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# Diabetic Coma: Serum Growth Hormone before and during Treatment*

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*Summary.* Serum growth hormone values in 37 patients with diabetic ketoacidosis were $5.4 \pm 0.8$ ng/ml (S.E.M.) in males and $6.7 \pm 1.1$ ng/ml in females before treatment; while in five hyperosmolar non-ketotic patients the HGH concentration was $3.9 \pm 0.5$ ng/ml. One hour after insulin 90% of patients showed a rise in HGH, to a mean of $33.7 \pm 9.8$ ng/ml for males and $25.5 \pm 6.0$ ng/ml for females in ketoacidosis; and to $27.1 \pm 9.9$ ng/ml for hyperosmolar coma patients. The rise, which was transient, was inversely correlated with pretreatment plasma glucose, the 1 h plasma glucose concentration and plasma urea, and directly proportional to the % fall in blood glucose after 1 h. When the ketoacidosis patients were divided into two groups according to HGH response, those with a small response had the greater disturbances of plasma glucose, blood ketone bodies, blood lactate, plasma urea, blood pH, and blood pressure, the smaller 1 h fall in blood glucose, and the higher mortality. Thus the most severely ketoacidotic patients had the poorest growth hormone response. Growth hormone is probably of little importance as an insulin antagonist in diabetic coma.

*Key words*: Diabetes, diabetic ketoacidosis, hyperosmolar non-ketotic coma, lactic acidosis, growth hormone, insulin, blood ketone bodies, free fatty acids, arterial pH, plasma glucose.

The role of growth hormone in diabetes has been controversial since Young (1939) suggested it to be involved in initiation of the disease. More recently serum growth hormone levels have been found to be raised and to show great fluctuations in newly diagnosed and poorly-controlled juvenile diabetics in whom plasma FFA and blood glucose are raised (Hansen and Johansen, 1970; Johansen and Hansen, 1971).

In diabetic coma there is widespread disturbance of metabolic and endocrine homeostasis (Hockaday and Alberti, 1972). This paper describes measurements of serum growth hormone (HGH) during treatment of diabetic ketoacidosis and hyperosmolar, hyperglycaemic non-ketotic coma. Abnormal growth hormone values have been reported in diabetic ketoacidosis before treatment, with a rise one to two hours later, by both Cryer and Daughaday (1970) and Assan *et al.*, (1969) although relatively normal pretreatment values were reported in most patients by others (Roth *et al.*, 1964; Unger, 1965; Jacobs and Nabarro, 1969; Gerich *et al.*, 1971; Sönksen *et al.*, 1972). The cause of the elevated concentrations is unclear.

There is no agreed explanation for the lack of ketosis in hyperosmolar coma. One suggestion is that lipolysis is not increased, as it is in ketoacidosis, because of low or normal concentrations of serum cortisol and HGH (Gerich *et al.*, 1971), while others postulate a block in hepatic ketone body production or the presence of sufficient insulin to restrain lipolysis (Johnson *et al.*, 1968; Vinik *et al.*, 1970). It is therefore important to compare HGH concentrations before and during treatment of both types of coma, and to see whether any metabolic parameter can be correlated with fluctuations in serum HGH values.

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## Methods and Patients

Plasma glucose (glucose oxidase Autoanalyser), potassium and urea were measured in the routine biochemical laboratory. Plasma free fatty acids (FFA) were measured colorimetrically (Itaya & Ui, 1965). Blood 3-hydroxybutyrate and acetoacetate were measured enzymatically (Williamson *et al.*, 1962) as was blood lactate (Hohorst *et al.*, 1959). Serum growth hormone and serum insulin were measured by modifications of the double antibody radioimmunoassay methods of Boden and Soeldner (1967) and Soeldner and Slone (1965) respectively. Free-flowing venous blood samples were deproteinized or separated as described previously (Alberti and Hockaday, 1972).

The subjects comprised the forty six of the fifty nine patients admitted between June 1970 and February 1972 to the Radcliffe Infirmary in diabetic coma or precoma, as defined by Hockaday and Alberti (1972), on whom adequate serial serum HGH measurements were available. Thirty seven had diabetic ketoacidosis, four had combined lactic and ketoacidosis, and five were in hyperosmolar non-ketotic coma. Of the ketoacidotics 23 were female and 14 male while only one of the hyperosmolar coma patients was female. Six of the ketoacidotic patients were clinically obese: only one female (70 kg) weighed more than 65 kg and three males exceeded 70 kg (74, 82 and 97 kg). Two ketoacidotic subjects had evidence of cirrhosis of the liver, as had one lactic acidosis patient. Twenty of the ketoacidotic and four of the hyperosmolar coma patients were not previously known to be diabetic. Nine of the ketoacidotic patients and one hyperosmolar patient were receiving insulin and seven were taking oral agents. Five patients with ketoacidosis died, two within the first 24 h of treatment (at 3½ and 17 h). Details of patients are shown in Table 1.

Control subjects comprised either laboratory personnel ('normal' subjects) or newly diagnosed diabetics or known,

Table 1. *Details of patients admitted with diabetic coma or precoma*

| | Subject | Sex | Age | Weight | Duration Diabetes | Previous treatment[a] | Acute episode: Liver Disease | Duration of symptoms | Duration of coma | Initial insulin dose | Plasma glucose | Serum growth hormone | Time of death after onset of treatment |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | years | kg | years | per day | | days | h | units | mg/100 ml | ng/ml | h |
| *a) Ketoacidosis patients* | | | | | | | | | | | | | |
| *Large response group* | 4 | M | 48 | 67 | 2 | S. 48 | — | 3 | — | 80 | 465 | 4.5 | — |
| | 14 | F | 71 | 56 | 4 | Tolbutamide 2g | — | 14 | — | 100 | 690 | 5.9 | — |
| | 15 | M | 55 | 65 | 0 | 0 | — | 35 | — | 100 | 280 | 3.8 | — |
| | 20 | M | 13 | 37 | 0 | 0 | — | 3 | — | 16 | 400 | 14.0 | — |
| | 21 | F | 25 | 62[b] | 7 | S. 44u P. 32u | — | 2 | — | 32 | 355 | 9.5 | — |
| | 27 | F | 58 | 42 | 0 | 0 | — | 8 | — | 80 | 750 | 3.9 | — |
| | 29 | M | 27 | 74 | 15 | S. 72u P. 72u | — | 2 | — | 100 | 380 | 3.2 | — |
| | 35 | M | 68 | 82[b] | 0 | 0 | — | 1 | 4 | 60 | 930 | 3.8 | — |
| | 44 | F | 59 | 46 | 0 | 0 | Alcoholic cirrhosis | 10 | — | 100 | 544 | 7.1 | — |
| | 47 | M | 62 | 58 | 0 | 0 | — | 6 | — | 32 | 350 | 4.8 | — |
| | 51 | F | 25 | 59 | 2 | S. 32u P. 24u | — | 7 | — | 80 | 345 | 8.5 | — |
| | 52 | F | 71 | 48 | 0 | 0 | — | 11 | — | 50 | 446 | 4.2 | — |
| *Small response group* | 10 | F | 48 | 61 | 0 | 0 | Mild cirrhosis | 7 | — | 100 | 720 | 4.3 | — |
| | 12 | F | 15 | 32 | 0 | 0 | — | 42 | — | 100 | 700 | 4.7 | — |
| | 19 | F | 66 | 51 | 13 | Phenformin 100 mg Chlorpropamide 500 mg | — | 1 | 2 | 80 | 780 | 9.8 | — |
| | 22 | F | 64 | 63 | 0 | 0 | — | 21 | — | 80 | 700 | 2.4 | — |
| | 25 | F | 54 | 56 | 0 | 0 | — | 7 | — | 100 | 540 | 2.6 | — |
| | 30 | F | 84 | 44 | 1/12 | Tolbutamide 1g | — | 7 | — | 40 | 620 | 3.9 | 28 |
| | 31 | M | 46 | 97[b] | 0 | 0 | — | 14 | — | 60 | 810 | 2.7 | — |
| | 32 | F | 71 | 50 | 4 | S. 28u P. 48u | — | 2 | 6—24 | 60 | 570 | 14.1 | — |
| | 33 | F | 47 | 52 | 10 | Chlorpropamide 500 mg | — | 4 | 6—24 | 60 | 645 | 3.2 | — |
| | 34 | F | 27 | 48 | 6 | S. 30u P. 28u | — | 1 | 6—24 | 40 | 425 | 19.8 | — |
| | 37 | F | 20 | 61[b] | 0 | 0 | — | 2 | 6—24 | 100 | 820 | 7.6 | — |
| | 38 | M | 52 | — | ? | ? | — | ? | ? | 60 | 640 | 7.3 | 3½ |
| | 40 | M | 16 | 51 | 0 | 0 | — | 14 | — | 150 | 690 | 5.5 | — |
| | 41 | M | 17 | 52 | 0 | 0 | — | 4 | 6 | 150 | 660 | 9.7 | — |
| | 45 | F | 84 | 59 | 15 | Chlorpropamide 500 mg Phenformin 50 mg | — | 4 | — | 30 | 640 | 3.7 | — |
| | 46 | F | 51 | 56 | 0 | 0 | — | 14 | 3— 4 | 100 | 1200 | 2.1 | — |
| | 48 | F | 41 | 63 | 24 | S. 44u | — | 4 | — | 80 | 400 | 9.6 | — |
| | 49 | F | 45 | 59 | 10 | S. 22u P. 26u | — | 1 | — | 40 | 1275 | 15.0 | — |
| | 50 | F | 41 | 63 | 24 | S. 44u | — | 3 | — | 100 | 480 | 1.8 | — |
| | 55 | F | 72 | 70[b] | 10 | Diet | — | 7 | — | 50 | 970 | 1.6 | 31 days |
| | 56 | M | 18 | 51 | 0 | 0 | — | 5 | 3 | 100 | 1080 | 4.4 | — |
| | 57 | M | 65 | 48 | 0 | 0 | — | 2 | 24 | 80 | 850 | 6.1 | — |
| | 62 | F | 60 | — | 5 | Chlorpropamide 500 mg | — | 5 | — | 80 | 820 | 4.3 | 156 |
| | 63 | F | 69 | 64 | 0 | 0 | — | 8 | 4 | 80 | 510 | 0.9 | — |
| | 65 | M | 29 | —[b] | 0 | 0 | — | 2 | 12 | 40 | 750 | 3.3 | 17 |
| *b) Hyperosmolar coma patients* | | | | | | | | | | | | | |
| | 9 | M | 65 | 66 | 0 | 0 | — | 6 | — | 100 | 1035 | 2.4 | — |
| | 17 | M | 73 | — | 0 | 0 | — | 7 | — | 40 | 480 | 6.3 | 79 |
| | 18 | M | 84 | 70 | 0 | 0 | — | 14 | — | 80 | 1005 | 5.2 | — |
| | 36 | F | 67 | 63 | 17 | P. 20u | — | 1 | 2 | 40 | 680 | 2.8 | — |
| | 54 | M | 73 | | 0 | 0 | — | 14 | 12 | 40 | 1350 | 2.9 | — |

[a] Previous treatment: $S$ = soluble insulin, $P$ = protamine zinc insulin; [b] Clinically obese.

stable, insulin requiring diabetics fasted overnight. All samples from them were obtained through an indwelling venous catheter after 30 to 60 min recumbency. Statistical significance was assessed by Student's t test.

## Results

### *Pre-treatment serum growth hormone concentrations*

The average pretreatment values of growth hormone for male ketoacidotics was $5.4 \pm 0.8$ ng/ml,compared with $2.5 \pm 1.4$ ng/ml in control diabetics ($p < 0.05$) and $0.6 \pm 0.3$ ng/ml in normal males ($p < 0.01$) (Table 2). In ketoacidotic females, however, values were the same as in normal or control diabetic females after an overnight fast. There was a wide scatter of values but only 4 (3 female and 1 male) of 37 exceeded 10 ng/ml.

In the present study the mean serum HGH value for hyperosmolar coma patients was $3.9 \pm 0.5$ ng/ml compared with the overall mean of $6.3 \pm 0.7$ ng/ml for ketoacidotic patients. The mean value of the male hyperosmolar patients (4 of 5) was $4.1 \pm 0.7$ which was significantly higher than normal overnight fasted males ($p < 0.001$) but not significantly different from the male ketoacidotic patients.

Four patients had combined lactic acidosis and ketoacidosis. Pre-treatment values were 496.0, 14.4, 9.7 and 3.1 ng/ml while 2 diabetic subjects with normoglycaemic lactic acidosis had growth hormone concentrations of 287.5 and 8.6 ng/ml. The two patients with the extremely high values both had liver disease as well as diabetes.

### *Correlation of pretreatment serum growth hormone concentration with blood metabolite values and other parameters in diabetic ketoacidosis*

When patients with HGH values above 8 ng/ml ($n = 9$) were contrasted with those below 8 ng/ml ($n = 27$), those with high HGH values had a significantly lower pH ($6.99 \pm 0.05$ v $7.19 \pm 0.03$; $p < 0.005$). Correlation of pH against pretreatment HGH gave an r of $-0.32$ ($p < 0.10 > 0.05$) with the correlation holding only in females ($r$, $-0.35$). There was no correlation between pretreatment serum growth hormone concentrations and pretreatment plasma glucose, blood ketone bodies, blood lactate, plasma FFA, plasma potassium, plasma urea, calculated osmolarity, blood pressure, weight or age.

### *Change in serum growth hormone concentration with treatment*

All but 4 of the ketoacidotic patients and all the hyperosmolar non-ketotic subjects showed a rise in serum growth hormone one hour after the first dose of insulin. There was no difference between males and females and the mean rises were similar to that found in the hyperosmolar group (Table 2). There was no correlation between the pretreatment value and the extent of the rise. At 5 h males were still higher than pretreatment while at 24 h values for both male and female ketoacidotic patients were significantly lower than for normal controls, but similar to diabetic controls. Interestingly, values for females tended to be lower than for males throughout the treatment period.

Hyperosmolar patients showed a similar trend and there was no significant difference between male hyperosmolar and ketoacidotic subjects at any time period. There was only one female hyperosmolar patient, and so separate sex analysis was not possible.

Table 2. *Serum growth hormone concentrations (ng/ml) (± S.E.M.) during treatment of diabetic coma*

| | | | Pre-treatment | 1 h | 5 h | 24 h |
|---|---|---|---|---|---|---|
| Normal | Male | (16) | $0.6 \pm 0.3$ | — | — | — |
| | Female | (8) | $6.7 \pm 2.1$ | — | — | — |
| Control diabetics | Male | (12) | $2.5 \pm 1.4$ | — | — | — |
| | Female | (9) | $5.5 \pm 2.0$ | — | — | — |
| Keto-acidosis | Male | (14) | $5.4 \pm 0.8$ | $33.7 \pm 9.8$[b] | $8.7 \pm 2.3$[a] | $3.9 \pm 1.4$ |
| | Female | (23) | $6.7 \pm 1.1$ | $25.5 \pm 6.0$[b] | $5.4 \pm 0.8$ | $3.1 \pm 0.4$[b] |
| Hyper-osmolar coma | Male | (4) | $4.1 \pm 0.7$ | $31.7 \pm 11.3$[b] | $7.5 \pm 2.3$[a] | $4.2 \pm 1.5$ |
| | Total | (5) | $3.9 \pm 0.5$ | $27.1 \pm 9.9$[b] | $6.8 \pm 1.9$[a] | $3.7 \pm 1.2$ |

[a] $p < 0.05$ compared with pretreatment.
[b] $p < 0.01$ compared with pretreatment; Numbers in parentheses indicate number of subjects.

### *Correlation of metabolic parameters with 1 h growth hormone response*

a) *Plasma glucose.* There was a strong negative correlation between pretreatment plasma glucose and the change in serum HGH found at 1 h after insulin

($r$, $-0.49$; $p<0.01$) in the ketoacidotic patients. The correlation was weakened by inclusion of hyperosmolar patients ($r$, $-0.34$; $p<0.05$). Thus the lower the initial glucose the greater the subsequent rise in growth hormone. This could not be attributed purely to insulin dosage as there was no correlation between this and HGH rise. Plasma glucose at 1 h also gave a negative correlation with rise in HGH ($r$, $-0.52$; $p<0.01$). Absolute fall in glucose showed only a loose

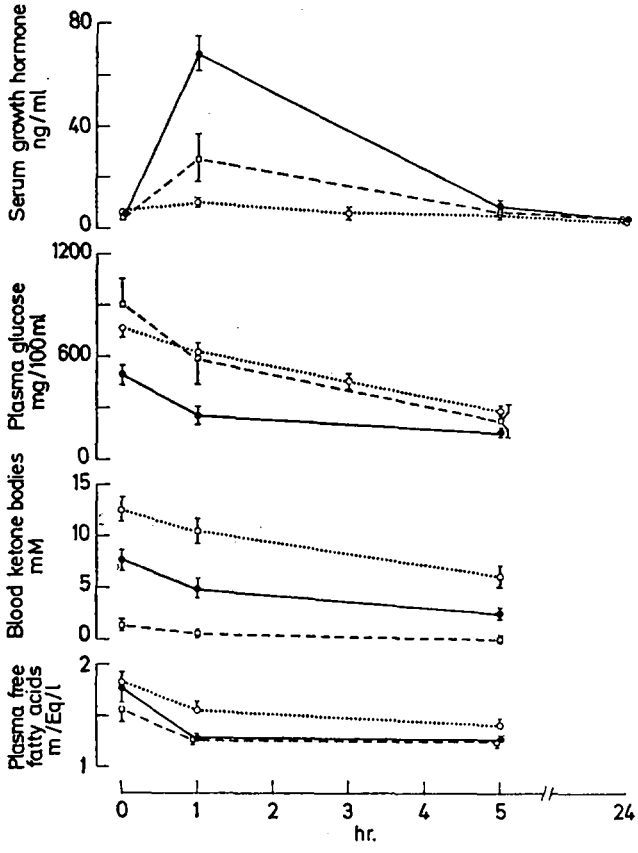


Fig. 1. Serum growth hormone, plasma glucose, plasma FFA and ketone bodies in diabetic coma. ● — ●, ketoacidosis, "large risers"; o .... o, ketoacidosis, "small risers"; □ ··· □, hyperglycaemic non-ketotic patients. "Large risers" were those subjects with a rise in serum growth hormone of more than 30 ng/ml one hour after insulin; "small risers" had a rise of less than 30 ng/ml

correlation with rise in growth hormone ($p<0.1>0.05$), although the correlation was better with % fall in plasma glucose at 1 h ($p<0.01$ for ketoacidosis patients alone and $p<0.05$ for all patients).

b) *Plasma urea.* Surprisingly the change in serum growth hormone was related to the initial plasma urea concentration (but not the change in urea with treatment) for both ketoacidotics ($r$, $-0.50$; $p<0.01$) and the whole coma group ($r$, $-0.45$; $p<0.01$). Those subjects showing low initial plasma glucoses, biggest percentage fall in glucose and lowest pretreatment plasma urea were the ones who showed the biggest rise in plasma HGH one hour after treatment.

c) *Other factors.* There was no correlation between rise in serum growth hormone and pretreatment values or change in plasma FFA, blood ketone bodies, blood lactate and plasma potassium.

*Classification according to growth hormone response*

There was a wide variation in the magnitude of the rise in serum growth hormone concentration one hour after onset of treatment. The ketoacidotic patients were therefore divided into two groups: the "large response" group with a change of more than 30 ng/ml ($n=12$) and the "small response" group with a rise of less than 30 ng/ml ($n=25$). Fig. 1 shows serum growth hormone values before and after treatment in the two groups. The hyperosmolar non-ketotic patients formed a third, intermediate group, two hyperosmolar subjects having large responses and three subjects small responses. Various metabolic characteristics have been compared in the two groups of ketoacidotic patients and the hyperosmolar nonketotic patients.

a) *Plasma glucose.* There was a striking difference between the two ketoacidotic groups (Fig. 1) with the "large response" group having significantly lower pretreatment glucoses ($494\pm57$ v $768\pm50$ mg%; $p<0.005$), and larger 1 h fall in glucose, expressed both as mg/100 ml and as per cent fall ($47\pm7$ v $18\pm3$; $p<0.001$). Plasma glucose was still significantly higher in the "small" response group 5 h after treatment commenced.

The hyperosmolar group with a higher initial plasma glucose showed a significantly greater absolute fall than the "small" response group. The % fall ($37\pm6$) was intermediate between the two ketoacidotic groups, as was rise in serum HGH.

b) *Plasma FFA, blood ketone bodies and arterial pH.* Fig. 1 shows also plasma FFA and blood ketone bodies in the 3 groups for the first 5 h following treatment. Plasma FFA showed no significant differences, although values tended to be higher throughout in the "small response" group. Blood ketone bodies were higher initially and at all subsequent times for the "small response" group while the hyperosmolar coma group had, by definition, low values throughout.

c) *Serum insulin and insulin dose.* There was a wide scatter of initial and one hour serum insulin concentrations when estimated in patients who had not previously had insulin therapy. Pretreatment values were $4.0\pm0.8$ and $7.9\pm1.4$ μU/ml in the large and small response groups ($p<0.10>0.05$) and at 1 h the values were $182.9\pm53.2$ and $649.2\pm209.7$ respectively (p, NS). The initial insulin dose for the two ketoacidotic groups and the hyperosmolar patients was similar ($69\pm9$ units for the "large response" group and $78\pm6$ for the "small response" group; $60\pm13$ for the hyperosmolar group).

d) *Plasma urea, blood pressure and mortality.* These

parameters were chosen as indicators of the overall clinical severity of the cases. Table 3 shows that those subjects with the low HGH response had markedly higher pretreatment plasma urea concentrations and significantly lower blood pressures than the "large response" group. Nearly half of the "small response" group were comatose and this was associated with 20% mortality, while in the "large response" group there was only one comatose patient and no mortality. The hyperosmolar patients had higher blood pressures than the small responders although plasma urea was not different. There was no difference in the weights of patients, proportion of new diabetics or previous treatment in the three groups.

other hand, Cryer and Daughaday (1971) in 4 of their 12 patients showed much higher pretreatment values, for which we have no explanation. They did however show a rise in HGH on treatment in 9 of their patients, as did Roth *et al.* (1964) in 1 patient and Sönksen *et al.* in their four patients (1972). The failure of other authors to note this rise was presumably because sufficiently early measurements after insulin were not made. Our results show that the main peak in HGH occurs early in treatment, not before one hour and not later than two to three hours (on the basis of multiple sampling in a few of our patients).

The pretreatment values in hyperosmolar non-

Table 3. *Biochemical and clinical characteristics of patients in ketoacidosis (separated according to HGH response to treatment) and in hyperosmolar nonketotic 'coma'*

| | Ketoacidotic coma Large HGH response | Small HGH response | Hyperosmolar nonketotic coma |
|---|---|---|---|
| n | 12 | 25 | 5 |
| Female | 6 | 17 | 1 |
| Dead | 0 | 5 | 1 |
| Age | 48 ± 6 | 48 ± 5 | 72 ± 3 |
| Weight kg | | | |
| Male | 64 ± 6 | 63 ±11 | 70 ± 4 |
| Female | 52 ± 3 | 56 ± 2 | — |
| Blood pressure mM Hg | | | |
| Systolic | 134 ± 7[b] | 112 ± 4 | 125 ± 6 |
| Diastolic | 81 ± 5[b] | 65 ± 3 | 79 ± 7 |
| Arterial pH | 7.28± 0.05[b] | 7.10± 0.03 | 7.38± 0.04[bc] |
| Plasma glucose mg% | 494 ±57[b] | 768 ±50 | 910 ±151c |
| Plasma urea mg% | 46 ± 5[b] | 120 ±13 | 145 ±21c |
| Serum HGH ng/ml | 5.9 ± 1.0 | 6.3 ± 0.9 | 3.9 ± 0.8 |
| Blood ketone bodies mM | 7.7 ± 1.0[a] | 12.5 ± 1.2 | 1.3 ± 0.6[bc] |
| Blood lactate mM | 1.5 ± 0.2[b] | 2.4 ± 0.2 | 2.0 ± 0.3 |

[a] $p < 0.05$.
[b] $p < 0.01$, compared with small HGH response group.
[c] $p < 0.01$, compared with large HGH response group. The large HGH response group were those ketoacidotic patients showing a rise of greater than 30 ng/ml at 1 h after treatment began, the rest form the small HGH response group. All measurements were made before insulin treatment was commenced.

## Discussion

The pretreatment growth hormone concentrations reported here for male ketoacidotic subjects follow the pattern of being higher than in normal or control diabetic subjects which one would predict from the results of Johansen and Hansen (1971). The deviation from control diabetics is smaller than would be expected, perhaps because of the opposing suppressive effect of hyperglycaemia (Roth *et al.*, 1963). Comparisons are more difficult with the females because of the much greater variation in HGH which is known to occur among females.

The pretreatment serum HGH values are similar to those reported by Jacobs and Nabarro (1969), and Gerich *et al.*, (1971). Sönksen *et al.*, (1972) described values of less than 5 ng/ml but this was in only 4 patients and the sex of the patients is not stated. On the ketotic coma did not differ significantly from either control diabetics or ketoacidotic patients, particularly when sex was taken into account. Gerich *et al.* (1971) and Jacobs and Nabarro (1969) reported low HGH values in equivalent patients but did not allow for sex.

The diabetic ketoacidosis patients could be divided into two groups according to their growth hormone response one hour after insulin. The "small response" group formed a more severe group with respect to nearly all parameters studied.

We were unable to find a correlation between rise in HGH and fall in FFA, a known stimulus to HGH secretion (Irie *et al.*, 1967; Quabbé *et al.*, 1971). However, plasma FFA were higher in the "small response" group throughout the first 5 h of treatment and may well have exerted a depressive effect on HGH release in this group (Blackard *et al.*, 1971).

Other circulating hormones may well have influenced growth hormone secretion in that plasma concentrations of cortisol (Jacobs and Nabarro, 1969), glucagon (Assan *et al.*, 1969) and catecholamines (Christensen, 1972) may all be elevated and remain thus for several hours in severe ketoacidosis. Glucagon (Cain *et al.*, 1970), and α-adrenergic stimulation (Imura *et al.*, 1968) both enhance growth hormone secretion, so these two factors cannot explain the decreased HGH in our more severe patients. However, Nakagawa *et al.*, (1969) have shown dexamethasone suppression of insulin-induced HGH release in normal males and this could be relevant to the present study. Plasma cortisol was measured in a few of our patients and tended to be higher in the "small response" group. Diminished total body potassium may also have played a role in that Podolsky *et al.* (1971) have shown that this is associated with a poor HGH response to arginine and insulin hypoglycaemia. Plasma potassium was not different in our two ketoacidotic groups, but it would seem reasonable to suppose that the more severe coma patients had the biggest total body potassium deficit.

The patho-physiological significance of these changes in growth hormone remains problematical. Growth hormone has a lipolytic effect in conjunction with cortisol (Fain *et al.*, 1965; Goodman, 1968) and it has been suggested previously that growth hormone may contribute significantly to the lipolysis and consequent ketoacidosis of severe uncontrolled diabetes (Gerich *et al.*, 1971). We would dispute that pretreatment HGH levels are sufficiently elevated to allow this, which is corroborated by the data of Sönksen *et al.*, (1972). The transient nature of the HGH rise would also militate against a role of growth hormone in the continued elevation of blood ketone body concentration, as would our observation that the patients with largest growth hormone rises were those with the most rapid fall in blood ketone bodies. We would agree with Cryer and Daughaday (1970) who were unable to find a connexion between high growth hormone concentration and a poor glucose response to insulin, so-called "insulin resistance".

Madison, Luft and Seyffert (1969) have shown that growth hormone can inhibit gluconeogenesis in the dog liver *in vivo* while growth hormone is well known to have an acute enhancing effect on muscle glucose uptake (Park *et al.*, 1952; Henderson *et al.*, 1961), followed albeit by a delayed inhibitory effect. Thus, in the acute phase of treatment it could be argued that growth hormone secretion was beneficial and that the "large response" group show a larger absolute fall in blood glucose partly, perhaps, because of growth hormone release. This remains speculative.

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