

Fatal asthma in a young patient with severe bronchial hyperresponsiveness but stable peak flow records

M. Saetta, G. Thiene*, S. Crescioli, L.M. Fabbri

Fatal asthma in a young patient with severe bronchial hyperresponsiveness but stable peak flow records. M. Saetta, G. Thiene, S. Crescioli, L.M. Fabbri.

ABSTRACT: We report the sudden death of a 16 yr old boy with asthma. At presentation, the patient had symptoms of active asthma, mild bronchoconstriction, severe airway hyperresponsiveness to methacholine, and increased variability of peak expiratory flow records. After the patient was placed on inhaled beclomethasone (1 mg *b.i.d.* preceded by inhaled fenoterol 0.4 mg *b.i.d.*) he rapidly felt better, lung function improved, but airway responsiveness remained severe. Four months later, on the day he died, he was well until a fatal attack of asthma occurred around midnight without identifiable precipitating factors. Taken to hospital, he was dead on arrival. Necropsy and microscopy showed the characteristic features of asthma death. This case report suggests that; a) asthma death may occur suddenly and unexpectedly; b) asthma death may not be prevented by long-term treatment with high-dose inhaled beclomethasone; c) severe bronchial hyperresponsiveness, even in the presence of stable peak flow records, may identify asthmatic patients at risk of sudden death.
Eur Respir J., 1989, 2, 1008-1012.

Institute of Occupational Medicine, University of Padova and *Dept of Pathology, University of Padova, Italy.

Correspondence: M. Saetta, Istituto di Medicina del Lavoro, Università degli Studi di Padova, Via Jacopo Facciolati 71, 35127 Padova, Italy.

Keywords: Asthma; airway responsiveness; inflammation, fatal asthma.

Received: 22 January, 1989; accepted after revision 9 August, 1989.

Presented at the Annual Meeting of the Societas Europaea Physiologiae Clinicae Respiratoriae, Athens, 20-24 June, 1988.

Supported by Italian National Research Council (Grants No. 87.00215.04 and 87.00266.56), by the Italian Ministry of Education, and by the European Community for Coal and Steel.

Bronchial asthma affects 3-5% of the population [1], and deaths from asthma, although uncommon, have received increasing attention for several reasons. A significant increase of asthma deaths, particularly in young people, has been reported in some countries such as the United Kingdom [2] and New Zealand [3], at a time when the advances made in the understanding of the pathogenetic mechanisms of asthma and the introduction of many effective therapeutic agents were expected to improve the prognosis of the disease.

There is some agreement that most deaths from asthma can be attributed to inadequate assessment and/or inadequate treatment [4], and there is a belief that asthma deaths might indeed be prevented by avoiding the triggering factors, when known, and by instructing patients and physicians to face the severity that the disease may achieve by using appropriate treatment [4, 5]. Prophylaxis of severe attacks is also important; treatment that reduces diurnal variations of airflow obstruction may decrease the risk of sudden death, since patients with a large diurnal variation are at greatest risk [5-8].

We hereby report the case of a young patient with asthma who died suddenly, despite the fact that pharmacologic treatment with inhaled steroids and bronchodilators was able to control symptoms and circadian variations in airflow limitation for weeks.

Case Report

A 16 yr old boy with a 13 yr history of asthma had been treated in the previous month with inhaled fenoterol (400 µg *b.i.d.*) and inhaled beclomethasone (1 mg *b.i.d.*), and was well until a few minutes before a fatal asthma attack occurred on November 17, 1987, around midnight.

Past history included infant eczema, bronchial asthma from the age of 3 and a positive skin test for grass pollen, *Dermatophagoides pteronissinus* and *Dermatophagoides farinae*. Radioallergosorbent test was positive for grass pollen and negative for mites. Family history was positive for atopy and allergic rhinitis, but not for asthma. Immunotherapy with grass pollen was performed from 1979 to 1983, and did not provide significant benefits or local or systemic reactions. The patient was not known to have any drug sensitivities, history of aspirin-induced asthma, rhinitis, or food allergy. Parents excluded addiction to any drug. In the last five years he had 1 to 2 severe asthma attacks per year and frequent episodes of mild dyspnoea with wheezing during the night in the summer-fall season. He also had exercise-induced asthma.

Until August, 1987, when he was admitted to our Asthma clinic, he was treated regularly with theophylline (Theo-Dur 200 1 tablet in the evening) and

with inhaled fenoterol, and with oral steroids during exacerbations. On August 10, 1987, when he came to our Clinic complaining of asthma symptoms, spirometry and inhalation challenges with methacholine were performed. Spirometry demonstrated mild bronchoconstriction (vital capacity) (VC = 5.0 l, 93% predicted; forced expiratory volume in one second (FEV₁) = 3.7 l, 79% predicted) and inhalation challenge with methacholine revealed extremely severe airway hyperresponsiveness (provocative dose of methacholine causing a 20% decrease in FEV₁ (PD₂₀ FEV₁) methacholine <0.02 mg). Airway responsiveness to methacholine aerosol was assessed with the dosimeter method as previously described [9]. With this method airway responsiveness is considered extremely severe if PD₂₀ FEV₁ is less than 0.02 mg, severe if PD₂₀ FEV₁ is between 0.02 and 0.1 mg, moderate if PD₂₀ FEV₁ is between 0.1 mg and 0.7 mg, and normal above 1.4 mg.

The patient was advised to buy a peak flow meter (Assess, Health Scan Products Inc., Cedar Grove, NJ) and the appropriate diary (Agendasma, Markos, Monza, Italy), and to return to our Clinic in one week. On the 2nd of September, 1987, his lung volumes were unchanged (VC = 5.4 l, 100% predicted; FEV₁ = 3.8 l, 80% predicted), but at the inhalation challenge he reacted to the inhalation of the diluent phosphate buffer saline (FEV₁ fall = 22%) so that the test could not be completed.

The patient was instructed to use the peak flow meter and to record peak expiratory flow rate (PEFR), symptoms, and therapy in the daily diary card. He was asked to record PEFRs at 7.00, 10.00, 14.00, 18.00, and 22.00 h, and to report measurements obtained shortly after bronchodilator (when needed) to assess the reversibility of bronchoconstriction. The variability of PEFR was calculated as described by RYAN *et al.* [10], *i.e.* the difference between the maximum and minimum PEFR of each day expressed as a percentage of the maximum. The reversibility to fenoterol was calculated as the percentage ratio between the PEFR value after the inhalation and the closest PEFR value before the inhalation of fenoterol.

The patient was recommended to use regularly inhaled steroids (beclomethasone dipropionate, Clenil Forte, Chiesi, Parma, 0.5 mg *b.i.d.*), and inhaled fenoterol only when required. During the first 4 days of treatment PEFRs remained highly variable (the mean variability of the four days was 32%), and the reversibility to fenoterol reached 62% (fig. 1a). Already during the following week (four days are represented in fig. 1b) the patient reported a significant improvement of symptoms, PEFR increased, and the diurnal variation of PEFRs decreased (the mean variability of the four days was 13%, a value very similar to the mean variability found in non-asthmatic subjects [10]), but occasional morning dip was still present (fig. 1b).

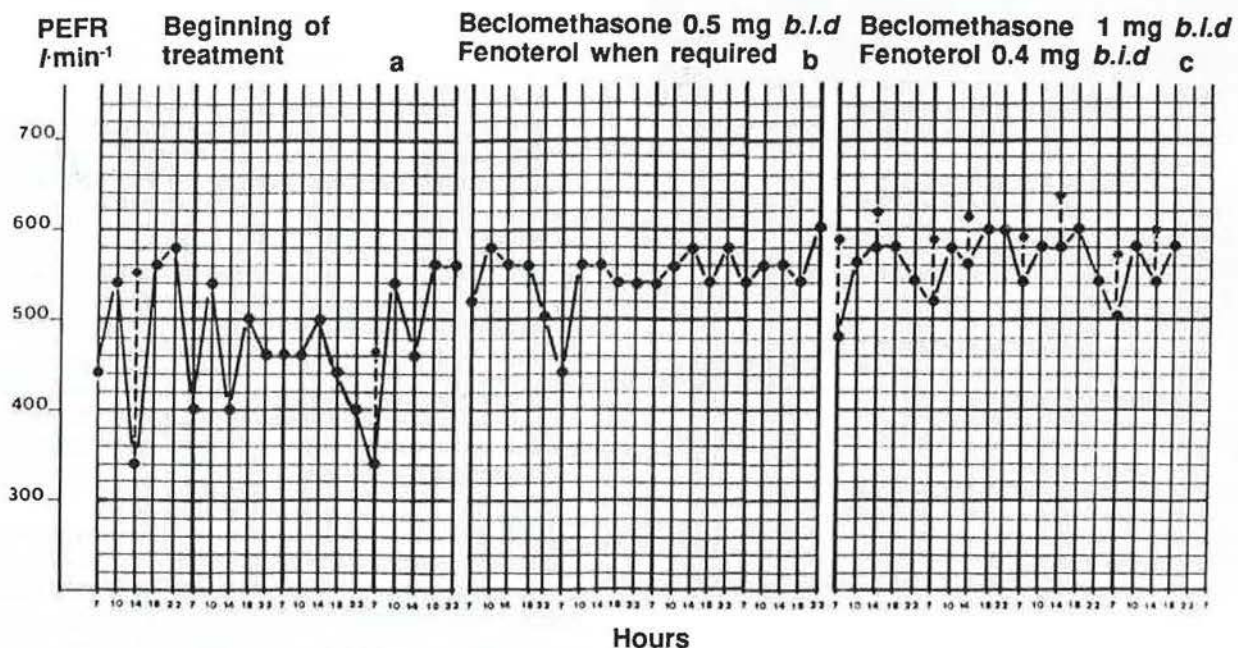


Fig. 1. - Peak expiratory flow rates (PEFR) at 7.00, 10.00, 14.00 and 22.00 hours during the first four days of treatment (panel a), during four days of the following week (panel b), and during the last four days before the fatal attack (panel c). Dotted lines and asterisks represent the reversibility to fenoterol. The daily variability of PEFR calculated as described in the text was: 41%, 26%, 20% and 39%, mean value = 32%, in panel a; 14%, 21%, 7% and 10%, mean value = 13%, in panel b; 17%, 13%, 10%, and 14%, mean value = 14%, in panel c. The reversibility to fenoterol, calculated as described in the text, was: 62% and 35%, mean value = 49% in panel a; 23%, 7%, 13%, 9%, 9%, 10%, 14% and 11%, mean value = 12% in panel c.

On October 7, 1987, spirometric values had almost completely returned to within normal values ($VC=5.5$ l, 103% predicted; $FEV_1=4.2$ l, 88% predicted); however, at variance with previous measurements, FEV_1 progressively decreased with forced manoeuvres alone (FEV_1 decreased from 4.2, to 3.6, and 3.2 in the three blows). Thus, again, the inhalation challenge with methacholine could not be performed, and, because this was interpreted as a sign of marked airway hyperresponsiveness, treatment was changed (fenoterol 0.4 mg *b.i.d.*, to be taken before beclomethasone; beclomethasone increased to 1 mg *b.i.d.*).

In the month before the fatal attack, he did not complain of asthma symptoms or exercise-induced asthma. He reported a cold around the end of October, but this event was not associated with asthma symptoms or with changes in PEFs. In the four days before the fatal attack (fig. 1c) the values of PEFs ranged between 480 and 600 $l \cdot min^{-1}$, and the mean variability of the four days was 14%. During the same days the patient regularly took the usual medications, and the mean daily reversibility to fenoterol was around 12% (fig. 1c).

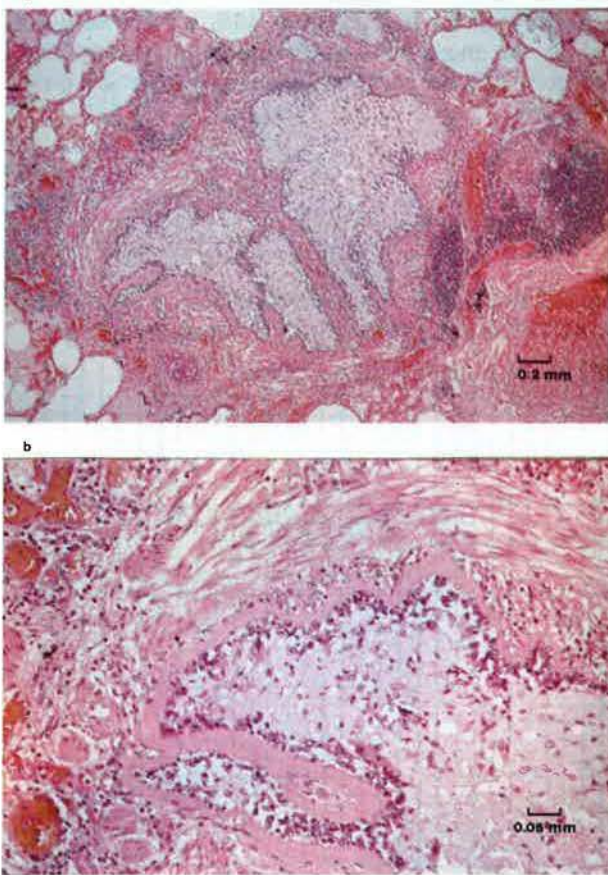


Fig. 2. - Panel a: cross-section of a cartilaginous bronchus occluded by mucous plug. Nodular inflammatory infiltrates are seen in the outer layer of the bronchial wall. Stain: haematoxylin-eosin; Panel b: detail of panel a, showing marked thickening of the basement membrane, oedema dissociating the smooth muscle cells, and scattered inflammatory infiltrates. Stain: haematoxylin-eosin.

On November 17, 1987, the day he died, in the morning he ran for about two miles because he missed the bus and was late for school. He did not report symptoms or additional medications in the diary, his PEFs ranged between 500 and 580 $l \cdot min^{-1}$ during the day, and the reversibility to fenoterol was 14% at 7.00 and 11% at 14.00 (fig. 1c). He took the usual medications (last dose of fenoterol and inhaled steroid at 18.00), and after a light dinner he went to bed around 22.00. His mother saw the patient sleeping well around midnight, and his breathing seemed normal to her. About 30 min later she heard the patient stepping into the bathroom where he kept his medicines: then she heard 4 actuations of a pressurized cannister, then identified to contain fenoterol. By the time she came to see him, he was already heavily dyspnoeic and unable to speak. The mother felt that he was already dead at home within 15 min. Taken by the father to the nearest hospital, he was dead on arrival.

Necropsy excluded cerebral or cardiovascular causes of death. The lungs were overinflated. Specimens from different lobes were obtained after fixation in 10% formaldehyde in saline. Specimens were embedded in paraffin wax, sections 7 μm thick were cut and stained with haematoxylin-eosin. Microscopy showed scattered alveolar oedema, oedematous thickening of the bronchial walls associated with dilatation of the bronchial vessels, mucous plugs with desquamated epithelial cells suboccluding most of the airways (fig. 2a), denudation of airway epithelium, marked thickening of the basement membrane (fig. 2b), smooth muscle hypertrophy and inflammatory infiltrate, including eosinophils, mainly in the outer layer of the airway walls.

Discussion

This paper reports a fatal attack of asthma in a young patient who was well-controlled by regular treatment with inhaled steroids and beta-agonists. He complained of no symptoms and his peak flow records had been quite stable in the last month before death, but he had an extremely severe degree of airway hyperresponsiveness which was not affected by therapy. Death occurred suddenly without premonitory symptoms or signs. The fatal attack was so sudden and progressed so rapidly that appropriate medical help could not be given in time. Previous reports have emphasized that up to one quarter of deaths from asthma occur within 30 min of onset of the attack [11], and that there are children with apparently trivial asthma who are at risk of sudden death [12].

In the present report two recent events could be related to the fatal outcome. Firstly, the patient had an infection of the upper airways, probably viral, about three weeks before. That episode was not associated with obvious exacerbation of asthma, as suggested by the records showing that peak flows were unchanged, and he did not require additional therapy. Recent editorials do not mention viral infection as a risk factor for fatal asthma [4, 5, 13]. Secondly, the patient underwent strenuous exercise in the morning of the day he died; he had run

for about two miles because he had missed the bus and was late for school. However, he did not report symptoms or additional medications in the diary, and the peak expiratory flow rate was $500 \text{ l}\cdot\text{min}^{-1}$ at 07.00 and $580 \text{ l}\cdot\text{min}^{-1}$ at 10.00, *i.e.* before and after the run. Several papers reported late asthmatic reactions after exercise, and indeed some of these reactions may occur with several hours delay [14], but it is still doubtful whether such reactions are indeed due to exercise or to withdrawal of therapy [15, 16]. Whether or not the morning's strenuous exercise may have been the cause of the fatal attack remains uncertain.

Airway hyperresponsiveness is believed to reflect the severity of asthma, both because it correlates with the amount of medication required to control symptoms [17], and because it correlates with the morning dips and the diurnal variations of PEFrs [10]. This correlation is probably true for most asthmatic subjects but, unfortunately, this was not the case for the patient reported here. In fact, after he started regular therapy, his PEFrs increased and diurnal variation decreased to the levels found in non-asthmatic subjects [10], even if the degree of bronchial hyperresponsiveness remained extremely severe.

Indeed, the most striking functional finding in this patient was the severe bronchial hyperresponsiveness, bronchoconstriction being triggered even by inhalation of an extremely low dose of methacholine, phosphate buffer saline solution, or deep inspiration. Woolcock *et al.* [18] have studied bronchial responsiveness in patients who had a "near-miss death" from asthma. At the time of the study, 3 to 10 weeks after the nearly fatal attack, all patients had FEV₁ above 70% of the predicted value, but all had severe bronchial hyperresponsiveness, with PD₂₀ FEV₁ values less than 0.1 μmol of histamine (*i.e.* less than 0.25 $\text{mg}\cdot\text{ml}^{-1}$ with the Canadian protocol [19], less than 2.5 unit with the North American protocol [20], and less than 0.01 mg with our protocol [9]), and extreme steepness of the dose-response curves. The authors attempted to decrease the severity of bronchial hyperreactivity in these patients by using aggressive therapy based on high dose steroids. The three patients in whom airway responsiveness significantly decreased after therapy survived, whereas the two patients in whom airway responsiveness did not change subsequently had a fatal attack. From this experience, Woolcock suggests that the severity of bronchial hyperresponsiveness must be considered the most important risk factor of fatal asthma, and that adequate treatment, particularly with oral and topical steroids [21, 22], must be attempted to decrease the severity of airway responsiveness.

Although we did not give oral steroids, we observed that high dose inhaled beclomethasone (1 mg *b.i.d.*) taken regularly by the patient was able to control symptoms and improve PEFrs, and thus we considered asthma under control. However, retrospectively, because of the outcome of this case, we suggest that a course of oral steroids should be considered in patients with severe bronchial hyperresponsiveness.

The patient described used regularly inhaled fenoterol (400 μg *b.i.d.*) and recorded PEFrs before and after in-

halation. Asthma deaths have been related in the past to abuse of bronchodilator aerosols [23, 24], and such abuse could be due to development of tachyphylaxis [25]. In the present case, abuse of fenoterol could be excluded from the dosage carefully reported in the diary, and tachyphylaxis can be excluded by the observation that on the day he died he reported an increase of PEFr after fenoterol similar to that in the previous days both in the morning and at 14.00 (fig. 1c). However, a recent paper relates asthma death in New Zealand to the use of fenoterol by metered dose inhaler [26].

Oedema of the airway walls and mucous plugs were the prominent features of lung pathology. Although beta-agonists are first choice potent bronchodilators and must be used to treat acute asthma, they do not affect vascular permeability [27], and therefore they may not decrease bronchial oedema. The pathology and the outcome of this case may reinforce the suggestion that adrenaline, an agent with vasoconstrictor effects due to stimulation of alpha receptors in addition to beta receptors, should be used in particularly severe attacks of asthma not reversed by the usual therapy [7, 28]. In this case the fatal attack developed and progressed so rapidly that appropriate medical help could not be given in time, and previous reports have emphasized that up to one quarter of deaths from asthma occur within 30 min of onset of the attack [11]. We wonder whether appropriate education of patients at risk of sudden asthma death to carry emergency sets including aerosol bronchodilators, adrenaline and steroids, and appropriate training to use them, and particularly to take adrenaline, might help to reduce the number of sudden asthma deaths [7].

Microscopic examination of the lungs showed some characteristic features of asthma death [29–31]: mucous plugs suboccluding most of the airways, oedematous thickening of the bronchial walls associated with dilatation of the bronchial vessels, denudation of airway epithelium, marked thickening of the basement membrane, smooth muscle hypertrophy and inflammatory infiltrate, including eosinophils, mainly in the outer layer of the airway walls. Among all these features, the most striking microscopic finding was the excess of secretions and tissue swelling due to oedema of the bronchial walls. As pointed out by Moreno *et al.* [32], in these conditions of organic bronchial obstruction, even a small smooth muscle contraction could produce an amplified increase in resistance that in turn may contribute to the fatal event.

Acknowledgements: We thank Dr. L. Tolin for revising and typing the manuscript.

References

1. McFadden ER, Austen KF. – Asthma. *In:* Harrison's principles of internal medicine, 11th ed. E. Braunwald, K.J. Isselbacher, K.G. Petersdorf, J.D. Wilson, J.B. Martin, A.S. Fauci eds, McGraw-Hill, New York, 1987, pp. 1060–1065.
2. Morrison Smith J, Harding LK, Cumming G. – The changing prevalence of asthma in school children. *Clin Allergy*, 1971, 1, 57–61.

3. Mitchell E. – Increasing prevalence of asthma in children. *NZ Med J*, 1983, 96, 463–464.
4. Benatar SR. – Fatal asthma. *N Engl J Med*, 1986, 314, 423–429.
5. Sheffer AL, Buist AS (Eds). – Proceedings of the asthma mortality task force. *J Allergy Clin Immunol*, 1987, 80, 361–514.
6. Hetzel MR, Clark TJH, Branthwaite MA. – Asthma: analysis of sudden deaths and ventilatory arrests in hospital. *Br Med J*, 1977, 1, 808–811.
7. Bateman JRM, Clarke SW. – Sudden death in asthma. *Thorax*, 1979, 34, 40–44.
8. Westerman DE, Benatar SR, Potgieter PD, Ferguson AD. – Identification of the high-risk asthmatic patient: experience with 39 patients undergoing ventilation for status asthmaticus. *Am J Med*, 1979, 66, 565–572.
9. Mapp C, Boschetto P, Dal Vecchio L *et al.* – Protective effect of antiasthma drugs on late asthmatic reactions and increased airway responsiveness induced by toluene diisocyanate in sensitized subjects. *Am Rev Respir Dis*, 1987, 136, 1403–1407.
10. Ryan G, Latimer KM, Dolovich J, Hargreave FE. – Bronchial responsiveness to histamine: relationship to diurnal variation of peak flow rate, improvement after bronchodilator, and airway calibre. *Thorax*, 1982, 37, 423–429.
11. Macdonald JB, Seaton A, Williams DA. – Asthma deaths in Cardiff, 1963–1974: 90 deaths outside hospital. *Br Med J*, 1976, 1, 1493–1495.
12. Colin F, Robertson F, Bowes G, Rubinfeld A. – Sudden death in pediatric asthma. *Am Rev Respir Dis*, 1989, 139, A130.
13. Li JTC, O'Connell EJ. – Viral infections and asthma. *Ann Allergy*, 1987, 59, 321–333.
14. Lee TH, O'Hickey SP. – Exercise induced asthma and late phase reactions. *Eur Respir J*, 1989, 2, 195–197.
15. McFadden ER. – Exercise and asthma. *N Engl J Med*, 1987, 317, 502–504.
16. Rubinstein I, Levison H, Slutsky AS, Hak H, Wells J, Zamel N, Rebeck AS. – Immediate and delayed bronchoconstriction after exercise in patients with asthma. *N Engl J Med*, 1987, 317, 482–485.
17. Hargreave FE, Ryan G, Thomson NC, O'Byrne PM, Latimer K, Juniper EF, Dolovich J. – Bronchial responsiveness to histamine or methacholine in asthma: measurement and clinical significance. *J Allergy Clin Immunol*, 1981, 68, 347–355.
18. Drazen GM, Boushey HA, Holgate ST, Kaliner M, O'Byrne P, Valentine M, Widdicombe JH, Woolcock A. – The pathogenesis of severe asthma: a consensus report from the workshop on pathogenesis. *J Allergy Clin Immunol*, 1987, 80, 428–437.
19. Ryan G, Dolovich MB, Roberts RS *et al.* – Standardization of inhalation provocation tests: two techniques of aerosol generation and inhalation compared. *Am Rev Respir Dis*, 1981, 123, 195–199.
20. Chai H, Farr RS, Froehlich LA *et al.* – Standardization of bronchial inhalation challenge procedures. *J Allergy Clin Immunol*, 1975, 56, 323–327.
21. Kerrebijn KF, van Essen-Zandvliet EEM, Neijens HJ. – Effect of long-term treatment with glucocorticosteroids and beta-agonists on bronchial responsiveness in asthmatic children. *In: Glucocorticosteroids inflammation and bronchial hyperreactivity*. Hogg JC, Ellul-Michalleff R, Brattsand R, eds. Amsterdam, Excerpta Medica, 1985, pp. 104–109.
22. Dutoit JJ, Salome CM, Woolcock AJ. – Inhaled corticosteroids reduce the severity of bronchial hyperresponsiveness in asthma but oral theophylline does not. *Am Rev Respir Dis*, 1987, 136, 1774–1778.
23. Greenberg MJ, Pines A. – Pressurised aerosol in asthma. *Br Med J*, 1967, 1, 563.
24. Douglas EM, Hillier T, Johnson IC. – Pressurised aerosols in asthma. *Br Med J*, 1967, 2, 53.
25. Reed CE, Kemp JP, Pierson WE. – A report from the workshop on pharmacology: beta-adrenergic agonists. *J Allergy Clin Immunol*, 1987, 80, 442–443.
26. Crane J, Flatt A, Jackson R, *et al.* – Prescribed fenoterol and death from asthma in New Zealand, 1981–83: case-control study. *Lancet*, 1989, i, 917–922.
27. Boschetto P, Roberts NM, Rogers DF, Barnes PJ. – Effect of anti-asthma drugs on microvascular leakage in guinea-pig airways. *Am Rev Respir Dis*, 1989, 139, 416–421.
28. Coupe MO, Guly O, Brown E, Barnes PJ. – Nebulised adrenaline in acute severe asthma: comparison with salbutamol. *Eur J Respir Dis*, 1987, 71, 227–232.
29. Dornil MS. – Problems in the pathology of asthma. *Bull Eur Physiopathol Respir*, 1986, 22 (Suppl. 7), 9–11.
30. Hogg JC. – The Pathology of asthma. *In: Bronchial asthma*. Weiss SB, Barsan GC, Segal MS, Stein M, eds. Boston, Little, Brown, 1985, pp. 209–217.
31. Saetta M, Danielli D, Fabbri LM, Allegra L. – Pathology of bronchial asthma and animal models of asthma. *Eur Respir J*, 1989, 2, Suppl 6, 477s–482s.
32. Moreno RH, Hogg JC, Pare PD. – Mechanics of airway narrowing. *Am Rev Respir Dis*, 1986, 133, 1171–1180.

Asthme mortel chez un jeune patient avec hyperréactivité bronchique sévère, mais valeurs stables du débit de pointe. Observation clinique. M. Saetta, G. Thiene, S. Crescioli, L.M. Fabbri.

RÉSUMÉ: Nous faisons état de la mort subite d'un garçon de 16 ans atteint d'asthme. A l'admission, le patient avait des symptômes d'asthme évolutif, une bronchoconstriction légère, une hyperréactivité sévère des voies aériennes à la Methacholine, et une augmentation de la variabilité des valeurs du débit de pointe. Après traitement à la beclométhasone en inhalation (1 mg 2 fois par jour précédé par 0.4 mg de fenoterol 2 fois par jour), il s'est senti rapidement amélioré, la fonction pulmonaire s'est améliorée, mais la réactivité bronchique restait sévère. Quatre mois plus tard, le jour de sa mort, il s'est senti bien jusqu'à ce que la crise d'asthme létale survienne vers minuit, sans aucun facteur précipitant identifiable. Il était mort à l'arrivée à l'hôpital. L'autopsie et l'examen microscopique ont montré les signes caractéristiques de la mort dans l'asthme. Cette observation suggère que la mort dans l'asthme peut survenir de façon soudaine et inattendue, que la mort dans l'asthme peut ne pas être prévenue par un traitement prolongé même avec de fortes doses de beclométhasone en inhalations, et qu'une hyperréactivité bronchique sévère même avec des débits de pointe stables peut identifier les patients asthmatiques à haut risque d'un décès par asthme. *Eur Respir J.*, 1989, 2, 1008–1012.