Asthma deaths in children—a continuing problem

C. M. MELLIS AND P. D. PHELAN

From the Department of Thoracic Medicine, Royal Children's Hospital, Melbourne, Australia

Mellis, C. M. and Phelan, P. D. (1977). *Thorax*, 32, 29–34. Asthma deaths in childhood—a continuing problem. The clinical and pathological features of five children who died of asthma over a recent 12-month period are reported. All had severe, chronic asthma requiring maintenance corticosteroid therapy. Three had been receiving beclomethasone dipropionate by inhalation and these had acute inflammation of the tracheobronchial tree at necropsy. Adrenal atrophy was found in all four cases examined histologically, despite normal short tetracosactrin tests in three of these shortly before they died. The need for high-dose corticosteroid by mouth for exacerbations of asthma in those weaned from oral steroids is emphasized by these deaths. The introduction of beclomethasone dipropionate by inhalation has led to an increase in the number of children in this high-risk group.

The changing pattern of mortality from asthma has been extensively documented (Gandevia, 1968; Speizer *et al.*, 1968). In a number of countries the death rate rose during the late 1950s and reached a peak in the mid-1960s. The mortality then fell slightly but remains above the pre-1960 level. This upward trend was particularly marked in the younger age group (under 35 years), the most disturbing increase occurring in 10 to 14-year-old children. In England and Wales the mortality rate in this latter age group increased almost eightfold from 1959 to 1966 so that asthma became the fourth most common cause of death (*Lancet*, 1969). This 'epidemic' of asthma deaths was noted in Australia, New Zealand (Gandevia, 1968), Britain (Speizer *et al.*, 1968), and Norway (Stolley, 1973). Other countries did not appear to experience this increase while Canada (*Canadian Medical Association Journal*, 1969) and the United States (Silverglade, 1971) reported a declining mortality during this period. The explanation for this rise and fall in the death rate and its geographical distribution is still uncertain. The widespread belief that it was caused by bronchodilator aerosols has not been substantiated in Australia (Gandevia, 1973). Australian children have been included in this rise and fall in mortality, although the trend appears to be towards a progressively increasing rate (Figure).

This report relates our recent experience with asthma deaths in childhood and draws attention to a new high-risk group of children who have

Figure Graph showing the mortality rate for Australian children aged 5–19 years, per million living children aged 5–19 years, over the past 10 years.

appeared following the introduction of beclomethasone dipropionate aerosol.

Patients and methods

The clinical and pathological features of five children who died from asthma during the 12-month period September 1973 to September 1974 are reported. All five patients were regularly attending the Chest Medical Clinic at the Royal Children's Hospital, Melbourne and were the total deaths from asthma for that year. Only two deaths from asthma had occurred during the previous three years. Over 300 asthmatic children attend the clinic and this includes the majority of severe, chronic asthmatic children in Melbourne, over 50 of these requiring long-term steroid therapy.

All five children were receiving maintenance oral steroids, and tetracosactrin (Synacthen, Ciba) stimulation tests were performed to assess adrenal function in three of the patients a short time before they died. Serum cortisol was measured from venous blood collected before and 30 minutes after a 0.25 mg intramuscular dose of tetracosactrin. The criteria used to define a normal response were those reported by Greig *et al.* (1969).

Pulmonary function had been tested regularly in four of the children. Maximum expiratory flow volume (MEFV) curves and lung volumes were measured with the patients seated in a flow-displacement body plethysmograph (Hill *et al.*, 1972). The children were tested before and after a 2-minute inhalation of 0.25% isoprenaline via an air-compressor unit.

Case reports

CASE 1 (UR: 156911)

This boy was aged 11 years when he died in September 1973. He developed atopic eczema at 3 months and asthma at 18 months of age. His asthma became severe and chronic, resulting in over 40 hospital admissions with acute exacerbations, and he was rarely completely free of wheeze. In his last 12 months he experienced a number of episodes of sudden, transient loss of consciousness from which he spontaneously recovered without any apparent ill-effects. These were thought to be episodes of cough syncope (Katz, 1970). There were long-standing severe, psychosocial problems in the family.

He required maintenance oral prednisolone from the age of 3 years. From the age of 8 years the dose varied between 7.5 and 10 mg daily. He also received sodium cromoglycate, oral theophylline, and salbutamol inhalations via an air-compressor unit.

The circumstances of his death were quite sudden. He 'fainted' in the playground at school, as he had done previously; however, this time he died almost immediately after collapse. According to his parents and school teachers there had been no cause for concern over his condition earlier that day.

Pulmonary function two weeks before he died was no different from previous assessments. He had a moderate reduction in maximal expiratory flow rates, which improved slightly following bronchodilators. Lung volume measurements indicated mild hyperinflation and air-trapping. No assessment had been made of adrenocortical function.

Pathology Both lungs were large, soft, and crepitant. The bronchial mucosa was congested and contained a moderate amount of mucopurulent material. Many small bronchi were plugged with viscous mucus. Histology of the bronchi was typical of chronic asthma (Dunnill, 1971) with thickening of the basement membrane, moderate muscle hypertrophy, infiltration with eosinophils, and submucosal oedema. In addition, there was desquamation of bronchial epithelium and hypertensive changes present in small pulmonary arteries. No pathogens were isolated from the lungs.

The adrenal glands were reduced in size and thickness, with a combined weight of 2.1 g. Microscopy revealed marked thinning of the capsule and adrenal cortex. The heart was moderately enlarged and there was myocardial hypertrophy involving the right ventricle.

CASE 2 (UR: 248012)

This boy was 7 years 4 months old when he died in May 1974. Atopic eczema appeared at 3 months and wheezing at 12 months of age. His asthma soon became severe and chronic. Before attending this hospital he was treated from age 3 to 5 years with oral betamethasone in a dose equivalent to 20 mg prednisolone per day. He was grossly 'Cushingoid' when first seen and had a negligible adrenal response to tetracosactrin stimulation. After several months of regular intramuscular tetracosactrin he was changed to 4 mg prednisolone per day and remained on that dose until his death. He also received oral theophylline and orciprenaline inhalations via an air-compressor unit.

He was found dead in bed by his mother one morning, having been reasonably well the previous day, and was not heard to wheeze during the night.

Pulmonary function had not been tested in this boy as reliable results could not be obtained.

Pathology The lungs were large and heavier than normal and remained expanded even after sectioning. A considerable amount of clear tenacious mucus was present in the major bronchi and their larger branches. No obvious inflammation was evident in the upper trachea, although the mucosa of the lower trachea and main bronchi was red. Histology of the bronchi was typical of chronic asthma. The lumen of the bronchi contained mucus and the alveoli were well distended. No pathogens were isolated from the lungs.

Both adrenal glands were extremely small and microscopy revealed a thin cortex, all zones being atrophic. The heart was slightly enlarged.

Asthma deaths in children—a continuing problem

with a dilated right ventricular cavity. Myocardial and pulmonary blood vessels were microscopically normal.

CASE 3 (UR: 311788)

This boy was aged 14 years 10 months when he died in July 1974. He was adopted at the age of 1 month and began wheezing at 9 months. His asthma was chronic but with few severe exacerbations. He had a chronic productive cough, with yellow sputum, from the age of 8 years. At the age of 13 years his height was below the 3rd percentile, his weight between the 3rd and 10th percentile, and he had a severe 'barrel chest' deformity. Until then he had received virtually no medical treatment. He was started on 5 mg prednisolone daily, oral theophylline, and salbutamol inhalations via an air-compressor unit. Five months before he died he was weaned off prednisolone and started on beclomethasone dipropionate by inhalation.

A tetracosactrin stimulation test before the withdrawal of prednisolone was normal. Pulmonary function tests two weeks before death were similar to his previous studies, with severe obstruction to flow rates and a moderate improvement following bronchodilators. Vital capacity (VC) was within normal limits, but he had evidence of severe air-trapping with a residual volume (RV) to total lung capacity (TLC) ratio of 50%.

Approximately 48 hours before he died he had an exacerbation of wheezing and took 10 mg of oral prednisolone. The following day he had improved and took 5 mg prednisolone. That night the wheeze and dyspnoea became more severe, he had difficulty sleeping, and required several inhalations of salbutamol (at 9 pm and 3 am). His parents did not seek medical advice and at 6 am he became extremely distressed and cyanosed, then collapsed, and died several minutes later.

Pathology Both lungs were emphysematous and heavier than normal. The trachea and bronchi were injected and granular and contained dark bloodstained mucus, the appearances suggesting an acute tracheobronchitis. Surprisingly, there was no macroscopic or microscopic evidence of mucus plugging. The typical histological findings of chronic asthma were present in the bronchial walls. In addition, there was mild septal cell metaplasia, patchy obliteration of bronchioles with resultant fibrosis, and chronic inflammatory changes in the trachea and major bronchi. No pathogens were isolated from the lungs.

The adrenal glands were very small and there was hypoplasia of the zona glomerulosa, con-

sistent with steroid therapy. The heart was considerably enlarged with obvious myocardial hypertrophy on microscopy.

CASE 4 (UR: 280588)

This girl was aged 13 years 2 months when she died in August 1974. She developed asthma and eczema in early infancy and had frequent episodes of wheezing from that time.

When first seen at this hospital at the age of 10 years, she had been receiving oral betamethasone in a dose equivalent to 20 mg prednisolone per day for the previous 12 months and was 'Cushingoid'. Her steroid dosage was gradually reduced to 5 mg prednisolone per day, and sodium cromoglycate and oral theophylline plus salbutamol inhalations via an air-compressor unit were added. The dose of prednisolone was subsequently reduced to 3 mg per day. Six months before her death oral steroids were withdrawn and she was started on beclomethasone dipropionate aerosol. A tetracosactrin stimulation test before cessation of prednisolone revealed abnormal adrenal responsiveness. A repeat test after six months on beclomethasone dipropionate was normal. Because she was taking part in a clinical trial comparing oral and aerosol steroids she was again given 3 mg of oral prednisolone daily (Mellis *et al.*, 1976). Ten days later she experienced a sudden severe bout of wheeze and dyspnoea, started an inhalation of salbutamol but collapsed and died while this was being administered.

Pulmonary function tests two weeks before death were better than many of her previous tests. Flow rates were moderately reduced but almost returned to normal following bronchodilators. VC was normal, but she had evidence of air trapping with a RV : TLC ratio of 40%.

Pathology Both lungs were congested and almost completely collapsed. The mucosal surfaces of the trachea and major bronchi were red, and the lumen contained green tenacious mucus. Intrapulmonary bronchi had gross mucosal thickening which in many instances obliterated the lumen. The lung tissue generally was collapsed and airless in contrast to the usual overdistended lungs seen in patients dying from asthma. Histology showed the bronchial wall changes of chronic asthma. The bronchial lumina were plugged with mucus which was infiltrated with eosinophils. Scattered areas of early pneumonic consolidation were present throughout both lungs. No pathogens were isolated from the lungs.

Both adrenals appeared smaller than normal, the outer zone of the cortex was obviously nar-

rowed, and their combined weight was 3.1 g. The right ventricle was hypertrophied both microscopically and macroscopically.

CASE 5 (UR: 178231)

This girl was aged 16 years 9 months when she died in September 1974. She developed asthma and eczema during early infancy and had frequent severe bouts of wheezing from that age. At the age of 2½ years she was requiring 5 mg of prednisolone per day to achieve reasonable control of her symptoms. By 14 years this had increased to 10 mg per day, plus oral theophylline and salbutamol inhalations via an air-compressor unit.

Five months before she died she was started on beclomethasone dipropionate aerosol and oral prednisolone was withdrawn. A tetracosactrin stimulation test at that time revealed borderline low adrenal responsiveness. Six weeks later she developed symptoms suggestive of adrenal insufficiency with headaches, lethargy, weakness, and vague joint pains. The symptoms subsided spontaneously after four weeks and did not recur.

One week before she died she had a sudden, severe bout of dyspnoea with marked pallor and central cyanosis lasting for several minutes. While at school one week later she had a similar episode but this time she lost consciousness and died within minutes. Several days beforehand she had been absent from school with a 'head cold'. On the day she died she was said to be back to her normal self, although she did experience several bouts of wheeze requiring bronchodilator inhalations during that day.

Respiratory function had been tested four weeks before death and showed only mild obstruction, with normal flow rates following bronchodilator. Lung volumes were within normal limits apart from a slightly elevated RV.

Pathology Both lungs were expanded and did not collapse after removal from the thoracic cage. The mucosal surfaces of the trachea and main bronchi were reddened and had adherent mucus. Secondary bronchi had congested, oedematous mucosa and contained tenacious mucus. The lung tissue was soft and crepitant. Macroscopically the appearance was that of acute tracheobronchitis. Streptococci were seen on microscopy and subsequently cultured (group F, beta-haemolytic) from secretions. Parainfluenza virus was also isolated from these secretions.

Histology of bronchial walls was again typical of chronic asthma. There was evidence of an intense inflammatory infiltrate involving the mucosa and submucosa with lymphocytes, plasma cells, and eosinophils but no polymorphs. A striking

feature was the virtual absence of mucus plugging of the smaller bronchi.

Discussion

In Australia and Britain there has been a genuine increase in the mortality rate from asthma during the past 15 years. This rise has been more marked in patients under the age of 35 years, and particularly in children between 10 and 14 years.

There are inherent problems with comparisons of asthma death rates from year to year. Changes in the classification of death from asthma have occurred regularly. In 1950 it was altered, allowing 'bronchitis' to be included among asthma deaths. After 1957 this potential ambiguity was removed, asthma and bronchitis being accorded separate labels. These alterations should have had little bearing upon the certification of childhood deaths, as diagnostic difficulties between the obstructive lung diseases are not a significant problem in this age group. Unwillingness to ascribe death to asthma in a child could have resulted in falsely low figures before the extensive documentation of the problem in the late 1960s. The consequent more ready acceptance that children die from asthma may be a contributing factor to the change in statistics. Inaccuracies and confusion are possible in distinguishing between 'death due to bronchopneumonia' and 'death due to asthma', particularly where the exacerbation of asthma has been precipitated by viral tracheobronchitis and/or bronchopneumonia.

Estimates of the actual mortality rate among asthmatic children vary widely. Richards *et al.* (1967) state that between 4 and 10% of children in the United States have asthma, and of these eventually 1–2% will die from the disease. In Australia 20% of schoolchildren have asthma, although less than 5% have troublesome symptoms (Williams and McNicol, 1969). The mortality rate from asthma in the 5–19 year age group in Australia is approximately 10 per 1 000 000 living children (Figure). The only asthmatic child who appears to be in real danger of dying is the severe, chronic asthmatic who represents only a small percentage of the childhood population, perhaps 0.5% (McNicol and Williams, 1973). This mortality rate among this group is considerable and may approach 1–2%, this risk being greatest between 10 and 14 years of age. Males are more likely to have asthma of this severity and are more likely to die from asthma.

From the five deaths in this report, a retrospective investigation of this hospital's experience over the past 20 years, and a review of the literature

Asthma deaths in children—a continuing problem

ture on the subject it is clear that only those children with severe chronic asthma are vulnerable. The features of these children include: asthma from early infancy; 'barrel-chest' deformity; shortness of stature; underweight; persistent presence of rhonchi on auscultation of the chest; and dependence upon continuous corticosteroid therapy in addition to maintenance bronchodilator therapy for control of symptoms. The chances of death from asthma among children with mild episodic asthma are remote; the few deaths reported in this category have resulted from toxicity due to gross overdosage of theophylline or sedatives. It is only in this group of asthmatic children that death can be considered 'unexpected'. The finding of right ventricular hypertrophy, indicating long-standing hypoxaemia, in four of the five cases reported here highlights the fact that children with severe, chronic asthma require only a minor deterioration in their ventilatory disturbance to develop gross life-threatening hypoxaemia.

The ultimate cause of death in these five children was presumably severe hypoxaemia from asthma alone or asthma associated with acute inflammatory disease of the lungs and tracheobronchial tree. A suppressed hypothalamic-pituitary adrenal (HPA) axis was almost certainly a contributing factor in all cases. The four children in whom the adrenal glands were examined had obvious atrophy. Tetracosactrin stimulation tests performed in three of the children shortly before they died were normal despite this obvious atrophy. This test gives no information regarding the hypothalamic-pituitary portion of the HPA axis and may be less sensitive in detecting adrenal atrophy than previous reports would suggest (Wood *et al.*, 1965; Greig *et al.*, 1969).

A factor which may have been relevant to the deaths of patients 3, 4, and 5 is that they had recently been weaned from oral prednisolone to beclomethasone dipropionate aerosol. This occurred approximately six months before their deaths, although during that period all had received intermittent short courses of oral prednisolone for exacerbations of wheezing, and two of the three were receiving oral prednisolone at the time they died. The dangers of withdrawing systemic corticosteroids from severe asthmatics after their long-term use are well known. Severe attacks of asthma are particularly likely to occur following 'weaning' from these drugs (Maunsell *et al.*, 1968). The duration of this high-risk period is unknown but probably extends for at least 12 months after cessation of long-

term systemic steroids and presumably varies, depending on the dosage and duration of such therapy.

A direct causal relationship between beclomethasone dipropionate and the deaths of patients 3, 4, and 5 seems unlikely but not impossible. Although the exact mechanism of action of corticosteroids in asthma remains unknown there is evidence to suggest that one of the major effects is the potentiation of sympathomimetic bronchodilators (Shenfield *et al.*, 1975). It is possible that the bronchodilator responsiveness to inhaled steroids is not as effective as that obtained with systemic steroids. At a clinical level there is no suggestion of an increasing bronchodilator requirement when patients are changed from oral prednisolone to beclomethasone dipropionate by inhalation. Moreover, respiratory function tests were performed while patients 3, 4, and 5 were receiving steroids by aerosol and did not show a measurable difference in bronchodilator response compared to when they were receiving prednisolone by mouth. It is possible that inhaled steroid may suppress local immune protective mechanisms in the tracheobronchial tree, resulting in a predisposition to infective agents. There are no previous reports to indicate that symptomatic respiratory tract infections are more frequent when patients receive beclomethasone dipropionate despite extensive use of this agent. Although the three children receiving beclomethasone dipropionate had evidence of inflammation of the lungs, in only one child was a likely pathogen isolated (Parainfluenza virus, case 5), thus making this an unlikely factor in these deaths.

Fraser *et al.* (1971) reviewed a large series of patients who died from asthma in Britain and found that over 90% had overdistended, voluminous lungs with widespread mucus plugging of small airways. These findings are now regarded as typical of asthma deaths, and the presence of acute inflammation is considered unusual (Dunnill, 1971). However, in the United States a number of reports have underlined the frequent presence of inflammation in the tracheobronchial tree, including bronchopneumonia, in children dying from asthma (Buranakul *et al.*, 1974; Richards and Patrick, 1965). It is not clear why there should be such a contrast between British and US necropsy findings. Viral respiratory tract infections commonly precipitate exacerbations of asthma in children, particularly in the very young. Therefore, it would not be surprising if inflammatory changes in the lungs were found in paediatric patients dying from asthma. The pathology findings in these five children were

more variable than in previous reports. Although this is only a small number of patients, there was a similarity in the pathology of those children who had received beclomethasone dipropionate. These three children (cases 3, 4, and 5) had acute inflammatory changes in the lungs. Moreover, there was a notable absence of mucus plugging of small airways in patients 3 and 5, and patient 4 had collapsed lungs. Those children who had not received beclomethasone dipropionate (cases 1 and 2) had the typical necropsy findings described by Fraser *et al.* (1971) and did not have acute inflammatory changes in the lungs.

In conclusion, it must be emphasized that the child with severe, chronic asthma is at significant risk of dying from the disease in childhood. The risk of dying is increased in those children who have been weaned from long-term systemic corticosteroids. An increasing number of children are now entering this category following the introduction of beclomethasone dipropionate. It is of the utmost importance that children in this situation, and their parents, are instructed to recommence oral corticosteroids in at least moderate dosage if an exacerbation of wheezing does not respond promptly to their usual bronchodilator therapy. Moreover, they must be aware that during exacerbations of airways obstruction effective use of corticosteroid aerosol is impossible.

Our thanks are due to Dr. A. L. Williams and Dr. P. Campbell who performed the necropsies; to Dr. J. Connelly for biochemical studies; to the Commonwealth Bureau of Census and Statistics, Canberra, Australia; and to Mrs. S. Willis for secretarial duties.

References

- Buranakul, B., Washington, J., Hilman, B., Mancuso, J., and Sly, R. M. (1974). Causes of death during acute asthma in children. *American Journal of Diseases of Children*, **128**, 343-350.
- Canadian Medical Association Journal (1969). Mortality from bronchial asthma. (Editorial) *Canadian Medical Association Journal*, **100**, 485-487.
- Dunnill, M. S. (1971). The pathology of asthma. In *Identification of Asthma: Ciba Foundation Study Group, No. 38*, edited by R. Porter and J. Birch, pp. 35-46. Churchill Livingstone, Edinburgh and London.
- Fraser, P. M., Speizer, F. E., Waters, S. D. M., Doll, R., and Mann, N. M. (1971). The circumstances preceding death from asthma in young people in 1968 to 1969. *British Journal of Diseases of the Chest*, **65**, 71-84.
- Gandevia, B. (1968). The changing pattern of mortality from asthma in Australia: 2. mortality and modern therapy. *Medical Journal of Australia*, **1**, 884-891.
- Gandevia, B. (1973). Pressurized sympathomimetic aerosols and their lack of relationship to asthma mortality in Australia. *Medical Journal of Australia*, **1**, 273-277.
- Greig, W. R., Maxwell, J. D., Boyle, J. A., Lindsay, R. M., and Browning, M. C. K. (1969). Criteria for distinguishing normal from subnormal adrenocortical function using the Synacthen test. *Postgraduate Medical Journal*, **45**, 307-313.
- Hill, D. J., Landau, L. I., McNicol, K. N., and Phelan, P. D. (1972). Asthma—the physiological and clinical spectrum in childhood: respiratory function studies in its assessment. *Archives of Disease in Childhood*, **47**, 874-881.
- Katz, R. M. (1970). Cough syncope in children with asthma. *Journal of Pediatrics*, **77**, 48-51.
- Lancet (1969). Aerosol bronchodilators and asthma mortality. (Editorial) *Lancet*, **2**, 305-307.
- McNicol, K. N. and Williams, H. B. (1973). Spectrum of asthma in children: I. Clinical and physiological components. *British Medical Journal*, **4**, 7-11.
- Maunsell, K., Pearson, R. S. B., and Livingstone, J. L. (1968). Long-term corticosteroid treatment of asthma. *British Medical Journal*, **1**, 661-665.
- Mellis, C. M., Steiner, N., and Phelan, P. D. (1976). Beclomethasone dipropionate aerosol in asthmatic children requiring maintenance oral steroid. *Medical Journal of Australia*, **1**, 957.
- Richards, W. and Patrick, J. R. (1965). Death from asthma in children. *American Journal of Diseases of Children*, **110**, 4-21.
- Richards, W., Siegel, S. C., Strauss, J., and Leigh, M. D. (1967). Status asthmaticus in children. *Journal of the American Medical Association*, **200**, 75-81.
- Shenfield, G. M., Hodson, M. E., Clarke, S. W., and Paterson, J. W. (1975). Interaction of corticosteroids and catecholamines in the treatment of asthma. *Thorax*, **30**, 430-435.
- Silverglade, A. (1971). Evaluation of reports of death from asthma. *Journal of Asthma Research*, **8**, 95-98.
- Speizer, F. E., Doll, R., and Heaf, P. (1968). Observations on recent increase in mortality from asthma. *British Medical Journal*, **1**, 335-339.
- Stolley, P. D. (1973). Asthma deaths and bronchodilator aerosols (Letter). *American Review of Respiratory Disease*, **107**, 1078-1079.
- Williams, H. and McNicol, K. N. (1969). Prevalence, natural history, and relationship of wheezy bronchitis and asthma in children: an epidemiological study. *British Medical Journal*, **4**, 321-325.
- Wood, J. B., Frankland, A. W., James, V. H. T., and Landon, J. (1965). A rapid test of adrenocortical function. *Lancet*, **1**, 243-245.

Requests for reprints to: Dr. C. M. Mellis, Department of Thoracic Medicine, Royal Children's Hospital, Parkville, Victoria 3052, Australia.