Acute Diabetic Ketoacidosis in Children: Role of the Stress Hormones

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Summary

Twenty-five cases of acute ketoacidosis, occurring in insulin-treated diabetic children in previous good health, were studied close to the onset of illness and throughout the first 24 hr of therapy. In most patients, symptoms of illness and ketonuria had been present for less than 12 hr; in 9 subjects, they had been present for less than 4 hr. Initial plasma glucose concentrations ranged from 252 to 849 mg/dl. The first pH values in 21 cases were less than 7.27, and in the remaining 4 studies, the CO₂ was less than 14 mEq/liter. Identifiable sources of stress, such as infections or emotional arousal, preceded the development of ketoacidosis in 20 cases.

Serial measurements were made of plasma glucocorticoid, growth hormone, and glucagon concentrations as well as urinary excretion of epinephrine and norepinephrine to assess the role of these hormones in acute ketoacidosis and to evaluate their relationship to the abnormalities in glucose and electrolyte homeostasis. Excessive urinary excretion of epinephrine was a frequent and striking phenomenon. Output was greater than 4 S.D. above the mean in 20 of 23 cases in the first 2 hr of the study. In 15 cases, the values fell into the normal range by approximately 14.5 hr, but in seven patients, epinephrine overproduction persisted for the entire study. Cortisol hypersecretion was present in 24 of 25 patients and persisted for 6 to 8 hr or longer before gradually subsiding. Initial growth hormone concentrations were elevated in seven patients (20 ng/ml or above), but the highest values (20 to 160 ng/ml) were observed after insulin administration. At the outset, plasma glucagon concentrations were less than 200 pg/ml in 11 patients; in 11 others, it ranged between 250 and 1250 pg/ml. The elevated values usually were transient. Of 22 cases in whom all five hormones were measured at the start of the study, 21 exhibited increased production of at least three of the stress hormones.

We conclude that some diabetic children who have received their usual dose of insulin develop hyperglycemia, dehydration, and acidosis within a few hr of experiencing stress because large amounts of counterregulatory hormones, especially catecholamines and cortisol, are released.

Speculation

Acute onset of ketoacidosis in previously healthy insulin-treated diabetic children occurs because their daily dose of insulin is insufficient to offset the effects of the counterregulatory hormones produced in response to stress (catecholamines, cortisol, glucagon, and growth hormone). Hyperglycemia, dehydration, and acidosis result from the glycogenolytic, lipolytic, and ketogenic action of the stress hormones.

Acute ketoacidosis may develop within a few hr in diabetic children who have been in previous good health and free of ketonuria. These crises appear to be precipitated by infection,

emotional arousal or other forms of stress. Often, the children have received their usual daily dose of insulin. Thus, absolute insulin deficiency can be excluded in these cases. It is likely that an acute release of "stress hormones" precipitates the decompensation in these diabetic children because their daily dose of insulin is insufficient to offset the profound effects of the counterregulatory hormones on carbohydrate and lipid homeostasis.

Previous observers of this phenomenon have speculated about the role of one or more of the stress hormones in ketoacidosis (1, 18, 36, 47, 48, 50), but none have included simultaneous serial measurements of all the major counterregulatory hormones except Waldhausl *et al.* (53) who studied six insulin-deficient diabetic patients during rehydration. Thus, the frequency, severity, and complexity of the hormonal derangements have not been thoroughly documented.

This is the first study of a large group of young diabetics wherein all of the major stress hormones have been measured close to the onset of illness and every hour during the subsequent 24 hr of therapy. Plasma levels of glucocorticoid, growth hormone, glucagon, and urinary excretion of epinephrine and norepinephrine were measured serially in 25 studies. The interaction between these hormones and the changes in glucose and electrolyte homeostasis were determined to evaluate the contribution of these factors to acute diabetic ketoacidosis.

MATERIALS AND METHODS

PATIENT SELECTION

Patients were selected for the study if they had ketonuria and symptoms of illness for less than 24 hr. Other criteria included clinical signs of dehydration, acetone odor of the breath, and a positive test for "acetone" in serum diluted four-fold or higher. In 21 cases, the initial pH was less than 7.27 (range 6.96 to 7.27); in the remaining four studies, the CO₂ was less than 14 mEq/liter, and the pH was less than 7.37. The anion deficit ranged from 14 to 38 mEq/liter with a mean of 24.3 mEq/liter. All the patients had received insulin regularly and had had satisfactory control in the recent past as judged by two to four daily urine tests for sugar and acetone.

Written consent of parents and of older patients was obtained for all the studies.

STUDY PROTOCOL

As soon as the patients arrived in the Emergency Room, a sample of arterial blood was obtained for measurement of glucose, acetone, pH, CO₂, and electrolytes. The patients were asked to void completely, and the time was recorded. If the precise time of the previous urination was known, this specimen was saved for catecholamine analysis. As soon as it was ascertained that the criteria for the study were fulfilled, the patients were transferred to the Clinical Research Center, usually within one hr of arrival.

COLLECTION OF SPECIMENS

Every hr, for a total of 24 hr, 1.5 to 2 ml of venous blood was obtained via an indwelling heparinized infusion needle for determination of glucose, growth hormone, corticoid, and glucagon. An additional 3 ml was taken at 0, 4, 8, 12, 16, and 24 hr for acid-base studies, electrolytes, and urea nitrogen.

Urine was collected quantitatively every hr for the first 8 hr and every 2 hr thereafter. If the patients were unable to void spontaneously, an indwelling Foley catheter was used. The timed urine specimens were analyzed quantitatively for glucose and electrolytes and qualitatively for ketones. A portion of every specimen was acidified immediately to a pH of less than 3 with HCl and frozen for later measurement of epinephrine and norepinephrine.

THERAPY

Every patient was cared for by one of a group of pediatric residents who were members of the study team.¹

Fluid therapy was as follows. During the first hr in the Clinical Research Center, balanced hydrating solution² was administered intravenously at a rate of 400 ml/M². For the next 8 hr, 5% glucose in electrolyte solution³ was infused at a rate of 250 ml/M²/hr. In the remaining hours of the study, 10% glucose in electrolyte solution⁴ was given intravenously at a rate of 125 ml/M²/hr.

Insulin therapy was initiated after baseline blood specimens had been obtained and after the infusion had been established. In 15 instances, one or two glucose measurements were made, and insulin was administered approximately one hr after the onset of the study. In the remaining cases (11–14, 17, 20, 24–27), insulin was not administered until 2 to 3 hr after initiation of parenteral fluid therapy because a spontaneous fall of blood glucose had been observed in several previous patients before insulin administration. This method of treatment was chosen to determine whether fluid therapy and general care would suffice to initiate recovery in these patients who were not insulin deficient.

In the first 16 studies, the initial insulin dose for the severely ill patients consisted of 1 or 2 units of regular insulin per kg.; one-half of the dose was given intravenously, and the remainder was given subcutaneously. In the moderately ill children, the dose was 1 unit/kg. Subsequent insulin therapy was given on the basis of the clinical and biochemical progress of the patient. This treatment regimen was termed the "high dose" method.

In the last nine studies, the initial dose was 10 units of regular insulin per M² of body surface administered intramuscularly. This dose was repeated every hr until the concentration of blood glucose was below 250 mg/dl (or plasma glucose below 300 mg/dl). Thereafter, one-half this dose was given at appropriate intervals to maintain the glucose level below 250 mg/dl. This latter regimen was termed the "low dose" method.

Vital signs, including blood pressure, were recorded every hr.

ANALYTIC METHODS

Glucose concentration was measured in a protein-free filtrate of whole blood with a glucose oxidase method (54). Plasma growth hormone was measured by double antibody radioimmunoassay technique (21, 40). Plasma corticoid was determined by the competitive protein binding method of Murphy (32). Antiglucagon antiserum (30K), purchased from Dr. R. Unger, was used to assay plasma glucagon according to the method of Faloona and Unger (15), except that double antibody precipitation was substituted for charcoal-dextran separation. Urinary norepinephrine and epinephrine were analyzed by spectrophotofluorimetry using previously described techniques (52).

¹ The collaboration of Drs. Joseph Repice, Robert Baker, Susan S. Baker, Martin Hoffman, Martin Brecher, John Braico, Kathleen Braico, and Steven Commins was vital to the success of the study and to the care of these sick patients.

² Hydrating solution (Na = 75; Cl = 50; lactate = 25 mEq/liter).

³ Na = 56; K = 25; Mg = 6; Cl = 50; lactate = 25; H₂PO₄ = 12 mEq/liter.

⁴ Same as Footnote 3 except K = 40; H₂PO₄ = 27 mEq/liter.

RESULTS

CLINICAL INFORMATION

Twenty patients were studied in 25 episodes of ketoacidosis. Table 1 summarizes the clinical data. There were 15 girls and 5 boys. Eleven girls (14 studies) and two boys were either pubescent or fully sexually mature; the other seven children (nine studies) were prepubertal. All had been followed in the Diabetic Clinic of Children's Hospital. The duration of ketonuria and of symptoms in most cases was less than 12 hr; in nine cases, less than 4 hr before admission. In 13 cases, the last insulin dose had been given within 3 hr before admission. None of the patients were comatose.

In 20 of 25 studies, the probable event which precipitated the ketoacidosis could be identified. In eight otherwise stable patients (cases 1, 8, 9, 12, 16, 19, 23, and 24), infection was the dominant factor. In six other studies (Cases 4, 6, 7, 13, 21, and 25), a combination of infection and emotional stress seemed to be present. Most of the infections were mild. The remaining six episodes of acute ketoacidosis appeared to be triggered by emotional and, on one occasion, physical stress.

LABORATORY DATA

The biochemical and hormone data in the 16 diabetic patients treated with the high dose insulin method were not significantly different from the nine who received "low dose" insulin therapy. The laboratory data from these two groups were combined for analysis and discussion.

Blood concentrations of glucose on admission ranged from 252 to 849 mg/dl; in 22 cases, the values were less than 594 mg/dl. There was no correlation between the glucose and pH values in individual patients. The highest blood glucose level, 849 mg/dl, was seen in a patient whose blood pH was 7.36. In 10 cases, the glucose concentration fell by as much as 100 mg/dl before insulin administration, sometimes while glucose-containing solutions were being infused. In four cases, it rose steeply before fluid or insulin therapy. There was no consistent relationship between these changes in glucose concentrations and the timing of insulin therapy or the initial hormone data. Only three patients had bacterial infections for which they received antibiotic therapy (cases 16, 19, and 24).

Excessive urinary excretion of epinephrine was a striking hormonal abnormality observed in the majority of patients, particularly at the outset. Figure 1 shows the catecholamine excretion in the first collection period. Epinephrine excretion ranged from 0.225 to 8.40 $\mu\text{g}/\text{M}^2/\text{hr}$. In 20 of 23 cases, urinary epinephrine excretion in the first two periods was greater than 4 S.D., and in 10 of these, it was more than 10 S.D. above the normal mean (52).

The pattern of epinephrine excretion throughout the 24-hr study period is shown in Figure 2. The magnitude and duration of epinephrine hypersecretion varied among the patients. In most cases, peak values were present on admission, and epinephrine excretion decreased gradually during the recovery from ketoacidosis. In 15 observations, the average time for the values to fall to within 2 S.D. of the normal mean was 14.5 hr (range, 2 to 27 hr). In seven cases, the rate of epinephrine excretion exceeded 2 S.D. above normal throughout the entire observation period. In only three studies (Cases 12, 21, and 22) did epinephrine production remain within 2 S.D. of the mean for the entire period.

The total 24-hr excretion of epinephrine was more than 2 S.D. above the mean in 16 complete urine collections and greater than 8 S.D. above the mean in five of 22 complete urine collections (Fig. 3). In six cases, the 24-hr output of epinephrine fell within the normal range even though three of these patients had increased amounts of epinephrine in the initial urine samples.

Norepinephrine excretion during the first collection period was elevated 2 S.D. above the mean in five patients (Fig. 1). The range of values for all participants was 0.32 to 15.85 $\mu\text{g}/\text{M}^2$. Only one patient, on two occasions, excreted more than 5 $\mu\text{g}/\text{M}^2/\text{hr}$ (cases 15 and 20). The 24-hr pattern of urinary norepinephrine excretion

Table 1

Case No.	Sex	Age at diagnosis of diabetes mellitus (yr)	Age at time of study (yr)	Interval since last insulin dose (hr)	Dose of Insulin (units)	Symptoms/ketonuria before admission (hr)	Admission laboratory data			No. of previous episodes of ketoacidosis	Apparent cause of acute episode of ketoacidosis
							Glucose (mg/dl)	pH	CO ₂ content (meq/liter)		
1	M	1 $\frac{1}{2}$	4 $\frac{1}{2}$	3	12 U + 10 R	8	410	7.21	11.0	0	Otitis media.
2	F	10 $\frac{1}{2}$	15 $\frac{1}{2}$	7 $\frac{1}{2}$	34 U + 16 S	9	394	7.13A	6.5	5	Vomiting, 7 hr. No identifiable cause.
3	F	8 $\frac{1}{2}$	13 $\frac{1}{2}$	$\frac{3}{4}$	26 U + 8 R	1	357	7.15V	10.2	4	No apparent cause.
4	F	6 $\frac{1}{2}$	14 $\frac{1}{2}$	7 $\frac{1}{2}$	34 U + 6 R + 24 S	7	316	7.03A	6.5	12	Recurrent carbuncles, cellulitis, vomiting, emotional stress.
5	F	8 $\frac{1}{2}$	11 $\frac{1}{2}$	2 $\frac{1}{2}$	10 U + 10 S	5	345	7.37A	10	7	No apparent cause.
6	F	1 $\frac{1}{2}$	11.0	15	13 U + 12 R	15	849-977	7.36A	14	5	Mild enteritis, emotional stress.
7	F	Same as case 4	14 $\frac{1}{2}$	<3	6 R + 34 U + 24 S	3	252	7.27	10	13	Possible Somogyi Syndrome, also frequent skin infections, slight URI (see case 4), emotional stress.
8	F	11 $\frac{1}{2}$	18 $\frac{1}{2}$	8	22 U + 8 R	6	310	7.19V	9	1	Severe, primary herpes vulvovaginitis.
9	M	1 $\frac{1}{2}$	2 $\frac{1}{2}$	4	5 U + 4 S	23	410	7.22V	10	0	Acute gastroenteritis.
10	F	Same as case 5	12.0	3	13 U + 13 S	3	577	7.24A	4.3	9	Vomiting, no identifiable cause.
11	M	13 $\frac{1}{2}$	20 $\frac{1}{2}$	7	70 U + 20 R	8	497	7.18V	6.8	12	Physical and emotional stress.
12	F	7 $\frac{10}{12}$	17 $\frac{1}{2}$	<3	8 R	3	704	7.25A	13.3	5	Respiratory infection.
13	F	9 $\frac{1}{2}$	17.0	24	42 U + 22 R	3	465	7.15	12	7	Gastroenteritis, emotional stress.
14	F	6.0	12 $\frac{10}{12}$	7 $\frac{1}{2}$	6 R + 44 U + 20 S	3	400	7.09	5.5	12	Emotional stress, vomiting.
15	F	16 $\frac{1}{2}$	17 $\frac{1}{2}$	27	28 U + 16 S	4	496-717	7.13A	12.9	8	Emotional stress.
16	F	3 $\frac{1}{2}$	10 $\frac{1}{2}$	24	72 U + 30 R	3	838	6.96V	6.5	1	Acute pharyngitis.
17	F	11 $\frac{1}{2}$	16 $\frac{1}{2}$	2	24 PZI + 10 R	8	420	7.12A	6.5	2	No identifiable cause.
18	F	3.0	6 $\frac{1}{2}$	5?	40 NPH + 16 R	5	336	7.08A	8	5	Emotional stress.
19	F	11.0	18 $\frac{1}{2}$	2 $\frac{1}{2}$	12 U + 8 R	3	454? or 481	7.30A	12.3	1	Severe vulvitis + carbuncles and staphylococcus bacteremia.
20	F	Same as case 15	17 $\frac{1}{2}$	$\frac{1}{2}$	12 U + 12 R	4	408-622	7.03A	3.0	10	Emotional stress.
21	F	Same as case 4	15 $\frac{1}{2}$	27	62 U + 32 R	6	594	7.13A	2.1	16	Emotional stress, nausea.
22	M	7 $\frac{1}{2}$	13 $\frac{1}{2}$	1 $\frac{1}{2}$	6 R + 32 U + 22 L	9	347	7.26	13.5	7	Emotional lability, vomiting, (7th of 12 admissions in 13 mos.)
23	M	5 $\frac{10}{12}$	6 $\frac{1}{2}$	9 $\frac{1}{2}$	36 U + 8 R	10	388	7.13V	14.3	0	Viral URI with vomiting.
24	F	11 $\frac{1}{2}$	14 $\frac{1}{2}$	2 $\frac{1}{2}$	5 $\frac{1}{2}$ U + 3 S	10	477	7.31V	17	0	Fever, pharyngitis, and vaginitis.
25	F	Same as case 18	7 $\frac{1}{2}$	2 $\frac{3}{4}$	30 U + 6 R	14	346	7.04V	7	11	URI with vomiting, emotional stress.

Fig. 1. Output of epinephrine (●) and norepinephrine (○) in the first urine collection, expressed as excretion rate per M^2/hr . Data are displayed according to the patients' ages along the *abscissa*. The mean and $+2$ S.D. range of normal children (50) is shown by the *cross-hatched area*. In 2 cases (□), the first urine specimen was lost, and the values shown were obtained in the second collection period. The catecholamine output is along the *ordinate*; norepinephrine and epinephrine scales differ by a factor of 10.

Fig. 2. Pattern of hourly excretion rate of epinephrine in $\mu g/M^2/hr$ for the whole group. Data include the range, the mean (●), and the median (▲) displayed for the hours of the study along the *abscissa*. The epinephrine scale is along the *ordinate*. The mean $+2$ S.D. range for normal children is shown by the *cross-hatched area* (50). The mean and median values did not vary significantly during the first 8 hr. The mean and median values are in the normal range during the last 6 hr although seven patients still excreted epinephrine at a rate above 2 S.D. of the normal mean. Of 337 timed urine specimens analyzed, 30 contained more than $2.0 \mu g$ of epinephrine per M^2 per hour (normal, 0.1 to $0.2 \mu g/M^2/hr$).

was different from that of epinephrine. The rate of output of hormone remained fairly constant during the study except in five children in whom it increased. The total output of norepinephrine in 24 hr was normal in 19 studies. In three cases, it exceeded $100 \mu g/M^2/24$ hr (Fig. 3).

Fig. 3. Total excretion of epinephrine and norepinephrine in 24 hr by individual patients. Code as in Figure 1. Epinephrine output per 24 hr was more than 2 S.D. above the mean in 16 patients. Norepinephrine excretion per 24 hr was greater than 2 S.D. above the mean in three cases.

Fig. 4. Hourly concentrations of plasma cortisol in $\mu g/dl$ are displayed for the 25 studies. Data include the range, the mean (●), and the median (▲). Peak values are present at the outset and gradually return to the normal range during the recovery period. An occasional patient had persistent hypersecretion of cortisol throughout the entire study period. The *line* depicts the upper limit of the diurnal range ($25 \mu g/dl$).

Cortisol hypersecretion was another prominent hormonal abnormality. In the majority of the patients, continuous hypercortisolemia, characteristic of a stress response, replaced the usual diurnal rhythm. Figure 4 shows the range, the mean, and the median values of plasma corticoid concentration in the 25 cases for each hour. The mean plasma corticoid concentration on admission was $38 \mu g/dl$ (range, 10 to $76 \mu g/dl$); in 17 cases, it was above $25 \mu g/dl$. Of the 25 initial cortisol values, 24 were elevated relative to the normal diurnal concentration. Hypersecretion of cortisol continued in most of the children for the first 6 to 8 hr and then gradually subsided. However, in a few patients, it persisted throughout most of the study. The three most severely ill patients had the highest corticoid levels for the longest time; one of these cases is illustrated in Figure 5. The 24-hr plasma corticoid pattern was similar to that of epinephrine with the peak values occurring in the early hours.

The growth hormone levels at the time of admission ranged from 1.6 to 39.6 ng/ml, and only seven patients had values of 20 ng/ml or higher. There was a significant difference ($0.02 < P <$

Fig. 5. Plasma concentrations of glucose, corticoids, and growth hormone and excretion rates of catecholamines in case 14. Clock time is given along the *abscissa*. The *inner scale* in the *center panel* refers to cortisol and growth hormone ($\mu\text{g/dl}$ and ng/ml , respectively). In the *two lower panels*, the *outer scale* refers to the urinary catecholamine output per M^2 per hr. Norepinephrine and epinephrine scales differ by a factor of 10, corresponding to the usual average ratio of these two catecholamines in urine. The "normal" excretion rate for both would be between 1 and 2 on this scale. Insulin doses are indicated by the height of the *arrows*. Note peaks of growth hormone following every injection of insulin. Extraordinary elevation of epinephrine was present at the outset and persisted for the first 12 hr but returned to normal by the 16th hr.

0.05) between the initial growth hormone levels of the 13 patients who had received insulin at home within 3 hr before arrival (mean, > 17.3 ; median, 20 ng/ml) and the levels of those who had not had insulin recently (mean, 9.8 ; median, 6.2 ng/ml). After administration of insulin in the hospital, growth hormone concentrations rose in 19 of 25 cases and reached a peak 1 to $2\frac{1}{2}$ hr after the injection (Fig. 6). In all cases, these peaks ranged from 30 to 160 ng/ml (Fig. 6). The highest concentrations of growth hormone were present in the 4 hr after the first insulin injection and then fell to below 8 ng/ml , but there were intermittent subsequent spikes which seemed related to insulin injections, sleep, or unknown causes.

Hyperglucagonemia (values ranging from 250 to 1250 pg/ml) was present on admission in 11 cases; four of these had levels

Fig. 6. Growth hormone concentrations in plasma in individual patients. *A*, at the time of admission (in the cases in which two or more samples were obtained before the first insulin injection); *O*, immediately before the first insulin injection; *P*, peak observed at any time during the first 3 hr after this injection. $\circ$, patients who had received insulin at home within 3 to $3\frac{1}{2}$ hr before admission; $\bullet$, patients who received their last insulin dose more than $3\frac{1}{2}$ hr before admission. (Because in several cases the growth hormone concentration exceeded the upper limit of the analytical method and insufficient serum was available for repeat on a diluted specimen, four of the values, indicated here by *arrows*, are only minimal estimates.)

Fig. 7. Plasma glucagon concentrations ($\text{pg/ml} \pm \text{S.E.}$) are shown for a group ($n = 11$) of ketoacidotic patients whose values were less than 200 pg/ml at the outset and for most of the study. This group falls into the "normal range" shown by *cross-hatched area*. A second group ($n = 11$) had high plasma glucagon values (250 to 1250 pg/ml) at the outset and throughout the study. The large S.E. illustrates the marked variability among these patients.

between 900 and 1250 pg/ml . In 11 other patients, the initial concentrations were below 200 pg/ml and remained so for most of the study. The glucagon values in these two groups are shown in Figure 7. Most of the very high concentrations of glucagon were observed during the first hr or two after admission, and usually, they were transient. However, throughout the study period, several patterns of glucagon secretion were observed which

account for the very large standard errors of the mean seen in Figure 7.

There was no correlation between the severity of the acidosis or hyperglycemia seen in these patients on admission and the first plasma level of cortisol, growth hormone, or glucagon. Likewise, the first urinary output of epinephrine or norepinephrine did not correlate with the degree of ketoacidosis.

DISCUSSION

Diabetic ketoacidosis is usually ascribed to an absolute (13) or relative deficiency of insulin (38). Absolute deficiency can be ruled out in most of the cases in this series because all but two patients had received their usual doses of short- and long-acting insulin on the day of admission one-half of them within 3 hr before arrival at the hospital. The rapid onset of ketoacidosis in these patients suggested that stress triggered the release of large amounts of counterregulatory hormones which overwhelmed the action of insulin. This hypothesis is supported by a recent study involving six insulin-treated diabetics given intravenous pseudomonas polysaccharide, a potent pyrogen. Malaise, chills, and fever were followed rapidly by increases in plasma concentrations of growth hormone, catecholamines, and cortisol which preceded by 30 min elevations in plasma ketones. However, acidosis *per se* was not reported (39).

Hyperexcretion of epinephrine was a frequent and striking phenomenon in our patients (20 of 23 initial observations). Epinephrine output was much more elevated than norepinephrine. However, urine measurements may not be representative of the total quantity of norepinephrine produced because the primary mechanism of inactivation of this catecholamine is reuptake into the storage granules and only small amounts are released into the circulation and subsequently excreted into the urine (29). Elevated plasma levels of norepinephrine have been reported in patients with ketoacidosis (11, 53).

The finding of peak epinephrine output close to the onset, followed by gradual return to normal baseline values during the recovery period, suggests that the catecholamine abnormality was provoked by some stressful stimulus. In 1950, Hinkle *et al.* (25) reported that both diabetic and nondiabetic humans have a rise in blood ketones within 2 hr after psychologic stress, but the ketone levels were higher in the diabetics. Subsequently, Baker *et al.* (2) reported that excessive epinephrine production, hyperglycemia, and elevated plasma free fatty acid levels occurred after a stressful psychiatric interview with an adolescent diabetic girl who had had repeated bouts of acute ketoacidosis precipitated by emotional conflict. In addition, Christensen *et al.* (10) observed elevated plasma concentrations of epinephrine and norepinephrine in diabetics during ketoacidosis. After treatment with insulin and correction of acidosis, the catecholamine values returned to normal. There is no evidence of a primary overproduction of catecholamines in patients with diabetes mellitus.

The catecholamines, particularly epinephrine, are the most potent of the lipolytic hormones. Furthermore, both epinephrine and norepinephrine stimulate glucagon secretion which enhances the capacity of the liver to convert fatty acids into ketone bodies (19, 28). Thus, the catecholamines and glucagon combine to promote both lipolysis and ketogenesis as well as glycogenolysis and hyperglycemia.

The role of glucagon in diabetes mellitus has been extensively evaluated. Müller *et al.* (31) found that plasma glucagon levels in insulin-deficient acidotic patients correlated with blood glucose and with the duration of insulin therapy required to reduce ketone bodies in serum. They concluded that increased circulating glucagon contributed to the severity of the metabolic derangement and hypothesized that primary abnormalities of both the alpha and beta cells were present in patients with diabetes mellitus (51). This conclusion now must be modified in view of reports which indicate that insulin deficiency is necessary for glucagon to cause marked hyperglycemia (3, 44, 46).

In our patients, the initial plasma concentrations of glucagon did not correlate with the degree of epinephrine overproduction, and elevated plasma glucagon levels were noted less frequently. In fact, glucagon concentrations at the outset were below 200 pg/ml in 11 patients. In several additional individuals, glucagon levels fell rapidly after admission even though increased epinephrine production continued. Although glucagon has been implicated as an important hormone in catabolic illness (49), low levels of glucagon were observed in our single patient with a severe bacterial infection (case 19). The emotionally stressed patient who excreted the largest amount of catecholamines had no significant hyperglucagonemia (cases 15 and 20).

Hypercortisolemia in the early phase of acute ketoacidosis was as impressive as the abnormality observed in catecholamine production by our patients (24 of 25 initial plasma levels). Increased secretion of cortisol in children with diabetic ketoacidosis has been described previously, but its relationship to the other counterregulatory hormones was not evaluated simultaneously (18, 47). In a large proportion of cases, high corticoid concentrations persisted for 6 to 12 hr whereas in a smaller group, it lasted for longer periods. Cortisol is known to promote gluconeogenesis which may contribute to the hyperglycemia seen in diabetic ketoacidosis. Studies suggest that glucocorticoids also enhance the lipolytic action of the counterregulatory hormones and possibly possess primary lipolytic activity (14, 33, 37, 42).

In contrast to the marked elevations of corticoid and catecholamines, growth hormone levels were not maximal at the time of admission (only seven had values > 20 ng/ml) but peaked after the first injections of insulin. After insulin administration, 17 patients had values which ranged from 20 to 160 ng/ml. Augmented growth hormone secretion due to stress has been reported in healthy subjects (5, 22, 24, 41) and is more pronounced in diabetic (23, 30) patients. Spikes of growth hormone have been described after insulin administration regardless of blood glucose concentrations (12, 16, 45).

Determinations of the major counterregulatory hormones at onset of ketoacidosis showed that 21 of 22 patients had increased production of at least three of the stress hormones. Although there was variability in the severity and duration of the hormonal responses, extraordinary increases in catecholamine and cortisol production were observed in almost every patient whereas glucagon and growth hormone concentrations were high in about one-half of the group. Increased lipolysis as well as conversion of liberated free fatty acids to ketone bodies via hepatic ketogenesis are prerequisites to ketoacidosis. The lipolytic effects of the catecholamines, growth hormone, glucagon, and cortisol have been documented, but their influence on ketogenesis is less well understood. The work of McGarry and Foster (28) indicates that glucagon is essential for augmentation of hepatic ketogenesis because of its ability to activate the carnitine acyl transferase system which transports fatty acid residues into mitochondria for oxidation to ketone bodies. The occurrence of acute ketoacidosis without hyperglucagonemia in some of our patients and the development of ketonemia in pancreatectomized humans (3) suggests that other stress hormones besides glucagon may enhance hepatic ketogenesis and lead to ketoacidosis.

A variety of stresses in humans provoke catecholamine, cortisol, glucagon, and growth hormone release, and the pattern of response is highly individualized (5, 9, 17, 20, 24, 26, 34, 35, 41, 55). The intensity and character of each response may depend on conditioning factors, including genetic disposition and past experiences (17, 26, 43). Inasmuch as all these hormones overwhelm the action of insulin at one or more of its target tissue(s), it is likely that the usual dose of insulin in diabetic patients is insufficient to offset the effects of these counterregulatory hormones. Thus, ketoacidosis ensues (38).

An important question concerns the difference in susceptibility to ketoacidosis among patients with juvenile onset diabetes mellitus. The majority of diabetic children seldom, if ever, require hospitalization although a minority have occasional or repeated

bouts of acute ketoacidosis despite competent medical care. It is indeed remarkable that in a 20-year review of hospitalizations of nearly 600 diabetic children in one institution, over 60% never required admission after the initial hospitalization which established the diagnosis, whereas 12% of patients accounted for all the cases with more than two admissions (6). One cannot ascertain from available data whether those who are not prone to acute ketoacidosis have different stress hormone patterns or whether they possess residual beta cell function which provides stability of metabolic control. In two recent studies, residual beta cell function was found in some diabetic children months to years after onset of disease (4, 27). Further studies of endogenous insulin reserves and stress hormone production in these two groups of juvenile onset diabetics are needed to improve our understanding of the factors which place diabetic children at risk for developing acute ketoacidosis.

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- Part of this material was presented at the Third International Beilinson Symposium on the Balance of Diabetes in Juveniles in Tel Aviv, Israel in May, 1975 (8). A preliminary report entitled "Stress Hormones in Diabetic Ketoacidosis" was also presented at the Annual Meeting of The American Pediatric Society and The Society for Pediatric Research in San Francisco, California, April 25-29, 1977 (7).
- The authors are deeply grateful to the Staff of the Clinical Research Center, to the technical personnel of the Endocrinology Laboratory and to our secretary, M. Link for their generous support of this project.
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59. This research was supported by Grant RR 628 from the General Clinical Research Centers Program of the Division of Research Resources, National Institutes of Health; by Grant AM 17879 from the Department of Health, Education, and Welfare; and by Grant RR 05493 from the Biomedical Re-

search Support Grant Program, Division of Research Resources, National Institutes of Health. Purified hormones were generously provided by the National Pituitary Agency for many of the radioimmunoassay procedures.
60. Received for publication March 7, 1980.
61. Accepted for publication May 19, 1980.

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0031-3998/81/1502-0099\$02.00/0

Printed in U. S. A.

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ANNOUNCEMENT

The annual meeting of the American Society of Pediatric Nephrology will be held at the Hilton Hotel in San Francisco, California, on Tuesday evening, April 28, 1981. This year the symposium will be entitled, "State of the Nephron: The Pediatric Nephrologist View." For further information, please contact Dr. Russel Chesney, Secretary-Treasurer, American Society of Pediatric Nephrology, University of Wisconsin Clinical Sciences Center, 600 Highland Avenue, H4/452, Madison, Wisconsin 53792.