persistent use of the bronchodilator aerosol. This is, of course, an understandable reaction in the frightening situation of a severe asthmatic attack and, in this context, it is perhaps significant that the steepest rise in mortality occurred amongst those aged between 10 and 14 years. The effect of too great a reliance upon the bronchodilator aerosol may have been to delay hospital admission and the commencement of emergency therapy to a point at which the patient was beyond help.¹²

Observations

The events of the 1960s made it clear that although the level of asthma mortality is extremely low in relation to the overall morbidity generated by the condition, the significance of the former should not be underestimated especially as severe asthmatic attacks can lead rapidly to death. They showed in this context the dangers of persisting with a medicine of diminishing effectiveness without seeking further medical assistance. That this in fact occurred probably reflected a fundamental misunderstanding on the part of some patients of the functions and limitations of the symptomatic treatment employed in the management of asthma and of the disease processes involved.

The experience of the 'asthma epidemic' also demonstrated that a change in the method of administration of a drug can create a new therapeutic entity which can no longer be seen in the same

11 Bronchodilators could be purchased 'over the counter' without a prescription until 1968.

12 A review of 173 patients who died of asthma during the epidemic found that 29 per cent had not received a corticosteroid, 18 per cent who had earlier been regarded as ill enough to need a corticosteroid had none in their terminal episode, and 30 per cent had received corticosteroids in only moderate or low doses. Thus 77 per cent received little or no corticosteroid during the fatal episode (Speizer *et al* 1968).

terms as the pre-existing formulation. Furthermore, it emphasised that although the pharmacological efficacy and safety of a new medicine can usually be tested with accuracy, the broader issues surrounding drug usage may present unpredictable problems. Thus the therapeutic value of some medicines can only be fully appreciated through substantial clinical experience.

Finally, the events in question illustrated the importance of monitoring disease trends and reporting drug safety problems¹³ and the need for efficient machinery to investigate the latter. Unfortunately, the Committee on Safety of Medicines monitoring system was at a very early stage of development when the possible hazards associated with the inappropriate use of bronchodilator aerosols were first becoming evident.

Yet in spite of the knowledge gained from and the widespread publicity given to the problems of the mid-1960s, a number of reports have subsequently indicated instances of excessive use of bronchodilator aerosols in the terminal episode (Fraser *et al* 1971; Dodds *et al* 1975). Furthermore, it may be considered surprising that the mortality rate for asthma in 1973 was at a similar level to that experienced in the immediate pre-epidemic years. Future developments in therapy may reduce the number of asthma deaths but perhaps there will always be a proportion of asthmatics who will die in spite of the best possible treatment (Inman 1973).

Part of the problem may lie in the failure to recognise the significance of asthma as a potential threat to life. Crompton (1975) suggests that the medical profession has been slow to realise that all asthmatic patients are at risk and that severe attacks can be rapidly fatal. It has also been postulated (Cochrane and Clark 1975) that some 'unexpected' deaths in hospital may be due to a failure to assess accurately the severity of an attack which may in turn result from a tendency to underestimate the possibility of death because the case fatality rate is low.¹⁴

13 Only six doctors reported suspicious deaths during the period under consideration.

14 At the other extreme, however, some hospitals operate an emergency service which facilitates the self admission of acute asthma patients to special care units and thereby ensures that the appropriate treatment is received as quickly as possible (Crompton and Grant 1975; Clark *et al* 1975; Jones 1976).

It is clear that the severity of asthma varies considerably between patients and over time in particular individuals and that many different factors can provoke the development of symptoms. It is therefore hazardous to generalise about either the extent and nature of treatment required or individual responses to it. Modern therapy is aimed at keeping the patient symptom free with the smallest amount of medication possible. This involves mainly the use of medicines to reverse the characteristic airways obstruction and to subdue the reaction in the lungs and, with more recently developed chemical agents, to prevent the asthmatic attack occurring in the first instance.

Bronchodilators

These drugs, which 'open-up' the airways, can be divided into two main groups. First, there are the modern sympathomimetic bronchodilators which relax bronchospasm by stimulating the beta 2 adrenergic receptors¹⁵ in the airways but these medicines have only been available since the late 1960s. For many years asthma was treated with adrenaline and ephedrine. However, not only do they affect both alpha and beta receptors but recent evidence indicates that alpha stimulation leads to the enhancement of histamine release (Palmer 1973). Isoprenaline was perhaps the most commonly used drug until recently although it stimulates both the beta 2 receptors of the bronchial smooth muscle to produce bronchodilatation and the beta 1 receptors of the heart, increasing its forcefulness and rate of contraction. Furthermore, although maximal bronchodilatation is achieved within a few minutes, the effect does not last longer than one or two hours (Chamberlain *et al* 1962).

Chemical manipulation of the isoprenaline molecule led to the discovery of the longer acting beta 2 stimulants like salbutamol and terbutaline which are the drugs of choice at the present time.¹⁶ These agents can be administered in several different

15 Adrenergic receptors are widely distributed throughout the body and are classified into alpha and beta 1 and beta 2 receptors. Alpha receptor stimulation causes vasoconstriction, beta 1 stimulation leads to an increased heart rate and beta 2 stimulation results in vasodilatation and bronchodilatation.

16 Much research is currently aimed at the development of improved bronchodilator agents and at the same time attention is being given to the efficacies of these drugs in treating asthmatic symptoms of varying degrees of severity. As examples, rimiterol, a beta 2 selective bronchodilator, may prove to be valuable in severe asthma when intravenous infusion is indicated (Marlin and Turner 1975), and inhaled salmefamal appears to have a longer duration of action than some of the currently employed beta 2 selective drugs (Kennedy *et al* 1975).

ways but their availability in aerosol form, which means that a smaller effective dosage is used (compared to oral administration) thereby reducing unwanted side effects, is of particular value for the many patients who suffer occasional asthma attacks.

The second major group of bronchodilator drugs used in the treatment of asthma are the methyl xanthine derivatives (for example, theophylline). They act by inhibiting the enzyme which, by destroying cyclic AMP,¹⁷ leads to bronchoconstriction. Other inhibitors of this enzyme, which is called phosphodiesterase, have been synthesised and although orally administered drugs of this type have sometimes been found to be disappointing in the relief of asthmatic airways obstruction (Palmer 1973) their intravenous use can be highly effective in very severe cases.

Corticosteroids

Steroid preparations, such as prednisone and prednisolone, are employed in the treatment of both acute and chronic asthma. They are almost always indicated in very severe asthmatic episodes but the use of steroids as a form of long-term therapy requires a careful balancing of the benefits these medicines offer against the familiar side effects which include, in particular, adrenal suppression. Steroid therapy in very young patients is further complicated by the danger of growth retardation or suppression¹⁸ and increased susceptibility to relatively simple infections with potentially severe complications.

The development of steroid preparations delivered by pressurised aerosol has had a major impact on the management of chronic bronchial asthma. Only very small doses of these drugs (beclomethasone dipropionate or betamethasone valerate) are required and they are particularly beneficial in permitting a reduction in the intake of oral corticosteroids, although the transfer from the latter to an aerosol preparation has to be carefully regulated. The only recognised side effect of these aerosols is a mild fungal infection of the mouth and throat (oropharyngeal candidiasis) which occurs in 5 to 10 per cent of patients (Crompton 1975a) although as yet there is little information about their long term effects on the human lung (*BMJ* 1975).

17 See Appendix 2.

18 Evidence in this area is conflicting. Murray *et al* (1976) found that children with chronic asthma tend to be short, although growth retardation was not just confined to those children who had received corticosteroids. Age at onset of wheezing appeared to be an important factor. However, Vimpani *et al* (1976) found asthma to be a relatively infrequent cause of short stature and concluded that organic illness contributes much less to growth restriction than do genetic or environmental causes.

In addition to their alleviative and prophylactic properties, corticosteroids have also been found to raise or restore some patients' responsiveness to bronchodilator therapy. Intravenous injection of prednisolone was recently shown to increase the response to inhaled isoprenaline in 8 out of 10 chronic asthmatics (Ellul-Micallef and Fenech 1975). It has been suggested, however, that the pharmacological interaction involved may not be specific to asthma patients (Tattersfield and Holgate 1976).

Disodium Cromoglycate (DSCG)

The recent development of DSCG, stemming from empirical pharmaceutical industry research, has opened up important new lines of investigation in the field of allergy. DSCG is one of only a very small number of drugs that do not appear to have significant unwanted side-effects. It inhibits the development of immediate and late asthmatic responses to various stimuli through its action on the mast cells in the lungs, preventing the release of spasmogens and inflammatory agents which follows the initial antigen/antibody reaction. It is a prophylactic treatment which is ineffective once bronchospasm has occurred. DSCG appears to be particularly valuable in younger patients with extrinsic asthma (Palmer 1973) although it has been shown to be effective in some intrinsic cases¹⁹ (Grant *et al* 1976).

Considerable interest has been generated in other chemical agents which may possess a more active anti-allergic effect and more favourable absorption characteristics. These include a phenanthroline, a series of xanthenes, oxanilic acids and a nitroindanedione (Goadby 1976). Unlike DSCG, which is taken as an insufflation of fine powder in order to reach the affected airways in sufficient concentration, the latter three series of compounds are claimed to be effective when administered orally.

Desensitisation

The raising of the patient's sensitivity threshold to a particular allergen (desensitisation or hyposensitisation) by the subcutaneous injection of increasing doses of extracts of the material has frequently been advocated but there is not much data to support its value. The method has proved beneficial in some cases of pollen-induced asthma but reports of hyposensitisation to the

¹⁹ Demin (1976) suggests that the potential value of DSCG is limited in allergic infectious bronchial asthma because of insufficient penetration and absorption of the preparation and that the combined use of DSCG and mucolytic enzymes (DNA-ase) can increase the effect of treatment in such patients.

house dust mite have been few in number, sometimes contradictory and indicative of only limited success (*BMJ* 1975a)²⁰.

One of the major drawbacks is that many allergic patients are susceptible to more than one allergen and thus protection of a specific nature may produce little overall benefit. Further problems include the development of severe reactions in some highly sensitised patients even when they are injected with only a small dose of the allergen. But these difficulties may be overcome by physical and chemical pre-treatment of the allergenic material and the use of an improved vaccine base.

Some American workers are currently investigating an alternative approach to conventional desensitisation (*American Scientist* 1976). Whilst the latter is focused on the part of the antibody molecule that recognises the different allergens, the new approach is directed at the other end of the molecule which fastens on to and then activates the cells that secrete chemicals leading to a contraction of the bronchial muscle. If the exact site that binds to the secreting cell can be identified, that fragment could be synthesised in isolation and used to block the access of the antibody to the cell.

The principal advantage of the new approach over desensitisation is that all the allergies could theoretically be abolished by a single injection. However, this benefit would have to be weighed against the risk that the individual might be left unprotected from those diseases (especially parasitic infections) against which these particular antibodies provide a defence.

Other measures

A wide variety of other measures have proved valuable for small subgroups within the total asthmatic population. Thus some children appear to benefit from a change of emotional and physical environment (for example, special schools). Removal of mucus from the lungs by bronchial lavage may ease the breathing difficulties of some patients suffering from chronic asthma (Nariman and Bell 1975). Antibiotics are sometimes prescribed during prolonged attacks. These may be valuable in warding off supervening infections although it is highly improbable that bacterial infection is a significant factor in the aetiology or subsequent progress of asthma (Stark 1975). The value of psychotherapy in asthma appears to be limited although it may be successful for a few individuals (Kerr 1974).

20 Gaddie *et al* (1976) recently failed to show any improvement in 45 patients with asthma sensitive to the house dust mite after hyposensitisation with house dust mite vaccine. It was noted that much higher doses of vaccine have been shown to produce better results but with an increased incidence of side effects.

Probably the most important non-pharmacological measure involves the avoidance, as far as possible, of known allergic material (such as certain foods or animal dander) by those who are susceptible to them. The commonest allergy incriminated in childhood asthma is the house dust mite. At present practical efforts at reducing inhalation of house dust are limited to simple hygienic measures like regular vacuum cleaning and the use of synthetic bedding material and an impervious mattress covering. Sarsfield *et al* (1974) demonstrated the benefit of these precautions and Wraith and Cunnington (1975) have indicated the value of removing old articles of bedding which are often found to have very high levels of mite infestation. However, a trial amongst mite-sensitive adult asthmatics (Burr *et al* 1976) found that undertaking similar measures for six weeks did not prove particularly useful. These results probably reflect the nature of the sample under investigation and should not, therefore, be taken to imply that anti-mite precautions are valueless (Burr *et al* 1976a).

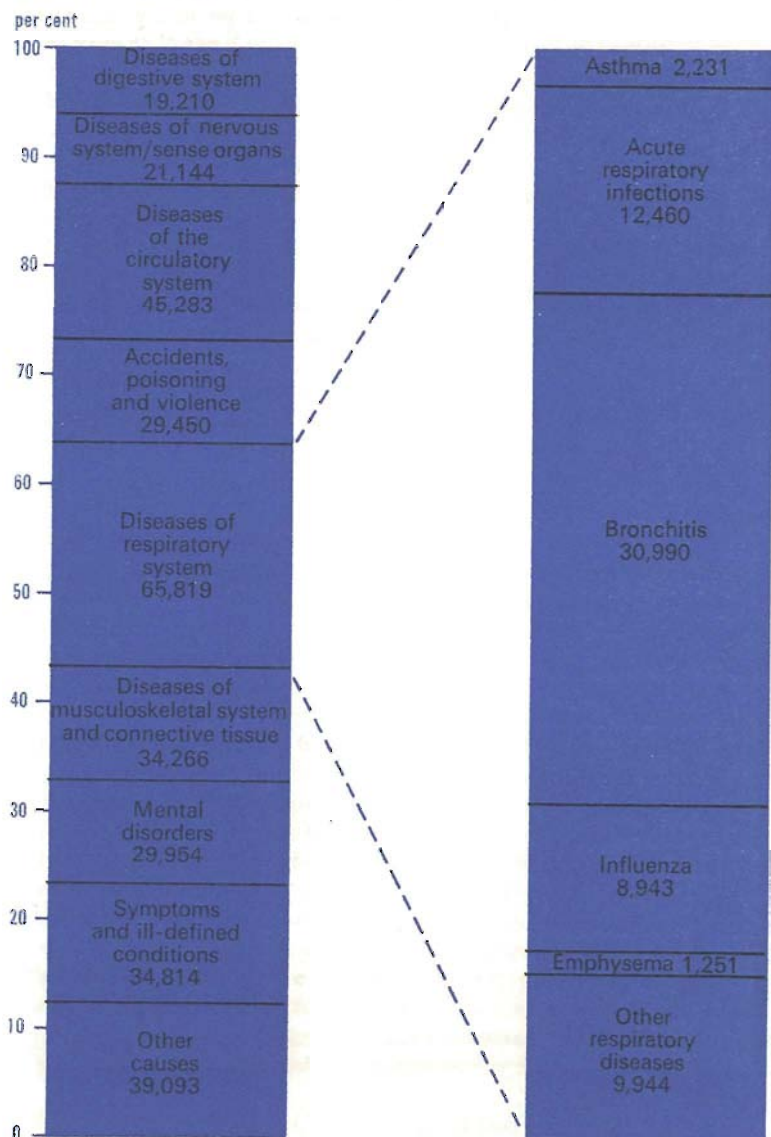
The cost of asthma

The financial burden of any disease to a community can only be calculated approximately and so such estimates should not be interpreted as if possessing importance in absolute terms. Rather, their value lies in providing a measure of comparison between diseases. The costs can be divided into three main groups: the expenditure on medical and welfare services, the value of production lost through sickness absence, and the personal hardships suffered by patients and their families.

The cost of asthma to the National Health Service in 1974 is estimated to be around £25 million, of which more than half (£13.8 million) is accounted for by expenditure on hospital inpatient services (Table 5). The latter figure is probably an underestimate as a large proportion of asthmatics are admitted, under emergency conditions, to the more expensive acute hospitals. The hospital sector cost figure would be raised further by the inclusion of outpatient treatment but the relevant statistics are not available. Pharmaceutical services account for one third of the total medical cost, reflecting the importance of drug therapy in asthma.

Another economic cost to be taken into account is the amount of sickness absence resulting from a particular illness. In 1973/74 asthma accounted for 2.2 million days of certified absence

Figure 7 Days of certified incapacity in the period 4 June 1973 to 1 June 1974, by cause, Great Britain, (thousands)



Source DHSS

Table 5 *Cost of asthma to National Health Service, UK, 1974, £ million*

	<i>Asthma</i>	<i>Total</i>	<i>% of Total</i>
Hospital services	13.84	2,630	0.53
General medical services	2.88	253	1.14
Pharmaceutical services	7.82	353	2.22
Dental and ophthalmic services	—	206	—
	24.54	3,442	0.71

Source OHE Estimates

Notes

- 1 The hospital services figure includes capital costs.
- 2 The cost of pharmaceutical services is calculated using the average cost for all prescriptions of £1.01 in 1974.

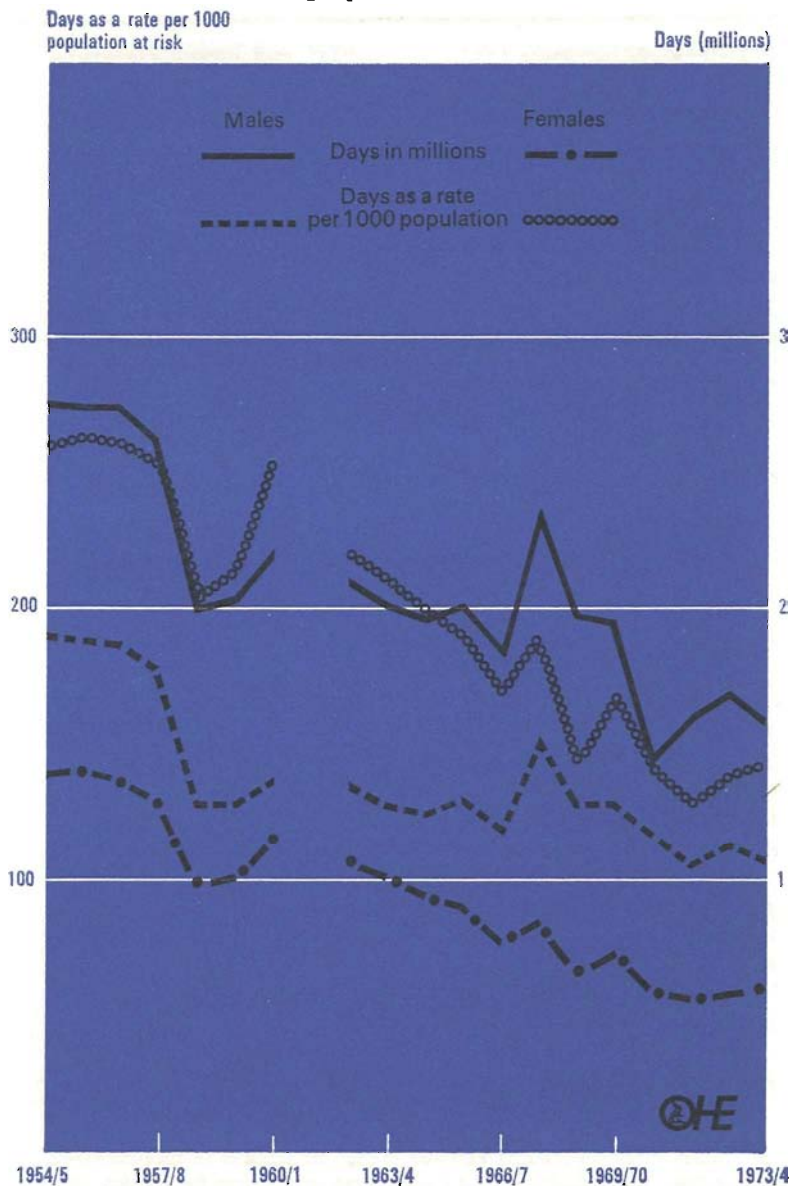
(Figure 7) which represented 0.7 per cent of all recorded lost working days in Britain, thereby incurring an expenditure of just over £2 million in sickness benefit grants. The trend in certified incapacity since 1954/55 is shown in Figure 8. The changes in the classification of asthma over time mean that these statistics have to be interpreted with caution. However, there is no evidence to suggest that the condition is becoming more important as a cause of absence, even though spells of less than three days, which may be significant because of the nature of asthmatic attacks, are not recorded.

The value of production which is lost through sickness absence can be derived crudely from estimates of earnings foregone and on this basis asthma cost approximately £16 million in 1974.²¹ Alternatively, if the cost of certified incapacity is expressed in terms of foregone Gross National Product a rough estimate of £22 million may be obtained. It is, of course, extremely difficult to evaluate accurately the financial significance of sickness absence when so many factors, particularly the level and adaptability of economic activity and the effects of inflation, have to be taken into account.

The personal costs of distress and lost potential vary considerably between individuals and are largely incalculable. Neverthe-

²¹ Based on average yearly earnings (1974) for workers in manufacturing and certain other industries of £2,530 for males and £1,400 for females.

Figure 8 Days of certified incapacity attributable to asthma, males and females, 1954-55 to 1973-74, Great Britain. Expressed in millions of days and as a rate per thousand of the average population at risk in the relevant sex group



less, this should not conceal the fact that asthma can have serious implications for the patient and his relatives and perhaps in particular for children who may experience considerable absence from school.

One final aspect of the cost of the complaint is the amount spent on research, although it is not always possible to identify specific expenditures, partly because advances may accrue from investigations in other areas. Thus the Medical Research Council does not provide a breakdown of the funds allocated to asthma research but of the £36.5 million spent in 1974/75, approximately £180,000 was accounted for by the unit investigating tuberculosis and chest diseases. A further £130,000 was spent on research into respiratory diseases by the DHSS in 1975/76. The proportion of the British pharmaceutical industry's research budget (estimated to be £70 million in 1975) which is devoted to asthma and allergy is unknown. But this is an area which is currently attracting considerable research interest not only in this country but throughout the world, thereby enhancing the likelihood of therapeutic advance. The main clearly identifiable source of finance is the Asthma Research Council. In 1974/75 grants totalling more than £44,000 were allocated to a wide variety of projects.

Social aspects

Much attention has focused on the possible mechanism by which psychological or emotional factors may precipitate an attack of asthma. However, there has been much less investigation of the social effects of this often extremely frightening disorder. This may stem in part from the fact that the social problems generated by asthma are not as immediately apparent as those resulting from more overtly physically debilitating conditions. Indeed, acceptance of the fact that most illnesses involve some form of handicap has been gained only recently as a result of the application of sociological approaches to medical care. Another possible reason why the disabilities experienced by asthmatics may not have been fully understood has been the widely held belief, until recently, that emotional stimuli play a major role in the aetiology of asthma. This may have encouraged the suspicion that some patients may be able to manipulate the development of asthmatic symptoms, resulting in a loss of sympathy for the problems they may genuinely experience.

Unfortunately, the value of many investigations into the social consequences of asthma is limited by methodological shortcomings, notably non-representative samples and inadequate

controls. In particular, concentration on patients attending hospital clinics has tended to distort the overall picture within which there are considerable variations in the severity of the condition, the reaction to it and in the individual's capacity to cope with his own situation.

A relatively large number of studies have been carried out amongst asthmatic children. Before the 1960s the principal objective often was to identify an 'asthmatic personality' which may act as an aetiological factor in the condition (see, for instance, Miller and Baruch 1958). Yet a survey of 65 such studies (Herbert 1965) shows that there was little agreement about the behavioural traits to be included in such a personality profile and today this concept is rejected by most authorities.²²

Even though the once fashionable tendency of emphasising the causal role of emotion has diminished considerably it is possible that there may be a sub-group of children in which psychological factors play a predominant role in the production of asthmatic symptoms. Thus a complete change of living environment or a temporary removal of the parents have sometimes led to significant improvements, especially in those in whom emotional triggering is important. But positive results such as these have not been universally obtained and much depends on the severity of the condition. Furthermore, it is necessary to consider the experience following the return to the status quo and whether the results may have been affected by such factors as a change in the degree of exposure to allergens such as the house dust mite.

Severe asthmatic symptoms are particularly frightening for a child but little attention has been given to the problems of emotional adjustment to such experiences (Pilling 1975). The available evidence suggests that there is a slightly higher rate of emotional disorder in asthmatic children compared to non-handicapped children but the rate is no higher than in those with other (non-psychosomatic) physical handicaps.²³ This 'excess' as

22 Occasionally some studies claim to identify 'new' behavioural characteristics. Thus Rubenstein (1976) found that individuals with well-controlled asthma were more likely to arrive late for clinic appointments, or not attend at all, than patients with other illnesses. Observations of this nature not only have to be interpreted with caution but are often unconfirmed (Herxheimer 1976).

23 A survey of all 10 to 12 year old handicapped children on the Isle of Wight found a slightly greater, though not statistically significant, extent of psychiatric disorder among asthmatic children (10.9 per cent) compared with that in the general population (6.6 per cent), and the rate was almost identical with that of children with other (non-brain involvement) disorders (Graham and Rutter 1970). However, a randomly selected sample of 10 to 15 year old asthmatic children from Aberdeen (Mitchell and Dawson 1973) was found to have almost the same rate of psychiatric disorder (8 per cent) as the general population (7 per cent).

compared with the general population may be accounted for by the most severely affected asthmatic children who have been shown to be less socially mature, more anxious and more demanding (McNicol *et al* 1973).

The presence of an asthmatic child may be expected to give rise to family tensions or strains although this again is an area which has been little researched. McNicol and his colleagues found that families of the most severely affected children showed stress but it was not clear whether this was a result of the asthma or whether it predated the onset of the condition. Economic restraints and personal hardships may be involved as well as parental anxiety and frustration. One particular problem is that anxiety can lead to excessive restrictions being placed on the child which may enhance the latter's feelings of isolation from members of the same age group and thus create difficulties in establishing social contacts.²⁴ In addition, there is a danger that this perceived separation from 'normal' society may persist even when asthmatic symptoms are no longer experienced simply because the child has been assigned to the status of a sick person since an early age.

It is possible that parental attitudes affect the child's ability to cope with an attack of asthma and his reaction towards it. It is clear, therefore, that in addition to instruction on what to do when the child has an attack, parents need explanation of the illness, advice on how to take necessary precautions without being unduly restrictive and the opportunity to express their feelings about having an asthmatic child. The Working Party on children with special needs set up under the auspices of the National Children's Bureau pointed out that in the absence of such supportive services parents' natural anxieties and concern may turn into over-protectiveness or resentment. Yet the adequacy of these services has undergone very little examination (Pilling 1975). Further investigations in this area would prove valuable as would long-term prospective studies in determining more accurately the social and emotional effects of asthma. Nevertheless, it can be concluded that the majority of asthmatic children, with parental assistance, appear to cope satisfactorily with the disorder and that the major problems are probably restricted to the more severe cases.

24 In particular an asthmatic child's participation in sport may be restricted. However, it has been shown that swimming is less likely to provoke asthma than other forms of exercise, possibly because there is less shaking of the chest (*BMJ* 1976). In addition to improvements in physical fitness, regular swimming may help to generate a sense of liberation from previous restrictions and reduce overprotective parental attitudes (Fitch *et al* 1976).

Intelligence and educational attainment

It has been suggested that asthmatic children may have a slightly higher level of intelligence than children of the same age in the general population. But this belief has been derived almost entirely from clinical impressions of selected series of children seen at clinics and only a small number of studies. Explanations for these 'findings' have been sought in terms of the social class distribution of asthma identified by some investigations and the tendency for asthmatic children to pursue hobbies of a more sedentary nature, such as reading, than do non-handicapped children (Mitchell and Dawson 1973). It is clear, however, that there is insufficient evidence for any firm conclusions to be drawn.

The belief that asthmatics achieve above average education standards is not supported by recent surveys. Indeed, the evidence is to the contrary, especially for the more severe cases, and this may be attributable to repeated short absences from school which can lead to discouragement and a lowering of self-confidence in addition to the actual loss of work (Yule and Rutter 1970). The extent to which this loss is compensated for by parental assistance at home is largely unknown but will, of course, vary considerably.

Conclusion

Asthmatic attacks can be frightening and occasionally lethal. However, the advances in chemotherapy during the last decade or so have yielded much greater medical control over the condition and at the same time they have generated considerable social benefits for many patients. Thus modern bronchodilator therapy, particularly in the early stages of an attack, can often prevent further development of symptoms. Moreover, confidence in these medicines has eliminated much psychological stress stemming from a fear of the next asthma attack. Considerable progress has also been achieved in the preventive approach to the disorder. The introduction of disodium cromoglycate was a major breakthrough which has stimulated much research into the pharmacology and immunology of allergic reactions. Desensitisation techniques continue to be improved and, finally, the problems associated with prophylactic corticosteroid therapy have diminished now that these drugs can be administered in low but effective doses by aerosol spray.

The development of this method of drug administration has been an integral part of the recent improvements in therapy. Aerosols deliver the pharmacological agents rapidly and directly

to the site of action. But reports of patient error²⁵ in the use of these aerosols have generated concern which has been enhanced by the fact that an increasing number of anti-asthmatic preparations are now available in this form. Improved patient tuition and occasional checks on technique would undoubtedly prove useful. But the finding that over 90 per cent of those patients unable to inhale correctly from a pressurised aerosol canister could use a breath activated inhaler efficiently (as employed in the administration of dry powder DSCG) suggests that there may be potential benefit in making corticosteroids and bronchodilators available in this latter form (Paterson and Crompton 1976).

With the exception of the experience of the 1960s – which appears to have its origins in the inappropriate use of otherwise safe medicines – the level of asthma mortality, although low in relation to the overall morbidity caused by the disorder, has changed little in recent years. This lack of improvement may in part stem from a failure to appreciate the significance of the condition as a potential cause of death. For a long time it was often believed that individuals died with their asthma and not from it.²⁶ Similar attitudes may inadvertently lead to an inaccurate assessment of the severity of an attack resulting in a dangerous delay before the commencement of appropriate therapy. It has also been suggested that there may occasionally be a failure to recognise the importance of following-up and providing adequate supervision²⁷ for the patient after the latter has undergone emergency treatment in hospital (Posner 1976).

The tendency on the part of some patients to underestimate the extent to which severe and persistent asthma can be life threatening may have been encouraged by the provision of highly

25 Orehek *et al* (1976) indicated that the bronchodilatation achieved by self-administration may be less than the maximum possible and that in general more careful inhalation yielded significantly better results. Paterson and Crompton (1976) found that 14 per cent of a sample of asthmatics used their inhalers inefficiently in spite of careful tuition. Coady *et al* (1976) observed that almost one-third of patients attending outpatient clinics failed to synchronise inspiration with the release of a metered dose from a bronchodilator aerosol. Misuse is probably even more likely during an asthma attack.

26 In 1786 Withering wrote: 'However distressing the disease (asthma) may be at the time it does not cut short the normal period of Life'. In the nineteenth century Oliver Wendell Holmes in America referred to asthma as a 'slight ailment that prolongs longevity' and in 1906 Sir William Osler maintained that 'death during the attack is unknown'.

27 Posner (1976) contends that this supervision should be undertaken by a specialist but it has been argued that long-term care by the family practitioner with knowledge of modern methods of investigation and treatment and access to specialist advice may be a suitable alternative in some cases (Tant 1976).

effective self-administered treatments for the relief of symptoms. Changes in the perceived effectiveness of therapy are particularly significant in asthma as they may herald modifications in the patient's condition which should perhaps be met by alternative medication rather than more intensive use of current measures. It is therefore necessary to educate patients to seek medical advice at an early stage in these circumstances if the rapidly lethal potential of severe asthmatic attacks is to be minimised (Macdonald *et al* 1976).

Classifications of bronchial asthma and related causes

Much emphasis has been placed upon the distinction between extrinsic and intrinsic asthma (Table 1) although in reality it is rather blurred. In the former the symptoms are provoked by an immediate type hypersensitivity reaction to one or more of a wide variety of allergens. Intrinsic asthma is the term applied to that group of patients which presents no historical evidence of allergic sensitivity and in whom skin prick tests to the standard range of allergens are negative. This is no more than a definition by exclusion. However, with the development of more sophisticated diagnostic techniques (for example, controlled bronchial provocation tests) it is becoming clear that some individuals currently termed as intrinsic asthmatics will have to be reclassified because extrinsic type reactions to previously unsuspected agents or those for which tests used not to be available can now be elicited (Pepys and Hutchcroft 1975).

Extrinsic asthma

Sensitivity to the house dust mite (*Dermatophagoides Pteronyssinus*) is one of the most important single causes of non-seasonal allergic asthma. It is found in large numbers in many domestic situations and particularly in upholstered furniture, feather pillows and old mattresses where it finds ideal requirements of warmth, moisture and its principal foodstuff, desquamated human skin scales. In recent years the house dust mite has been established as an extremely common and potent allergen in childhood asthma. Skin prick testing with *D. Pteronyssinus* extract reveals positive weal responses in over 80 per cent of children suffering from the complaint (Sarsfield 1975).

Another large group of allergic asthmatics only experience symptoms at certain times of the year. The commonest seasonal asthma encountered is due to grass pollen. It is released into the air in large quantities between May and July and is often distributed over vast distances. Few other pollens are of clinical significance in Britain although some individuals are susceptible to those of the plane and birch trees. Symptoms which persist well beyond the normal grass pollen period may be attributable to the airborne spores of certain moulds such as *Alternaria*.

Other sources of airborne allergy include domestic animal dander, the dust from disintegrated insects which collects on vegetation and the vapours released during the preparation of certain foods, for example, the frying of eggs and cooking of vegetables. Considerable progress has also been made in the identification of specific chemical dusts, vapours and gases which can provoke asthma in the course of occupational exposure and also non-occupational exposure.¹

1 The sources of hypersensitivity reaction are clearly numerous and often obscure. For example, the sudden development of asthmatic symptoms among a small number of nursery workers over the age of 40 years in Sussex was shown to be due to the presence of *aspergillus* in the greenhouses (Long 1976).

Table 1 *The features of extrinsic and intrinsic bronchial asthma*

<i>Allergic asthma</i>	<i>Intrinsic asthma</i>
Usually presents before age of 30	Usually presents after age of 30
Often positive family history	Absence of family history
Demonstrable provoking factors, i.e. pollen, dust mites, animals	Non-specific provoking factors only, i.e. stress, exertion, chest infections
Other allergic disorders (e.g. eczema) often present at some-time	Eczema not usually a feature
Skin tests positive	Skin tests negative
Serum ige usually raised	ige normal or low
Nasal polyps unusual	Nasal polyps common
Majority respond well to disodium cromoglycate	Majority do not respond well to disodium cromoglycate
Prognosis good	Prognosis poor

Source Buisseret 1975

Intrinsic asthma

Respiratory infection is often considered to be an important factor in intrinsic asthma although its precise mode of action remains obscure. It may be that the condition is due to an allergic reaction to bacterial or viral antigens or that these infectious agents are non-specific inflammatory factors (Aaronson 1973). Infection can certainly exacerbate the condition by further obstructing the bronchi and bronchioles through increased mucus production.

Exercise may occasionally be the only obvious factor which precipitates an attack. It has been shown that the type of exercise performed may significantly affect the severity of the post-exercise symptoms: running appears to be more asthmagenic than cycling, and walking seems to have very little effect (Godfrey 1973). It is also clear that the duration and the intensity of the exercise are important factors. Paradoxically, it has also been pointed out that breathing difficulties may sometimes be eased by a certain amount of physical activity (Feinberg 1973).

Another special category of intrinsic asthma is that induced by the ingestion of aspirin. The symptoms may develop between 20 minutes and 2 hours after the drug has been taken (Samter and Beers 1968). Its prevalence among adult asthmatics has been reported as varying from 2.3 per cent to 20 per cent (McDonald *et al* 1972). The mode of action is again unclear but Szczeklik and Czerniawska-Mysik (1976) suggest that it may be related to the ability of certain anti-inflammatory drugs (for example, aspirin, ibuprofen and phenylbutazone) to inhibit prostaglandin biosynthesis.² Other analgesics which do not have this effect, such as salicylamide and chloroquine, are easily tolerated by this group of patients. It is suggested that the removal of prostaglandin E_2 , which is identified in the bronchial wall, by aspirin-like drugs disturbs the

² Pyrazolone and phenazone derivatives may also produce severe asthmatic attacks in some individuals although there is no clear evidence that these compounds inhibit prostaglandin synthetase (Bartoli *et al* 1976).

Table 2 *The main causes of asthma by age group*

<i>Age group</i>	<i>Percentage of patients</i>		
	<i>Extrinsic causes</i>	<i>Intrinsic causes</i>	<i>Both significant</i>
0-4	28.7	71.3	29.5
5-14	56.0	44.0	60.3
15-29	82.9	17.1	23.5
30-44	72.2	27.8	29.8
45-59	29.5	70.5	58.4
60+	12.3	87.7	20.6
	53.7	46.3	37.4

Source Ford 1969

modulatory mechanisms regulating bronchial tone, enhances the release of histamine and thus enables bronchoconstriction to occur.

The importance of psychological factors in asthma has been recognised for a long time but the relationship is a complex one. Anger and anxiety, for example, may aggravate the severity of established asthma and provoke attacks. Alternatively, emotional arousal may cause the already unstable bronchi to become even more responsive to allergy, infections and other stimuli. These two explanations are not mutually exclusive but the main point is that a hyperreactive bronchi is the essential prerequisite and it is now thought unlikely that this can be caused directly by emotional factors.

There is an extensive range of non-specific factors which may trigger off an episode of bronchospasm through an irritant type of effect³, although susceptibility to each of these varies considerably between patients. Thus, air pollutants, smoke, chemicals, and the fumes of fresh paint, gasoline or turpentine can provoke an attack. Laughter and coughing have been found to be significant in some cases. It is well known that the inhalation of cold air can occasionally lead to the development of symptoms and the importance of other climatic and meteorological factors has also been noted. For example, Steer (1976) reported that an unusually large number of patients with an acute attack of asthma attended the casualty department of a Melbourne hospital during a thunderstorm which led to a drop in temperature and rises in relative humidity and barometric pressure.

Only a few attempts have been made at assessing the relative importance of the two principal types of asthma and the evidence that is available is sometimes conflicting. Furthermore, comparisons between studies are hindered by differences in methodology and diagnostic criteria. Thus although Ford (1969) observed that extrinsic and intrinsic factors dominated in 54 per cent and 46 per cent of cases respectively, the finding that this relative standing altered markedly with age is possibly of much greater significance (Table 2).

3 There is evidence to suggest that some can be specific causes of asthma as well.

Appendix 2

Asthmatic mechanisms

In the extrinsic form of asthma the contraction of bronchial smooth muscle is thought to be the result of an antibody-antigen reaction. The initial stage involves the formation of antibodies (part of the body's defence mechanism) as a result of antigen (those substances to which asthmatics may be particularly susceptible) entering the body. The antibodies involved in allergic responses are of the Ige Class⁴ and these become strongly bound to certain cells. These target cells are known to include the mast cells which are found in abundance in many tissues including the mucous membrane lining the respiratory air passages.

When the antigen next enters the body it combines with cell fixed antibody and a reaction, principally a type 1 hypersensitivity reaction in the case of asthma, takes place (Table 3). In response to this stimulus the cell then liberates a humoural messenger substance (which may be one or more of those described in Table 4) which then interacts with specific receptors on the surface of the bronchial muscle cell. This interaction leads to the depletion within the cell of an intracellular messenger, thought to be cyclic adenosine 3' 5' monophosphate, and, through a sequence of enzymatic processes, this results in the contraction of the muscle cell and the production of mucosal oedema.

This is a simplistic explanation of a chain of events that is probably complicated by feed-back loops which serve to reinforce or inhibit the sequence. Furthermore, this classical concept has been challenged by recent observations, notably on the grounds that the known chemical mediators released from the mast cells fail to account for the observed pathologic changes other than bronchocontraction. As the alterations in pulmonary function associated with bronchial asthma become better characterised additional mediators may require identification or new biological activities will be attributed to those agents already recognised (Orange 1974).

The non-allergic mechanisms

Since the discovery of Ige in 1966 much of asthma research has centred on understanding allergen-provoked reactions. However, allergy does not account for the condition in all patients, notably those with negative skin tests and young allergic asthmatics with positive skin tests in whom chest infections and exercise are frequent provoking factors. But the mechanism which exists in so-called intrinsic asthma has yet to be established.

4 Antibodies belong to the globulin class of plasma proteins and are consequently known as immunoglobulins. Five classes of human immunoglobulin have been identified: Igd, Igc, Iga, Igm, Ige. A deficiency of Iga in some allergic disorders has been reported and, recently, evidence has been presented that Iga, the principal immunoglobulin in mucus secretion, is responsible for preventing absorption of antigenic material. Thus a deficiency of Iga could be a reason for the sensitivity of certain individuals to antigenic stimulation.

1 Anaphylactic reactions

This reaction is also referred to as immediate type hypersensitivity (atopy or allergy) or reaginic hypersensitivity. Conditions which arise as a result of this type of action include skin reactions (urticaria), mucosal oedema and inflammation (hay fever, rhinitis), and smooth muscle contraction (extrinsic asthma). Principally, type 1 reactions are those where antigen reacts with antibody which is fixed to cells. This causes release of the cell contents which in turn gives rise to the symptoms of the allergy.

2 Cytotoxic or cytolytic reactions

Alternatively this reaction group is referred to as complement dependent cytotoxicity. These involve damage exerted on particular cells or tissues. The cells have or acquire antigenic surface characteristics which are then attacked by circulatory cytotoxic antibody, and complement is then activated. This mechanism may be directed against incompatible cell transfusions, cells altered by sensitising drugs, or even normal cells.

3 The toxic-complex reaction

Alternatively soluble complex or immune complex hypersensitivity. The basic mechanism involves the introduction of circulatory antigen either locally or systemically in relatively large quantities (in contrast to type 1 reactions which may require minute amounts of antigen in a highly sensitive individual). Antibody is produced or is pre-existent in such proportion as to form antigen-antibody complexes upon reaction with antigen. The overall outcome involves inflammatory changes in blood vessels as well as damage to surrounding tissue. Conditions thought to result from type 3 reactions include serum sickness and a variety of pulmonary allergic conditions such as farmer's lung and pigeon breeder's lung.

4 Delayed hypersensitivity reactions

These reactions are characterised by (1) a 24 to 72-hour delay in the onset of the reaction after exposure of a sensitised individual to specific antigen, and (2) non-mediation by the conventional circulating antibodies. Rather, specifically 'sensitised' small lymphocytes are the agents which directly interact with antigen and effect the characteristic reaction. Examples of this are tuberculosis and dermatitis of the contact sensitivity type.

Asthmatics have hyperreactivity of bronchial muscle which is continuously present. It has been suggested that the biochemical key to this abnormality rests in the intracellular balance between the cyclic nucleotides adenosine and guanosine 3' 5' - monophosphate (Cyclic AMP and Cyclic GMP) which together work in a see-saw fashion to modulate function of many cell-types (Schreiner *et al* 1975). Bronchial hyperreactivity may, therefore, result from a disadvantageous re-setting of this balanced biochemical system.

On this model of asthma pathways can be defined by which non-allergic provoking factors further perturb the system to cause clinical symptoms. Stimulation of irritant receptors lying in the bronchial epithelium causes bronchoconstriction through a vagal reflex pathway (Sellick *et al* 1971), but it is not necessary to postulate any increased sensitivity of these receptors if smooth muscle hyperreactivity is accepted

Table 4 *Chemical mediators of anaphylaxis***Histamine**

Injections of histamine cause bronchoconstriction similar to that of asthma but anti-histamines are only effective in some forms of allergy and are comparatively ineffective in anaphylaxis and asthma. There must, therefore, be other mediators involved as well. Although histamine has been released *in vitro* from the lungs of allergic patients upon challenge of the tissues with specific allergen and although it is capable of contracting bronchial smooth muscle *in vitro*, there is no compelling evidence that this mediator elicits bronchospasm in man through a direct effect on smooth muscle. Indeed, some studies indicate that histamine induced bronchomotor effects depend appreciably on the stimulation of 'irritant receptors' in the bronchial epithelium.

Slow reacting substance of anaphylaxis (SRS-A)

This is a spasmogen produced during anaphylaxis so named because of its ability to cause a slow contraction of intestinal smooth muscle. Its importance in asthma has still to be established. Human bronchial strips contract strongly in its presence and the effect is resistant to atropine. SRS-A must be synthesised as a result of the antigen-antibody reaction as the quantity detectable before anaphylaxis is smaller than that detected following the reaction. Some findings suggest that in the guinea pig, SRS-A may produce effects mainly on the elastic properties of the lungs.

Eosinophil chemotactic factor (ECF-A)

This is a low molecular weight peptide which appears to be stored in mast cell granules in its final form and, upon release, it demonstrates a remarkable selectivity for homologous eosinophils. But the role of the eosinophil in these reactions is still poorly understood.

Rabbit aorta contracting substance (RACS)

This substance, as its name suggests, contracts strips of rabbit aorta. It does not appear to be released immunologically from human lung but this apparent precursor of prostaglandins is released from human tissue following agitation.

Bradykinin

In the sensitised guinea pig an antigen challenge appears to result in increased amounts of plasma bradykinin *in vivo* and challenge of sensitised lung tissue *in vitro* results in the release of kallikrein. Similar observations have not yet been made in man. However, the intravenous administration of bradykinin in normal subjects appears to produce a decrease in total lung capacity which might be attributed to alveolar duct constriction. Although the immunologic activation of the kinin system has not yet been demonstrated in the human lung tissue, it has been suggested that kinins may be formed secondary to immunologic tissue injury.

Prostaglandins

Prostaglandins appear to have a marked diversity of potential effects in human allergic bronchospasm. Whereas prostaglandins E₁ and E₂ (PGE₁ and PGE₂) are bronchodilators, PGF_{2a} produces bronchoconstriction. It is noteworthy that whereas atopic asthmatics showed a tenfold increase in sensitivity to aerosolised histamine as compared to healthy controls, they were 8,000 times more sensitive to PGF_{2a}. Besides direct effects on smooth muscle, it has been shown that PGE₁ increases cellular levels of cyclic AMP and inhibits the immunologic release of histamine from human lung. Conversely, PGF_{2a} decreases tissue levels of cyclic AMP and enhances the immunologic release of chemical mediators.

as an underlying biochemical abnormality. The irritant receptors provide a pathway by which inhaled chemicals and possibly physical manoeuvres such as deep breathing and exercise may provoke asthma (*Lancet* 1975).

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