times normal in coeliac disease (Croft *et al.*, 1968). The jejunal mucosal cells contain small but significant amounts of folate mainly in the polyglutamate form (Hoffbrand and Peters, 1969). Failure of reabsorption of this folate as well as of that contained in bile (S. J. Baker *et al.*, 1965) could well contribute to the development of folate deficiency in both coeliac disease and dermatitis herpetiformis.

Most workers consider that dietary folate deficiency occurs frequently in Western communities. This is consistent with the generally accepted concept of Herbert (1968), that minimal daily requirements for folate (100 μg.) are not many times lower than normal daily dietary folate intake (500 to 1,000 μg.). A few workers, however, suggest that daily folate requirements are as little as 10 μg. (see Vitale, 1966). If this were so it would be extremely difficult to develop the deficiency simply by taking a poor diet. It would therefore be necessary to postulate that some degree of malabsorption of dietary folate occurred in many patients diagnosed clinically as suffering from "pure" nutritional folate deficiency. The present results, however, show normal absorption of pteroylpolyglutamates and normal jejunal mucosal pteroylpolyglutamate hydrolase levels in three such patients and thus support the concept of inadequate dietary intake of the vitamin as the sole cause of their deficiency.

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Diabetic Ketoacidosis During the Influenza Epidemic

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Summary: During eight weeks of a recent influenza epidemic 29 patients with ketoacidosis were admitted to the General Hospital, Birmingham. This was an exceptionally large number of cases. Of these, 14 had complained of a cough, nine had clinical evidence of respiratory infection, and four extensive bronchopneumonia. Hypokalaemia was present on admission in several instances and caused respiratory failure and death in three patients. Since the dangers of initial hypokalaemia are increased during the treatment of ketoacidosis, especially when sodium bicarbonate is used, serum potassium levels must be estimated initially and, if necessary, potassium chloride given intravenously at more frequent intervals than usual.

Introduction

Diabetic ketoacidosis often occurs as a result of infection. Malins (1968) considered infection to be the commonest cause of ketoacidosis, and Sheldon and Pyke (1968) observed that 9% of all cases were the result of respiratory infections. Respiratory disease may be responsible for the larger number of patients with ketoacidosis seen in the winter months (FitzGerald *et al.*, 1961). Some infections may disturb diabetic control more than others, and this paper reports an "epidemic" of diabetic ketoacidosis which occurred during the recent influenza outbreak.

Methods

Twenty-nine patients were admitted to hospital as medical emergencies, either sent by general practitioners or brought in by anxious relatives. Of these patients, 23 already attended the diabetic clinic at the General Hospital, Birmingham, where about 5,000 patients are currently treated. The remaining six were found to be diabetics on admission.

Blood glucose was measured by the AutoAnalyzer ferricyanide method, blood acetoacetate by the AutoAnalyzer method of Salway (1969), serum potassium by the AutoAnalyzer, and blood pH, P_{CO_2}, and standard bicarbonate by the Astrup microelectrode. Patients are described as "non-ketotic" when the ketonaemia was insufficient to cause alteration of the blood acid-base status: this is usually the case when the blood acetoacetate is less than 1·5mM.

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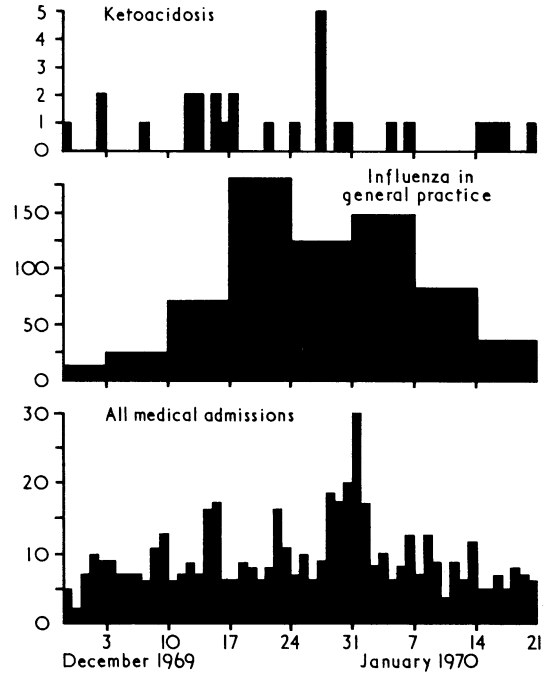
Epidemic

During the eight-week period from 29 November 1969 to 21 January 1970 29 diabetic emergencies were admitted to the General Hospital, Birmingham. Details of the patients and the blood biochemistry at admission are shown in Table I. The dates of admission compared with general medical admissions during the same period, and with the incidence of influenza (including the common cold and influenza-like illnesses) seen in two Birmingham general practices, are shown in the Chart. Nine patients were admitted during the six days 13 to 18 December, five on 29 December, the remainder being distributed evenly throughout the eight weeks. Only seven cases of ketoacidosis were seen during the ensuing eight-week period.

Of the 29 patients, 14 complained of a cough, nine had clinical evidence of respiratory infection, and four extensive bronchopneumonia. Six patients were found to be diabetics for the first time on admission; of these two had pneumonia. Three (aged 70, 71, and 43 years; Cases 7, 13, and 26 respectively) had "non-ketotic" diabetes, two being finally controlled with oral hypoglycaemics. One patient (Case 17) had presumed lactic acidosis and died from multiple pulmonary emboli on the seventeenth day.

Of the seven deaths (Table II), four were due to unrelated causes long after recovery from ketoacidosis, while the remainder occurred earlier and were related to hypokalaemia. Four cases are reported in detail.



Dates of admission of the diabetic emergencies compared with general medical admissions and weekly incidences of influenza in general practice (see text) during the same period.

Case 5

A 47-year-old woman had had diabetes for 19 years. She was a known asthmatic who had previously required several courses of prednisone, but none during the last two years. She was admitted to hospital after four days of thirst, polyuria, and lethargy followed by cough, anorexia, and vomiting. Though dehydrated and suffering an attack of asthma, her general condition was fair. She was fully conscious, and was allowed to suck ice because of her intense thirst. The blood glucose was 1,275 mg./100 ml., blood pH 6·96, and P_{CO_2} 34 mm.Hg. She was treated with intravenous insulin and fluids and also given hydrocortisone for the bronchospasm. After six hours her breathing suddenly became laboured and stertorous, and since she was also cyanosed she required mechanical ventilation. Half an hour later her blood pressure suddenly fell; though electrocardiographic activity (sinus rhythm) continued, no pulse could be detected and she died. During this period the serum potassium was subsequently reported as 1·4 mEq/l.

TABLE I.—*Details of the 29 Patients Admitted During the Epidemic*

Case No.	Date of Admission	Sex	Age	Blood Glucose (mg./100 ml.)	Blood Acetoacetate (mM)	Blood pH
1*	29/11/69	F.	74	1,250	4·6	7·0
2	3/12/69	M.	30	875	3·2	6·91
3	3/12/69	F.	53	635	1·9	7·02
4	8/12/69	F.	39	1,360	3·4	7·1
5*	13/12/69	F.	47	1,275	—	6·96
6	13/12/69	M.	50	625	2·3	7·38
7†	14/12/69	F.	70	1,010	0·83	7·34
8	14/12/69	M.	18	250	2·4	7·24
9	16/12/69	M.	27	315	4·2	7·18
10	16/12/69	M.	32	775	2·1	7·02
11*	17/12/69	F.	32	1,975	3·7	6·95
12	18/12/69	F.	38	900	2·7	7·16
13†	18/12/69	M.	71	1,230	0·74	7·4
14†	22/12/69	M.	62	775	—	7·13
15	25/12/69	M.	50	390	—	7·1
16*	29/12/69	M.	38	880	3·6	6·78
17†	29/12/69	F.	72	750	0·23	—
18	29/12/69	F.	15	700	3·6	6·74
19	29/12/69	M.	56	1,915	3·4	—
20	29/12/69	M.	64	650	3·9	7·1
21	31/12/69	M.	41	1,200	—	—
22*	1/ 1/70	F.	58	650	2·70	7·32
23	5/ 1/70	F.	40	625	3·7	6·87
24	7/ 1/70	F.	36	452	—	7·02
25	15/ 1/70	M.	45	330	—	7·15
26†	16/ 1/70	F.	43	1,055	0·28	7·38
27*	17/ 1/70	F.	55	500	—	6·99
28†	18/ 1/70	F.	31	825	—	7·04
29	21/ 1/70	F.	80	775	—	7·06

*These patients died (see Table II).
†These six patients presented as new cases of diabetes.

TABLE II.—*Causes of Death in 7 Patients*

Case No.	Age	Time of Death after Admission	Cause of Death	Time of Respiratory Arrest after Admission	Serum Potassium at Time of Arrest (mEq/l.)
5	47	6½ hours	Hypokalaemia	6 hours	1·4
11	32	6 days	Hypokalaemia	1 hour	1·7
16	38	24 hours	Hypokalaemia	10 minutes	1·8*
1	74	14 days	Cerebrovascular accident		
17	72	17 days	Multiple pulmonary emboli		
22	58	16 days	Ischaemic heart disease; cardiac arrest		
27	55	9 days	Meningitis		

*Serum potassium recorded three hours after arrest.

Case 11

A 32-year-old woman had had diabetes since the age of 19 and was generally well controlled. Four days before admission she developed a cold with productive cough and after two days began vomiting. She had become confused the evening before admission and on arrival was moribund. She was then semicomatose, shocked, with peripheral cyanosis and severe dehydration. She was overbreathing and extensive fine crepitations were heard in both lower zones of the chest. The systolic blood pressure was 80 mm.Hg; the blood glucose was 1,975 mg./100 ml., blood pH 6·95, P_{CO_2} 24 mm.Hg, blood acetoacetate 3·65 mM, and serum potassium 2·4 mEq/l.

Treatment was started with 100 units of soluble insulin, normal saline, and sodium bicarbonate (1%) intravenously; potassium supplements were given as soon as the low serum potassium result became available. A nasogastric tube was passed and a large quantity of stale gastric contents aspirated. During the first hour her condition seemed to have improved a little, but suddenly the respirations became stertorous, she became cyanosed, and her eyes were fixed and staring. The pulse was irregular, and an E.C.G. showed multiple ventricular extrasystoles and subsequently periods of atrial arrest. Serum potassium was 1·7 mEq/1. She required mechanical ventilation and was therefore intubated, vomiting during this procedure. The cardiac rate increased slightly in response to isoprenaline, but after administration of about 50 mEq of potassium chloride during 20 minutes atrial fibrillation occurred and later sinus rhythm was restored. It proved impossible to wean her from the respirator, and she died on the sixth day after admission.

Case 16

A Pakistani man aged 38 had had diabetes for 12 years and had previously had a right midtarsal amputation and left midthigh amputation following a road traffic accident. He was found in a city hostel comatose and surrounded by "meths" drinkers. He was deeply unconscious and hypothermic. Shortly after arrival in the casualty department he had a cardiac arrest and, though his pulse returned spontaneously, respiratory movements were inadequate and mechanical ventilation was required. When this emergency was over his blood glucose was 880 mg./100 ml., blood pH 6·78, P_{CO_2} 55 mm.Hg, standard bicarbonate 6·9 mM, and blood acetoacetate 3·6 mM. After three hours his serum potassium was 1·8 mEq/l. He was treated with intravenous and intramuscular insulin and intravenous fluids, and received 120 mEq of potassium chloride during the first 15 hours. Irrecoverable cardiac arrest occurred after 24 hours.

Case 18

A 15-year-old girl had been diabetic for four years, and though control of her diabetes was not ideal she was generally in good health. About four days before admission she developed an unproductive cough with aching around the trunk and on the left side of the chest. She started vomiting the day before she was admitted, and later "collapsed." She presented in a stuporous, severely shocked, and dehydrated condition. Fine crepitations were heard in both lower zones of the chest. The systolic blood pressure was 70 mm.Hg. The blood glucose was 700 mg./100 ml., blood pH 6·74, P_{CO_2} 15 mm.Hg, blood acetoacetate 3·6 mM, and serum potassium 2·4 mEq/l. She was treated with intravenous insulin and fluids which included 60 mEq of potassium chloride given during the second and third hours. Her recovery was uneventful.

Discussion

Though ketoacidosis is commoner during the winter months (FitzGerald *et al.*, 1961; Sheldon and Pyke, 1968), the recent "epidemic," which occurred concurrently with the influenza epidemic, was of dramatic proportions. Twenty-nine patients were seen during eight weeks. Fewer than 40 patients a year are usually admitted in ketoacidosis to the General Hospital, Sheldon and Pyke (1968) noting an overall frequency of 1% of clinic patients each year (about 5,000 patients attend the clinic at the General Hospital). Though influenza cannot be proved to be the precipitating cause, the circumstantial evidence is considerable (see Chart); physicians in charge of diabetic clinics do not recall a similar outbreak of ketoacidosis cases during previous epidemics.

The most disturbing feature of the epidemic was death related to hypokalaemia. Respiratory failure occurred in three patients in whom the serum potassium levels were very low (1·4, 1·7, and 1·8 mEq/1.), and these patients required mechanical ventilation. The episodes in two of the patients were witnessed one and six hours after starting treatment, but in the third case occurred before treatment had begun, only a few minutes after admission to hospital. Respiratory paralysis is a well-known consequence of severe hypokalaemia (Holler, 1946; Fischer and Nichol, 1963) and electrocardiographic changes are often associated with it (Henderson, 1953; Fischer and Nichol, 1963). Bizarre electrocardiographic features were certainly observed in Case 11. Unfortunately, electrocardiographic monitoring does not provide a reliable guide to the serum potassium level (Henderson, 1953) and may be very deceptive.

Initial hypokalaemia is unusual in diabetic ketoacidosis, the serum potassium being in fact generally normal or high (Danowski, 1957). According to some workers hypokalaemia is rare (Sheldon and Pyke, 1968) and it did not occur at all in 61 episodes reported by Cryer and Daughaday (1969) or in 73 cases described by Cohen *et al.* (1960). Among 30 ketoacidotic patients of Malins (1968) none had serum potassium levels of less than 3·4 mEq/l. Moreover, it is unusual enough to have warranted a special report by Abramson and Arky (1966) describing five cases. Martin *et al.* (1958) stated that the serum potassium was low in 15% of 145 patients but gave no actual figures; the occurrence of normal and occasionally low potassium levels in children has been described by Danowski (1957).

Of our patients two were hypokalaemic on admission (Cases 11 and 18, serum potassium in both was 2·4 mEq/l.), and from the events described two others (Cases 5 and 16) may also have been. Thus four cases were probably hypokalaemic initially and three of these certainly appeared moribund on admission. We do not know why there was a high incidence of hypokalaemia in this epidemic, but both mild and severe hypokalaemia have recently been observed in influenza patients (Crockett, 1970; Stevenson *et al.*, 1970).

The grave dangers of initial hypokalaemia in patients with ketoacidosis are apparent from the fatal outcome in three of the four patients we have described. Further lowering of serum potassium inevitably occurs during treatment, and if the initial level is already low disastrous hypokalaemia is very likely. Even when potassium supplements are given the serum potassium may continue to fall (Abramson and Arky, 1966). The rising blood pH itself causes a decrease of the serum potassium (Burnell *et al.*, 1956) and administration of sodium bicarbonate naturally accelerates this. The amount of intravenous sodium bicarbonate given to patients in whom severe metabolic acidosis exists should therefore be limited; some workers oppose its routine use altogether (Root and Nichols, 1959; Young and Bradley, 1967). The use of excessively large doses of insulin probably also provokes a more rapid decrease of serum potassium (Sheldon and Pyke, 1968). Though some workers advocate giving potassium supplements after three to four hours (Malins, 1968; Sheldon and Pyke, 1968) the initial serum potassium levels must be estimated and potassium chloride added to the intravenous infusion sooner if necessary. This measure may be life saving.

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