Discussion

The foregoing comments and recommendations on the hygiene of haemodialysis units are tentative and point the need for further work in this field. The clinical, engineering, and microbiological problems posed by these units call for interdisciplinary study. In particular, hospital bacteriologists should squarely accept responsibility for giving advice and practical help on the disinfection and monitoring of the machines now in use, and on the associated problems of cross-infection in dialysis unit patients and staff. We would also strongly recommend that physicians and surgeons dealing with increasingly sophisticated new medical and surgical procedures should consult their bacteriological colleagues at an early stage on the planning and management of units in which problems of cross-infection may arise.

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Arterial Blood Gas Tensions and pH in Acute Asthma in Childhood

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Brit. med. J., 1968, 3, 460-464

Summary: Studies of the arterial blood gas tensions and pH in 21 children during 24 acute attacks of asthma showed that all were hypoxic on admission to hospital, and in 10 there was evidence of carbon dioxide retention. Cyanosis, invariably present when the SO_2 was below 85%, and restlessness in patients breathing air were the most reliable indices of the severity of hypoxia. There were no reliable clinical guides to the P_{CO_2} level. Conventional oxygen therapy in tents (25-40%) did not always relieve hypoxia, and in three cases the administration of oxygen at a concentration of 40% or over failed to produce a normal arterial oxygen tension. Uncontrolled oxygen therapy may aggravate respiratory acidosis, and three of our patients developed carbon dioxide narcosis while breathing oxygen. The necessity for blood gas measurements in the management of severe acute asthma in childhood is emphasized.

Introduction

The arterial blood gas tensions in bronchial asthma in adults have been the subject of several recent reports (Rees, 1966 ;

Waddell *et al.*, 1967 ; Tai and Read, 1967 ; Palmer and Diamant, 1967). The situation in childhood asthma is not so well studied despite the evidence that respiratory failure is not uncommon (Tsuchiya and Bukantz, 1965 ; Downes and Wood, 1965) and death by no means rare in status asthmaticus in children (Lanoff and Crawford, 1964 ; Richards and Patrick, 1965). In addition, there has been the increase in mortality from asthma at all ages, most pronounced at ages 10-14 years (Speizer *et al.*, 1968).

In severe asthma in adults respiratory acidosis may be aggravated by injudicious oxygen therapy (Schiller *et al.*, 1951), but the importance of this potential danger in children with severe acute asthma is uncertain. We report here the clinical features and arterial blood gas findings in 21 children studied during 24 acute exacerbations of asthma and describe the response to therapy, in particular the administration of oxygen.

Patients and Methods

The patients (12 males and 9 females) ranged in age from 2 to 12 years and were admitted to the Royal Hospital for Sick Children, Edinburgh, between September 1965 and December 1967. Clinical details on admission are summarized in Table I. Case 1 was studied on two separate admissions and Case 2 on three. The severity of asthma was graded according to the classification of Kraepelin *et al.* (1958), grade I consisting of

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TABLE I.—Clinical Features on Admission, and Treatment

Case No.	Age in Years	Weight (kg.)	Duration* (years)	Grade†	History‡ (hours)	Cyanosis	Resp. Rate/min.	Pulse Rate/min.	Pre-assessment Sedation§	Response to Adrenaline	Other Treatment¶
1a	2	13.2	1	I	22	+	44	164	P, T	None	S; Inf. NaHCO ₃ ; Inh. E; I.P.P.R.
1b	2	14.2	1	I	12	+	56	182	T	None	S; Inf. NaHCO ₃ ; Inh. E; I.P.P.R.
2a	7	17.2	5	III	2	—	21	—	P, Pa	Not given	E; T; S; Inf. NaHCO ₃ ; Inh. E; I.P.P.R.
2b	8	17.8	6	III	24	—	32	160	None	Satis.	E; S
2c	8	18.0	6	III	15	+	30	138	None	None	S; Inf. NaHCO ₃ ; Inh. E; I.P.P.R.; A
3	5	18.6	3	II	18	—	46	146	None	None	A; S
4	4	12.8	1	II	48	+	65	160	P, T	None	O; S
5	5	16.8	4	I	30	+	36	168	None	None	E; S; Inf. NaHCO ₃
6	8	22.0	5	III	24	+	48	160	P	Not given	E; T; S
7	2	11.7	1	II	80–100	+	—	152	None	None	E; S
8	8	18.3	7	II	36	+	40	148	None	None	Inf. NaHCO ₃ ; S
9	4	15.0	3	I	46	+	54	166	None	None	E; S
10	12	35.1	8	III	24	+	44	140	None	None	O; S
11	11	26.7	9	III	60	+	30	112	None	None	E; O; S
12	12	25.9	5	III	72	—	30	132	P	Not given	E; T; S
13	12	28.4	11	III	48	—	28	132	P	Not given	E; S
14	2	11.4	1	II	24	—	76	168	T	None	E; T; S
15	3	15.1	1	II	18	—	65	160	None	None	E; T
16	7	16.8	6	III	12	—	34	140	None	Satis.	E; S
17	6	13.3	4	II	24	—	36	144	None	Satis.	B
18	12	41.2	11	III	—	—	36	140	None	Not given	E; S
19	7	22.1	3	II	6	—	38	180	None	Not given	E; S
20	9	27.9	7	I	—	—	32	114	None	Satis.	E; I
21	2	11.2	1	I	18	—	34	132	None	None	E; S

* Duration in years from age at onset of asthma until present admission.

† From classification of Kraepelin *et al.* (1958): grade I, <5 attacks per year; grade II, 5–10 attacks per year; grade III, 10 or more attacks per year or presence of continuous symptoms.

‡ Time in hours from onset of audible wheeziness until admission to hospital.

§ Sedation in 12 hours before initial studies: P = Phenobarbitone 0.5–2.0 mg./kg. T = Trichlorol 50–100 mg./kg. Pa = Paraldehyde 0.75 ml./year of age intramuscularly.

|| Satisfactory response to adrenaline is defined as disappearance of audible wheeze within two hours and progressive lessening of inspiratory retractions.

¶ Prescribed after admission: A = Aminophylline. E = Ephedrine. I = Isoprenaline. O = Orciprenaline. S = Steroids. T = Theophylline. Inf. NaHCO₃ = Infusion of sodium bicarbonate. Inh. E = Inhalational ether. I.P.P.R. = Intermittent positive-pressure respiration.

5 attacks per year, grade II of 5 to 10 attacks per year, and grade III of 10 or more attacks or the presence of continuous symptoms. All grade III cases in this study had been on continuous steroid therapy for one to three years. Each child had moderate to severe respiratory distress with recession of the supraclavicular spaces, intercostal spaces, and costal margins during inspiration. Several of the children were restless and others were very drowsy. On auscultation the breath sounds were diminished, with prolonged aspiration, and were accompanied by rales and rhonchi. Chest x-ray films showed overinflation and hypertranslucency in all cases, but in Cases 1b, 6, 9, 11, and 15 there were also zones of collapse or consolidation.

Plan of Investigation

Each case was assessed clinically by one of us (H. S.) soon after admission to hospital. Respiration and pulse rates were counted for one minute before arterial sampling, and cyanosis of the lips was assessed as present or absent by two independent observers. All equivocal observations were classed as "cyanosis absent." Lighting conditions were not uniform, as the children were studied at different times of night and day. Any restlessness or impairment of consciousness was noted. Blood samples were taken after the child had been breathing air or one constant oxygen concentration for at least 20 minutes. Arterial blood was then obtained from the brachial or femoral artery.

Oxygen was administered in an Oxyginaire Universal Tent at a flow rate of 4–10 litres per minute and the patient was positioned with one limb extruded from the tent to facilitate arterial sampling without opening the tent. Four to six samples of inspired gas were taken as described previously (Simpson and Russell, 1967) during the 20 minutes before and during blood sampling. The mean values of the oxygen concentrations of these samples (F_{iO_2}) are given in Table II. Individual samples were within the range mean value $\pm 3\%$ on all occasions but one (Case 7). After the initial period of air-breathing, oxygen was administered and subsequent blood and gas samples were taken as determined by clinical progress. In most cases therapy also included adrenaline hydrochloride 1:1,000 0.2–0.5 ml. subcutaneously and prednisolone 40 mg./day irrespective of body weight (see Table I). Cases 1a, 1b, 2a, and 2c were also given 100 mg. of hydrocortisone intravenously every two hours during the acute phase of their ill-

nesses. Sedation was avoided in most cases. All cases were treated with antibiotics, the majority being given ampicillin 50 mg./kg./day. Dehydration was corrected by oral or intravenous fluid therapy, and 8.4% sodium bicarbonate was administered intravenously in Cases 1a, 1b, 2a, 2c, 5, and 8, the initial dose being calculated as body weight (kg.) $\times$ base excess (mEq/l.) $\times$ 0.4 milliequivalent. Intermittent positive pressure respiration and inhalational ether were used in the treatment of Cases 1a, 1b, 2a, and 2c.

Laboratory Methods

Duplicate analyses of oxygen tension (P_{O_2}), carbon dioxide (P_{CO_2}), and pH were carried out at 37° C. within 10 minutes of blood sampling. Whenever the patient's temperature deviated more than 1° C. from this appropriate corrections were made, the data of Kelman and Nunn (1966) being used. The Radiometer P_{O_2} electrode (Type E5046), the Severinghaus P_{CO_2} electrode (Type E5036), and the pH electrode G297/G2 were used with the PHM 27 meter to measure P_{O_2} , P_{CO_2} , and pH respectively. A DCL 101 paramagnetic oxygen analyser calibrated with air and nitrogen (Nunn *et al.*, 1964) was used to measure the oxygen concentration of gas samples.

Calculations

Oxygen saturation (SO_2) and base excess values were calculated by means of the Severinghaus (1966) blood gas calculator. The alveolar oxygen tension (PA_{O_2}) was calculated from the alveolar air equation (Comroe *et al.*, 1962), assuming a respiratory quotient of 0.8. The alveolar-arterial oxygen tension gradient ($A-aDO_2$) was then obtained by subtraction.

Results

All 21 patients in the present series recovered. Their arterial blood gas tensions, pH, and calculated data on admission to hospital are shown in Table II. The arterial P_{O_2} was below 75 mm. Hg in all cases breathing air and in four it was less than 50 mm. Hg. Carbon dioxide retention, with a P_{CO_2} of 50 mm. Hg or over, was present in 10 admissions (six breathing air, four breathing oxygen), but in Case 14 the P_{CO_2} was 26 mm. Hg. pH ranged from 7.05 to 7.46 and was below normal (<7.36) in 11 admissions.

TABLE II.—Arterial Blood Gas Tensions and pH on Admission

Case No.	Measured Data				Calculated Data			
	Fio ₂	PO ₂ (mm. Hg)	PCO ₂ (mm. Hg)	pH	SO ₂ (%)	PAO ₂ (mm. Hg)	A-aDO ₂ (mm. Hg)	Base Excess (mEq/l.)
1a	35	45	78	7.16	66.5	145	100	-3.1
1b	21	55	56	7.25	82.5	77	22	-3.8
2a	40	89*	110*	7.05	91.4	138	49	-4.8
2b	21	65	39	7.36	92.0	95	30	-3.5
2c	21	60	45	7.32	88.5	92	32	-3.3
3	50	144	58	7.31	98.5	274	130	+1.5
4	21	50	61	7.32	81.0	73	23	+3.8
5	21	42	56	7.25	68.1	76	34	-3.6
6	21	51	58	7.31	81.5	72	21	+1.4
7	35	—	62	7.22	—	—	—	-0.3
8	21	47	54	7.22	73.6	80	33	-6.2
9	21	43	50	7.28	71.4	88	45	-3.8
10	21	59	46	7.36	89.4	91	32	+0.2
11	21	61	45	7.43	91.8	89	28	+5.0
12	21	54	36	7.41	88.3	103	49	-1.3
13	21	59	36	7.46	91.9	104	45	+2.4
14	21	73	26	7.38	94.6	103	30	-8.0
15	21	61	41	7.40	91.2	97	36	+0.7
16	21	67	42	7.37	92.8	91	24	-1.1
17	21	66	40	7.39	92.9	95	29	+0.4
18	21	69	45	7.39	93.6	95	26	+1.8
19	21	70	39	7.38	93.8	96	26	-1.8
20	21	70	37	7.40	94.2	103	33	-1.4
21	21	74	43	7.37	94.5	92	18	-0.4

Fio₂ = Inspired oxygen concentration as percentage at the time of blood-sampling.SO₂ = Arterial oxygen saturation.PAO₂ = Alveolar oxygen tension.A-aDO₂ = Alveolar/arterial oxygen tension gradient.* Previous investigations had been performed in air when the PO₂ was 30 mm. Hg and the PCO₂ 87 mm. Hg. A pH value was not obtained on that sample.

On admission the respiration and pulse rates of patients breathing air did not correlate with either arterial PO₂ ($P=0.9$) or PCO₂ ($P=0.9$). Cyanosis was noted on 19 occasions (admission and follow-up assessments). In all but one the arterial SO₂ was less than 90% and in 14 less than 85%. When cyanosis was absent the SO₂ was always over 85%, being over 90% on all but four occasions. The mean arterial PO₂ in the group of seven patients who were restless when breathing air on admission was significantly lower than the PO₂ in those who were not restless at this time ($P<0.05$). Restlessness, however, was not a reliable guide to the PO₂ when assessments were made with the patients breathing oxygen.

Drowsiness and confusion proved difficult to assess, particularly in the younger patients in the series, and precise correlation with either PO₂ or PCO₂ was not possible. Cases 1b, 4, 5, and 14, however, became very drowsy at a stage when their respective PCO₂ levels were 85, 72, 80, and 26 mm. Hg and when in each the PO₂ exceeded 70 mm. Hg.

Details of treatment are summarized in Table I. Adrenaline was given to 18 patients. The pH was below normal in 9 of the 14 in whom the response to adrenaline was unsatisfactory. In four patients who responded satisfactorily the pH was within normal limits (7.36–7.42). In Cases 1a, 2a, 2c, and 5 the base deficit was corrected by infusion of sodium bicarbonate in the dose stated. Larger infusions were required to maintain a pH>7.20 in Cases 2a and 2c before assisted ventilation.

Carbon dioxide retention increased on several occasions during the course of treatment, and Cases 1a, 2a, and 2c developed carbon dioxide narcosis while breathing oxygen.

TABLE III.—Arterial Blood Gas Tensions and pH Before Treatment with Ether and I.P.P.R.

Case No.	Values Before Ether and I.P.P.R.				Clinical State
	Fio ₂	PO ₂	PCO ₂	pH	
1a	35	52	125	7.10	Comatose; no response to stimulation
1b	33	85	85	7.25*	Increasing fatigue, confusion, and drowsiness
2a	40	47	110	7.02	Comatose; no response to stimulation
2c	40	89	137	7.05	Comatose; no response to stimulation

* NaHCO₃ infusion before pH measurement.

Table III shows the blood gas status of these patients before the use of intermittent positive-pressure respiration and inhalational ether. After clinical recovery a normal acid-base status

was restored in all cases within one to three days, but hypoxaemia in air often persisted for 7 to 10 days.

Discussion

These results confirm the findings of Downes *et al.* (1966) that hypoxaemia and respiratory acidosis are not uncommon in acute asthmatic attacks in childhood. Moreover, this study allows an assessment of the clinical signs of hypoxaemia and carbon dioxide retention and of the effects of oxygen therapy.

Correlation with Clinical Features

The severity of hypoxia and hypercapnia in these children was unrelated to the grade of severity of asthma as determined by the classification of Kraepelin *et al.* (1958) or to the duration of acute symptoms. Case 1a had previously had only one mild asthmatic attack. Case 2a, a child with chronic asthma on long-term steroid therapy, developed severe respiratory failure (Table II) within two hours of the onset of symptoms.

A raised respiration rate and tachycardia could result from multiple causes in these patients. It is not surprising, therefore, that these indices did not correlate with PO₂ measurements. Severe hypoxaemia may occasionally be present without cyanosis, but cyanosis, when present, was a reliable sign of hypoxia, all cases being cyanosed when the SO₂ was below 85%. Restlessness was a useful sign of hypoxia in patients breathing air but was not of value in patients breathing oxygen. Perhaps claustrophobic effects accounted for the agitation and restlessness occasionally present in oxygen tents when hypoxaemia had been relieved. Carbon dioxide narcosis abolished restlessness completely.

Though patients with hypercapnia are often very drowsy, Case 14, with a PCO₂ level of 26 mm. Hg, was confused and difficult to rouse at first, presumably because of the combined central effects of hypoxia, hypocapnia, and previous sedation. This patient was not clinically different from many others in the series with hypercapnia. Loss of consciousness, noted in Cases 1a, 2a, and 2c, during oxygen therapy must be regarded as due to severe carbon dioxide retention demanding immediate treatment. The danger of sedation in producing respiratory depression has been emphasized by Neder *et al.* (1963), and it is noteworthy that several patients with marked carbon dioxide retention in the present series had been sedated before the initial study (Tables I and II).

Of the clinical signs discussed, therefore, cyanosis is of most value as a guide to the arterial SO₂, while there are no really reliable guides to the PCO₂ level. In this respect our experience is similar to that of Bates and Christie (1964) in adults.

Hypercapnia and Acid-Base Balance

Feldman (1962) emphasized the grave prognostic significance of an increase in arterial PCO₂ in adults with severe asthma, and in no fewer than 10 of our 24 admissions the PCO₂ was 50 mm. Hg or above (Table II). This confirms previous observations that ventilatory failure is not uncommon in severe acute asthma in children (Tsuchiya and Bukantz, 1965; Downes *et al.*, 1966) and contrasts with the usual findings in adults. Rees (1966) found that carbon dioxide retention was uncommon in his 24 adult patients in status asthmaticus and that one-third were hyperventilating with a PCO₂ level below 35 mm. Hg. On the other hand, Tai and Read (1967) found that in 8 out of 12 adult cases, most of whom were breathing oxygen at the time, PCO₂ levels were greater than 50 mm. Hg on admission to hospital. Only one of our patients (Case 14, PCO₂ 26 mm. Hg) was hyperventilating initially, but could not be distinguished clinically from other children in the series.

An association between a low pH and an unsatisfactory response to adrenaline was noted in our patients. Blumenthal *et al.* (1961) postulated that asthmatics become adrenaline-resistant because of respiratory acidosis and found that responsiveness to adrenaline was restored in some patients after infusions of alkali. Turiaf *et al.* (1962) and Tsuchiya and Bukantz (1965) showed, however, that there is no constant relation between adrenaline resistance and acidosis, though severely acidotic patients invariably fail to respond to adrenaline. Tenney (1956) has suggested that this apparent inhibition of response to adrenaline may be due to an increase in circulating pressor substance caused by the rise in the PCO_2 .

Several of our cases had moderate metabolic acidosis on admission (Table II), corrected in Cases 1a, 1b, 5, and 8 by sodium bicarbonate infusion. In Cases 2a and 2c bicarbonate was infused to maintain the pH above 7.20 while preparations for assisted ventilation were being made. Striking clinical change or improvement in blood gas tensions did not follow in any case so treated, which contrasts with the experience of Mithoefer *et al.* (1965) in adults.

Cases 3, 4, 11, and 15 showed increasing metabolic alkalosis for one to two days after admission, though none of them had been given parenteral bicarbonate. This renal reabsorption of bicarbonate is an important defence against respiratory acidosis in adults (Refsum, 1964) and in children with acute lower respiratory tract infections (Simpson and Flenley, 1967), but it is too slow a mechanism to be of great importance in acute asthma, where dangerous hypercapnia may develop very rapidly.

Intermittent positive-pressure respiration has been used increasingly in the treatment of acute respiratory failure in asthma, both in adults (Marchand and van Hasselt, 1966; Ambavagar and Sherwood Jones, 1967) and in children (Downes and Wood, 1965; Beam *et al.*, 1965). In our cases so treated (Table III) a satisfactory reduction in PCO_2 was obtained only when manual ventilation was used in association with inhalational ether (Tausig *et al.*, 1952). A detailed account of the treatment of these patients is in preparation.

Effects of Oxygen Therapy

Oxygen was given to all acutely ill children on admission and was assumed to be adequate when the arterial PO_2 rose to 80 mm. Hg or more. In Fig. 1 the arterial PO_2 is plotted against the F_{IO_2} at the time when arterial blood samples were taken—all data being obtained in the first 24 hours after admission to hospital. This shows that oxygen therapy in the 25–40% concentration range may fail to relieve hypoxia in many cases. On four occasions (Cases 1a, 2c, and 5) an oxygen concentration of 40% or more did not ensure a normal PO_2 , which supports the findings of Downes and Wood (1965), who

suggest, however, than an inspired oxygen concentration of 50–60% should be used in the routine conservative treatment of acute asthma. Unfortunately, the uncontrolled use of oxygen may precipitate carbon dioxide narcosis (see below), and controlled oxygen therapy in the 25–30% concentration range, designed to correct hypoxia partially and to minimize further carbon dioxide retention, may be more appropriate in certain cases. However, precise control of the inspired oxygen concentration over a prolonged period cannot be achieved in oxygen tents in current paediatric use (Simpson and Russell, 1967), and masks used for this purpose in adults are not likely to be well tolerated by children.

Carbon Dioxide Narcosis

An increase in PCO_2 during oxygen therapy is a recognized danger in treating respiratory failure in the adult asthmatic (Schiller *et al.*, 1951). Downes and Wood (1965), however, found that the administration of 100% oxygen to seven children in status asthmaticus did not produce a rise in PCO_2 . The actual PCO_2 levels in these cases were not stated. In our series the PCO_2 was 50 mm. Hg or above in 10 admissions (six breathing air and four oxygen), and oxygen therapy or further oxygen therapy did produce a rise in PCO_2 . This is illustrated in Fig. 2, where PO_2 is plotted against PCO_2 in the same

FIG. 2.—Changes in arterial PO_2 and PCO_2 after oxygen in the first three hours.

patient, both at the time of admission and within three hours of beginning oxygen therapy. As the PO_2 increased with oxygen therapy, the PCO_2 rose in all but one patient (Case 9, PCO_2 50 mm. Hg). Previous infusion of sodium bicarbonate may have influenced the PCO_2 response in Case 1b. In normal adults a small rise in PCO_2 may follow the infusion of sodium bicarbonate (Katsaros *et al.*, 1960), but Mithoefer *et al.* (1965) reported a fall in PCO_2 in six hypercapnic asthmatics soon after bicarbonate infusion. Case 2a had been sedated with phenobarbitone and paraldehyde before being studied in either air or oxygen, which almost certainly contributed to the severity of her respiratory depression.

Hypoxia and Its Mechanisms

The importance of disturbed ventilation-perfusion ratios in the lungs as a mechanism of hypoxia in asthma has been shown by several studies in children (Ledbetter *et al.*, 1964; Lecks *et al.*, 1965), and the increased A-a DO_2 values (normal 10 mm. Hg) in our patients breathing air (Table II) probably reflected

FIG. 1.—Arterial PO_2 at various levels of inspired oxygen concentration. In Cases 1a, 2c, and 5 the inspired oxygen concentration did not produce a PO_2 of more than 80 mm. Hg.

such ventilation-perfusion imbalance. This persisted for some time after clinical recovery, as the arterial PO_2 was often below normal for 7 to 10 days (Fig. 3) despite the fact that the PCO_2 was generally normal within 48 hours. There was a significant correlation ($P=0.001$) between arterial PO_2 and PCO_2 in cases breathing air on admission (Fig. 4), which suggests that alveolar hypoventilation is also important as a mechanism of hypoxia in the acutely ill asthmatic child.

Fig. 3.—Mean arterial PO_2 levels (± 1 S.D.) in patients breathing air up to 10 days after admission.

Fig. 4.—Relation between arterial PO_2 and PCO_2 on admission, when breathing air. PCO_2 (mm. Hg.) = -0.79 ; PO_2 (mm. Hg.) = $+93$; $r = -0.75$; $P = 0.001$.

Conclusion

As clinical signs relate poorly to dangerous degrees of hypoxaemia and hypercapnia in acute asthma in childhood, it is important to measure the arterial blood gas tensions in all severely ill asthmatic children. Serial estimations of PCO_2 in particular are essential during oxygen therapy in view of the risk of aggravating respiratory acidosis.

To ensure greater accuracy our observations were all made on arterial rather than arterialized capillary blood. In routine practice, however, capillary blood measurements, though less precise, might sometimes be more appropriate and could obviate the need for repeated arterial punctures when frequent blood samples became necessary.

We express our thanks to Dr. J. W. Farquhar and Dr. D. C. Flenley for advice and help, to the physicians of the Royal Hospital for Sick Children for permission to study cases under their care, and to Staff Nurse D. J. Russell and Miss M. Hogg for technical assistance. Financial support was provided by the South-eastern Regional Hospital Board, Scotland, and the Edinburgh Central Hospitals Group Endowment Fund.

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ADDENDUM.—Since this article was prepared one patient (Case 18) died at home during a severe bout of asthma. Necropsy was not carried out and no details are known.

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