activity of physicians").[20] Certainly it is an iatrogenic condition of incomparable magnitude. In 1966 Matthew[21] described deliberate self-poisoning as "a major epidemic" and this appears to be continuing. But epidemic is defined as "prevalent among a people or a community at a special time, and produced by some special measures, not usually present in the affected locality,"[22] so perhaps "endemic" is a more appropriate adjective to describe the present situation ("habitually prevalent in a certain country and due to permanent local causes").[22] In the interest of preventive medicine the identification of these local causes, whether social or medical, or both, must surely be of the greatest importance.

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Asthma: analysis of sudden deaths and ventilatory arrests in hospital

M R HETZEL, T J H CLARK, M A BRANTHWAITE

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Summary

The incidence of episodes of unexpected ventilatory arrest, some of which led to sudden death, was studied in 1169 consecutive hospital admissions for asthma. Of the most acute cases, 458 were initially managed in a special care unit where only one ventilatory arrest occurred. A further nine cases of arrest, three of which proved fatal, happened on general wards. Accepted clinical criteria of a severe attack were not present in those episodes occurring outside the unit, which were apparently mild attacks. The risk of sudden death could not be related to the severity of the attack but it did correlate with the presence of excessive diurnal variation in peak expiratory flow rate (PEFR). Special treatment of patients with this sign might reduce mortality.

Introduction

Death may occur suddenly in asthma patients in hospital.[1] There is usually little information about the severity of the premorbid attack and it is difficult to understand why some patients die. We therefore analysed asthma admissions to the Brompton Hospital to evaluate accepted criteria of acute attacks[2] as indicators of patients at risk of sudden death. We also studied the possible association of excessive diurnal variation in PEFR with sudden death. We included as potential sudden deaths episodes of sudden ventilatory arrest that were successfully treated by the resuscitation team. We called these "respiratory crises."

Treatment in specialised units may reduce mortality.[3 4] To assess our own unit's effectiveness in preventing sudden death, we compared the fate of patients initially treated there for severe acute asthma with that of apparently less severe cases managed on general wards.

Patients and methods

The study was retrospective for two years from January 1974 to December 1975 and prospective for a further six months to June 1976. All patients admitted to adult wards with a diagnosis of asthma were studied. Retrospectively patients were located from a diagnostic index, and those who had been treated in the unit were cross-checked from unit records. A further check for asthma deaths was made by review of all death certificates. Prospectively admissions were monitored on the high dependency unit and general wards, and a further check for respiratory crises and deaths was made with ward sisters and the switchboard, who recorded calls for the resuscitation team.

CONFIDENCE OF DIAGNOSIS

Patients were classified into a "historical" group, in which diagnosis relied on a history of variable wheezy breathlessness, and a "physi-

Brompton Hospital, Fulham Road, London SW3 6HP
M R HETZEL, MB, MRCP, research assistant
T J H CLARK, MD, FRCP, consultant physician
M A BRANTHWAITE, MD, MRCP, consultant anaesthetist

ological" group, in which the history was supported by evidence of reversible airways obstruction during the current admission. Reversibility was assessed by a >20% increase in forced expiratory volume in one second (FEV_1) on treatment, a >15% fall after challenge tests, or by appreciable diurnal variation in PEFR. Having reviewed the incidence of respiratory crises and sudden deaths in all admissions, we confined further analysis to patients with physiological asthma uncomplicated by other disease.

ABNORMAL FINDINGS ON ADMISSION

In the physiological group we recorded the numbers of patients in whom observations on admission were outside any of the following limits: PEFR <100 l/min; pulsus parodoxus >20 mm Hg; pulse rate >120/min serum potassium concentration <3·5 mmol (mEq)/l.

In those patients in whom blood gas measurements were made within 24 hours of admission, the incidence of results outside each of the following limits was recorded: pH <7·38; Pco_2 >5·3 kPa (40 mm Hg); Po_2 <8·0 kPa (60 mm Hg).

Peak flow charts of routine four-hourly readings from 0600-2200 hours each day were reviewed in all prospective admissions and retrospectively when available. Diurnal variation was measured as the morning fall expressed as a percentage of the highest reading each day. Variation was then classified as insignificant (<25%), moderate (>25%), or large (>50%), from the largest variation seen for at least two consecutive days.

SEVERITY OF ATTACK

Episodes were classified as "acute" if the attack was considered sufficiently severe for initial treatment in the unit or "subacute" if patients were considered fit for management on general wards. The severity of acute episodes was subsequently graded from I-IV using a modification of Jones's classification:[3] grade 1—able to work with difficulty; grade II—confined to chair but able to move about with difficulty; grade III—confined to bed; grade IV—moribund. Treatment before and after admission with any form of corticosteroid was noted.

Results

There were 1345 admissions among 993 patients (540 women, 453 men), of which 1169 were for treatment of asthma uncomplicated by other disease. Of these 1169 episodes, 458 were initially treated in the unit where the mean duration of treatment was 2·7 days (SD 1·8 days). Physiological criteria for uncomplicated asthma were satisfied by 827 patients, 351 of whom were initially treated in the unit.

ABNORMAL FINDINGS AND SEVERITY OF ATTACK

Further analysis is confined to the 827 patients with physiological asthma. Of the 351 patients with acute asthma, there were 67 in group I, 109 in group II, 171 in group III, and 4 in group IV. The percentage incidence of abnormal findings on admission in the acute and subacute groups is shown in table I. Tachycardia and pulsus paradoxus were rare in the subacute group (1% and 3% respectively), and increasingly frequent among those with more severe grades of acute asthma (58% and 57% in acute grade III). A similar trend was seen in the incidence of PEFR <100 l/min, although this was also found in 12% of subacute patients. Hypokalaemia was common only in acute grades III and IV (16% and 25%, respectively).

Blood gases were analysed on admission in 382 cases (271 acute and 111 subacute). Hypercapnia was common only in acute grades III (34%) and IV (100%) but hypoxia was frequently seen (20-57% in acute grades I-III). Sixty per cent of patients with subacute asthma who had blood gas estimations showed at least one measurement outside our limits, but 23% of patients in acute grade III had results within these limits.

Table II shows the incidence of diurnal variation in PEFR. The samples were large in each group (76-100%) but the incidence of insignificant variation (about 20%), moderate swings (about 45%), and large swings (about 35%) was little affected by the designation acute or subacute or by the severity of the attack.

TABLE I—*Incidence of abnormal findings on admission among 827 asthma patients*

Group	Pulse >120/min (%)	Pulsus paradoxus >20 mm Hg (%)	Peak expiratory flow rate <100 l/min (%)	Plasma K <3·5 mmol (mEq)/l (%)
Subacute (n=476) ..	3 (1)	13 (3)	56 (12)	20 (4)
Acute:				
Grade I (n=67) ..	5 (8)	6 (9)	5 (7)	7 (10)
Grade II (n=109) ..	16 (15)	32 (29)	42 (39)	10 (9)
Grade III (n=171)..	99 (58)	97 (57)	115 (67)	28 (16)
Grade IV (n=4) ..	3 (75)	3 (75)	4 (100)	1 (25)

TABLE II—*Incidence of diurnal variation in peak expiratory flow rate among sample groups from acute and subacute asthma patients*

Group	No (%) of group sampled	Without variation (%)	25% swings (%)	50% swings (%)
Subacute (n=476) ..	360 (76)	82 (23)	173 (48)	105 (29)
Acute:				
Group I (n=67) ..	52 (78)	11 (21)	23 (44)	18 (35)
Group II (n=109) ..	84 (77)	13 (15)	39 (46)	32 (38)
Group III (n=171)	141 (82)	31 (22)	64 (45)	46 (33)
Group IV (n=4) ..	4 (100)	2 (50)	1 (25)	1 (25)

TREATMENT WITH STEROIDS

The frequency of treatment with steroids before admission was similar in the subacute (58%) and all acute groups (average 55%). After admission the frequency of inpatient treatment with steroids paralleled clinical grading of severity (70% of subacute admissions: 100% in grade IV).

OUTCOME

Table III shows the outcome of all 1345 admissions with the confidence of the diagnosis in each case. Mechanical ventilation was successfully instituted for refractory hypercapnia in six episodes treated in the unit. Death was expected in three patients whose previous history of crippling asthma contraindicated controlled ventilation. Ten patients died of other diseases with their asthma under control. Nine patients suffered 10 respiratory crises; one survived two crises on separate admissions. They are reviewed in table IV. Three episodes, all on general wards, proved fatal. Two patients were initially treated in the unit, but only one crisis occurred there; the other patient was transferred to the general ward after 24 hours. Only these two had tachycardia or pulsus paradoxus on admission. PEFR was <100 l/min in four patients. Three patients had blood gas analyses on admission. Results were normal in one patient, showed hypoxia in the patient whose crisis occurred on the unit, and hypoxia and hypercapnia in a patient with additional chronic bronchitis and mitral stenosis. Plasma potassium had fallen to the 3·0-3·5 mmol(mEq)/l range in two patients, one of whom died. Four patients were treated with >10 mg prednisone/day. Two received no steroids. Eight crises occurred between midnight and 0600 hours.

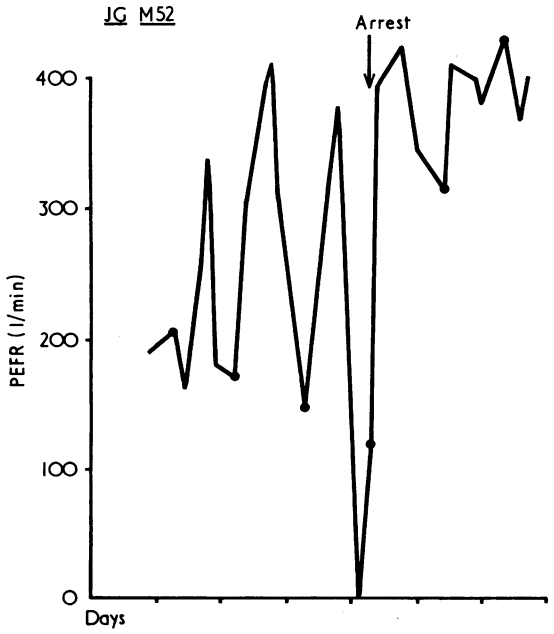
TABLE III—*Mortality and morbidity of 1345 asthma admissions*

	Mechanical ventilation	Respiratory crises	Deaths		
			Sudden	Expected	Other causes
Acute admissions:					
Physiological ..	6	1		2	1
Historical ..					3
Subacute admissions:					
Physiological ..		6	3		4
Historical ..				1	2
Total	6	7	3	3	10

TABLE IV—*Clinical features of 9 patients who sustained respiratory crises with ventilatory arrest*

	General ward	High dependency unit
Number of episodes	9*	1
Occurrence between midnight and 0600	7	1
Pulse rate >120/min on admission	0	1
Pulsus paradoxus >20 mm Hg on admission	1	0
Peak expiratory flow rate <100 l/min on admission	4	0
Diurnal variation in peak expiratory flow rate >50%	8†	1
Treated with >10 mg prednisone/day	3	1
Blood gas analysis on admission	2	1
Failed resuscitation	3	0

*One patient suffered two episodes on two separate admissions.
†Remaining one patient had severe nocturnal symptoms but no peak flow chart recovered.



Daily four-hourly (0600-2200) recordings of peak expiratory flow rate (PEFR) in male patient aged 52. Days are marked at 0000, solid circles indicate readings at 0600. Recurrent >50% morning falls in PEFR precede respiratory crisis at 0400 on 5th day.

Peak flow charts, available in nine instances, all showed >50% swings in PEFR. The figure shows an example. The remaining fatal case had recurrent early morning wheezing before death. All patients had asthma histories of at least 10 years. Four had had previous hospital admissions for asthma but these attacks were not considered severe.

The seven successfully treated crises occurred within four days of admission. Five patients had clinical signs of both ventilatory and circulatory arrest on arrival of the resuscitation team but all were easily resuscitated. Their mean age was 56 years (range 48-84). The three fatal crises occurred five to eight days after admission. Efforts were not prolonged in two patients aged 71 and 75 years but were vigorous in the third, aged 53 years, in whom mitral stenosis and chronic bronchitis hampered success. Post-mortem examinations performed in two patients showed extensive mucus plugging of airways.

Discussion

In 458 admissions for acute asthma to the unit only one non-fatal respiratory crisis occurred. This is in keeping with previous observations of low mortality rates in these units.[3 4] The incidence of sudden death in all asthma admissions was 0·25% (three in 1169 admissions). Although 80% of cases were studied retrospectively and there were differences in diagnostic criteria, this figure may be compared with previous estimates of an 0·9-1·3% incidence in other series.[1 5 6]

The unit has, however, failed to eradicate sudden asthma deaths because only two of 10 potentially fatal cases were recognised as dangerous and treated in it; moreover, one of these patients was prematurely discharged to the ward where a crisis subsequently occurred. Our analysis of abnormal findings on admission, which undoubtedly influenced selection of patients for treatment in the unit, explains the failure to identify the other eight patients at risk. Thus, tachycardia, pulsus paradoxus, low peak flow rate, and hypokalaemia paralleled the apparent severity of the attack but were rarely seen in patients who later sustained respiratory crises.

Among acute asthmatics results of blood gas analysis were in keeping with the trends seen in previous studies of acute asthma.[5 7] Nevertheless, blood gas analysis was considered unnecessary in most patients subsequently shown to be at risk and the result was normal in one of three patients who had blood gas analysis before their crises. Patients at risk could not be identified by a past history of status asthmaticus, which has been associated with increased risk of death,[6 8] and, in general, they presented with an apparently mild attack which aroused little concern. Attempts to identify patients at risk from the severity of the attack therefore missed the major source of risk that arose in patients admitted with apparently less severe asthma. Risk of death could rarely be associated with the severity of the attack and may not be related to it.

A feature common to all patients sustaining crises was, however, the presence of large diurnal swings in PEFR with an early morning fall. Although this was seen in some 30% of all admissions it correlated best with the risk of ventilatory arrest and sudden death. Unlike the other signs it showed no relationship to the designation acute or subacute and was peculiar to the individual patient. This phenomenon might therefore account for the frequent occurrence of asthma deaths in hospital in the early morning.[1] No diurnal trend is seen in the time of asthma deaths at home however,[9] and excessive diurnal variation in airways obstruction may be relevant only to hospital mortality.

Respiratory crises were common in the first few days of admission, and those patients treated for acute asthma in the unit who also showed large diurnal variation in PEFR might have been protected from this danger period as rapid treatment of early morning attacks was facilitated. The three fatal episodes occurred after about seven days, and extensive mucus plugging was seen at necropsy—a common finding in sudden asthma death.[10 11] The rapid recovery of the survivors, who only required short periods of ventilation by hand, suggests that their crises were due to a profound, sudden decrease in airway calibre alone. In the fatal cases this proved untreatable when associated with mucus plugging that had developed over longer intervals. Large doses of steroids did not prevent respiratory crises in four patients and it seems unlikely that wider use of steroids would have influenced the incidence of sudden death.

Patients may die suddenly of asthma in hospital, even if their attack is not severe. Specialised units may reduce mortality but patients at risk of sudden death are not easily recognised and conventional criteria for diagnosing severe attacks have little value in predicting potentially fatal cases. Wide diurnal variation in PEFR may be a better clue to prevention of sudden death and we believe patients who show this phenomenon should receive intensive treatment.

We thank the physicians, ward sisters, records department, and switchboard of the Brompton Hospital for their co-operation.

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SHORT REPORTS

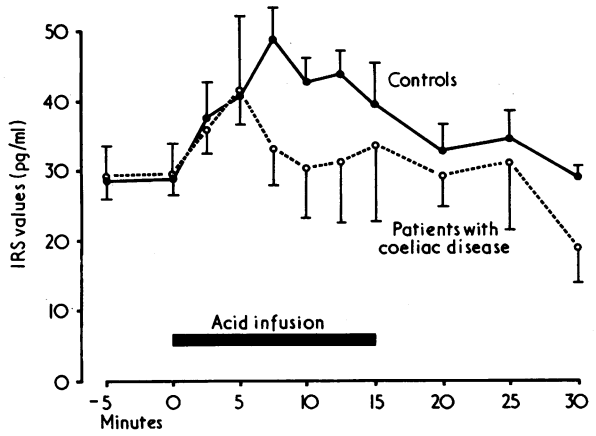
Impaired immunoreactive secretin release in coeliac disease

Studies using bioassays have suggested that secretion of enteric hormones may be abnormal in coeliac disease.[1] In children with coeliac disease increased numbers of secretin-producing S-cells have been described.[2] Using radioimmunoassay we have assessed the plasma secretin response to duodenal acidification in coeliac disease.

Patients, methods, and results

After an overnight fast, eight patients with untreated coeliac disease and 12 control subjects had 100 ml 100-mM HCl infused over 15 minutes into the upper duodenum. The position of the tube was checked radiologically. Peripheral venous blood samples for secretin determination were taken at −5, 0, 2½, 5, 7½, 10, 12½, 15, 20, 25, and 30 minutes after the acid infusion was started. Blood was collected into heparinised tubes, plunged into an ice bath, and plasma separated at 4°C. Plasma secretin was immediately extracted by ethanol and assayed in a sensitive and specific radioimmunoassay.[3] The sensitivity of the assay was 6 pg/ml with 95% confidence. The statistical significance of differences was estimated using the paired *t* test.

The figure illustrates the results. Fasting immunoreactive secretin (IRS) levels were similar in controls and "coeliacs," all being less than 70 pg/ml.



Mean (±SE of mean) plasma secretin (IRS) levels after intraduodenal acid in patients with coeliac disease and in controls.

In controls there was a rapid and significant rise (average $P < 0.005$) in IRS levels during acid infusion, which fell rapidly on termination of the infusion. In the coeliac group as a whole the rise in IRS was not significant. Some coeliac patients, however, showed a response but this was less in magnitude and duration than in the control group; these patients had less severe mucosal abnormalities than the remainder of the coeliac group.

Comment

Children with coeliac disease have increased numbers of secretin-containing S-cells which appear to be full of hormone granules.[2] The data presented here indicate that IRS release is impaired in coeliac disease and so suggests that the S-cells are full of hormone because of failure of release rather than as a result of excessive synthesis of the hormone.

The reason for the failure of secretin release is not clear. Possibly the mucosal damaging process, brought about by gluten, also damages the S-cells or their apical projections; or because of the greatly deepened crypts, known to occur in coeliac disease, it may be more difficult for the acid stimulus to reach the S-cells. Gastric acid secretion is reduced in coeliac disease and, possibly owing to the lack of endogenous acid stimulation, S-cell function becomes sluggish and cannot respond even to an adequate exogenous acid stimulus. In view of the partial IRS response in the patients with milder mucosal flattening, it seems likely the degree of impairment of IRS response reflects the severity of the mucosal lesion.

The lack of IRS response to acid may have several consequences. Pancreatic exocrine function may be impaired and this could further aggravate malabsorption. There may also be important metabolic consequences. Secretin has a lipolytic function and during starvation it may play a major part in regulating lipid metabolism.[4] Secretin may also participate in producing the augmented insulin response to oral glucose as compared with the insulin response to intravenous glucose.[5] Thus, in coeliac disease where secretin response is abnormal, this may lead to impairment of islet response with consequent widespread effects on glucose, fat, and protein metabolism and also, as outlined, to abnormalities in lipid metabolism directly.

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Department of Medicine, Queen's University, Belfast
F A O'CONNOR, MD, MRCP, senior tutor
J C McLOUGHLIN, MB, MRCP, research fellow
K D BUCHANAN, MD, FRCP, professor of metabolic medicine

Biochemical differences between amniotic fluid and maternal urine

Amniocentesis is being used increasingly for the antenatal diagnosis of congenital abnormalities such as open neural tube defects and several chromosomal abnormalities. With this method there is a risk of inadvertently tapping maternal urine instead of amniotic fluid, especially when the placenta is placed anteriorly. Therefore it is important to establish the biochemical differences between these two fluids.