Pediat. Res. 5: 33–39 (1971)

Amino acids
free fatty acids
glucagon
glucose
growth
growth hormone
infantile malnutrition
insulin

Metabolic and Hormonal Responses to Glucose and Glucagon in Patients with Infantile Malnutrition

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Extract

The interrelations of plasma levels of glucose, free fatty acids (FFA), α-amino nitrogen (α-aaN), insulin, and growth hormone (GH) were studied in 26 malnourished infants shortly after admission to the hospital and again several weeks later when they had recovered. In the sick children (SC) fasting levels of FFA and GH were high, and insulin and α-aaN were low; with recovery FFA, α-aaN and insulin levels became normal, and GH levels fell. No change occurred in glucose levels.

Ten infants were given glucose (0.5 g/kg body weight) intravenously on the 1st or 2nd day after admission and again 6–12 weeks later. Glucose tolerance was impaired in the sick group and, although improved, was not normal when the children had recovered from the nutritional insult. Insulin secretion was stimulated by glucose in those that had recovered (RC), but not in the SC. No significant change occurred in either FFA or α-aaN levels in these groups.

Nine infants received glucagon (0.1 mg/kg body weight) intravenously on the 2nd to 6th day after admission and again 6–12 weeks later. Glucagon caused a rise in glucose levels that were greater in RC than in SC but did not cause a significant change in insulin levels in either group. Free fatty acid levels were higher in SC throughout the test, but in both groups FFA levels responded similarly to glucagon administration, falling 10 and 60 min after the injection.

Changes in GH levels in plasma after glucose or glucagon administration were compared with the changes caused by five venepunctures in RC. Venepunctures and glucose caused similar rises in GH levels, but glucagon caused a greater rise than either. It was concluded that the stress of repeated venepunctures caused a rise in GH levels in plasma in all three tests, but that, independent of this, glucagon stimulated GH secretion.

Speculation

Insulin secretion is impaired in infantile malnutrition and does not improve at the same rate as clinical recovery occurs, suggesting that normal β cell function is not essential for rapid growth. The role of growth hormone in malnutrition is not clear, but it appears to be involved more in the metabolic adaptation to malnutrition than in the control of growth.

Introduction

The hormonal adaptation to malnutrition is complex [15] and study of the endocrine responses to infantile malnutrition can be doubly rewarding, for from it may come information on the mechanism of adaptation to starvation in infancy and subsequently on the hormonal aspects of "catch-up" growth.

Children with kwashiorkor have a poor glucose tol-

erance [3, 4, 7] whereas children with marasmus may have a normal [4, 7] or abnormal tolerance [22]. Patients with these diseases have low fasting insulin levels [3, 7] and high levels of GH [24, 25], both of which return to normal on recovery [7, 24, 25]. No systematic study of insulin and GH levels in the same malnourished child has been reported, and the relation of the two hormones to each other or to changes in blood glucose during recovery from malnutrition is a matter of conjecture.

The present study sought to investigate this problem in two ways. Recovery from infantile malnutrition is characterized by an increased rate of growth which, in children admitted to this Unit, is approximately 15 times that of a normal child of the same age or 5 times that of a normal child of the same weight or height [2]. The metabolic and hormonal responses to glucose and glucagon were studied in malnourished children shortly after admission and again, several weeks later, when they were past the peak of their catch-up growth. The response to intravenous glucose served to characterize the infants for comparison with other reports and to test if hyperglycemia stimulated secretion of insulin and caused a rise in GH levels as it does in the newborn [6, 30], or a fall, as seen in the adult [26]. Glucagon was used because it stimulates insulin secretion both by direct action on the β cell [27] and by causing hyperglycemia. Also, glucagon causes a rise in GH levels in the newborn [16], and it was of interest to see if it would do this in older infants who were of a similar size. By studying each child twice, it was possible to use each subject as his own control.

Subjects and Methods

Subjects

The children studied were patients admitted to the Unit for investigation and treatment of infantile malnutrition. On admission a careful explanation was given to the parent or guardian and permission was obtained for the tests to be performed. Twenty-six children were studied; the ages ranged between 6 and 17 months with one exception of 27 months. Clinical classification was made on the basis of two objective criteria: weight and edema. Ten had edema and were less than 60% of the 50th percentile for weight [20]; these may be described as having had marasmic-kwashiorkor, the commonest type of malnourished child admitted to the Unit. Nine had marasmus; *i.e.*, they were less than 60% of their expected weight but had no edema. Five had edema and were more than 60% of their expected weight; they had kwashiorkor. Two had no edema and were 61 and 66% of their expected weight. Each child was treated with milk feeds of increasing strength and for most of the stay received approximately 150 kcal and 3 g protein/kg body weight/24 hr. Folic acid, ferrous sulfate, and vitamin supplements were given routinely; infection was treated when present. Each child was weighed daily.

Investigations

Blood samples were collected at various times after an overnight fast (8–9 hr). In six recovered patients, five fasting blood samples were collected in 1 hr, at 0, 3, 10, 30, and 60 min. Most samples were collected by venepuncture; a few were capillary blood.

Ten patients (seven boys, three girls; six marasmic-kwashiorkor, two marasmus, one kwashiorkor, one first degree malnutrition), who had fasted overnight, received glucose (0.5 g 50% glucose/kg body weight) by intravenous injection on the 1st or 2nd day after admission. Blood samples were drawn before (0 min) and at 3, 10, 30, and 60 min after the injection. The test was repeated 6–12 weeks later when the patients had recovered clinically.

Nine patients (seven boys, two girls; five marasmic-kwashiorkor, two marasmus, two kwashiorkor), who had fasted overnight, received glucagon (0.1 mg/kg body weight) by intravenous injection on the 2nd to 6th day after admission and again 6–12 weeks later. Blood samples were collected as described for intravenous glucose tests.

Methods

All blood samples were collected in bottles containing heparin and fluoride and were centrifuged within 30 min. Glucose and FFA levels were estimated the same day. Aliquots of plasma were stored at −20° until α-aaN, insulin, and GH levels were measured. For duplicate determinations of glucose, FFA, α-aaN, insulin, and GH, 300 μl plasma sufficed, thus making feasible repeated blood samples on one infant on 1 day.

Methods used were as follows: glucose, by a glucose oxidase assay [10]; FFA, by a modification [28] of the method of Novak [21]; α-aaN, by the method of Stein and Moore [29]; insulin, by immunoassay [8], using an ox insulin standard and an antibody, which did not discriminate between ox and human insulin [33]. Growth hormone in the plasma was measured by radioimmunoassay with preprecipitated antibody, filtration for the separation of "free" and "bound" hor-

mone, and a human GH standard [34]. Standard GH solutions and plasma diluted in parallel in the assay.

Statistical analyses were done by Student's t test. Where the difference between two values is stated to be significant without further qualification, $P < 0.05$.

Results

Growth during Recovery from Malnutrition

Figure 1 shows the average growth rate of the 26 children during hospitalization. During the 1st week, when the initial intravenous glucose and glucagon tests were performed, the rate of weight gain ranged from −19.2 to +5.4 g/kg/24 hr. Catch-up growth occurred mainly in the 2nd to 5th weeks. The second glucose or glucagon test was performed when the child had passed the peak growth rate but was still growing more rapidly than normally and was close to his expected weight for height.

Fasting Levels of Metabolites and Hormones

Table I shows the fasting levels of glucose, FFA, α-aaN, insulin, and GH in 19 pairs of blood samples. These were the initial samples from the glucose and glucagon tests and came from 15 infants, since 4 had both tests. There was no significant change in glucose levels with recovery. Insulin and α-aaN levels rose, and FFA and GH levels fell when the children had recovered from malnutrition. Figure 2 is a scattergram showing fasting GH plotted against length of stay in the hospital. The rate of fall of fasting GH levels could not be assessed accurately because of the paucity of information between days 10 and 30.

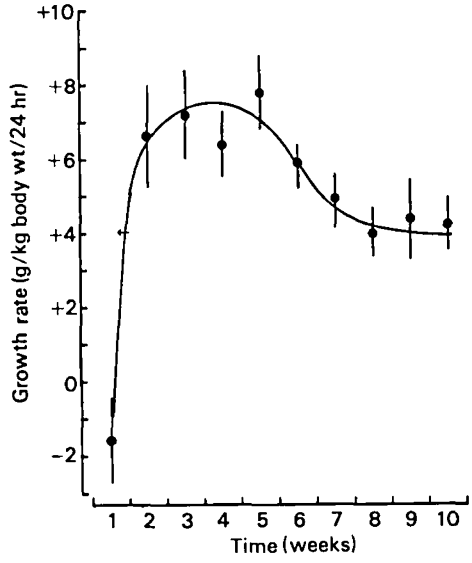

Fig. 1. Mean ± SEM growth rate of the 26 malnourished infants studied.

Table I. Plasma levels of metabolites and hormones in fasted malnourished infants

Levels of metabolite or hormone in plasma	Time after admission to hospital	
	1–6 days	6–12 weeks
Glucose, mg/100 ml	67 ± 4[1] (19)[2]	73 ± 3 (19)
FFA, μmoles/liter	707 ± 91 (19)	238 ± 39 (19)[3]
α-Amino nitrogen, mmoles/liter	2.6 ± 0.2 (19)	3.2 ± 0.2 (19)[3]
Insulin, μU/ml	7 ± 1 (19)	12 ± 1 (19)[3]
GH, ng/ml	24.5 ± 4.6 (17)	8.7 ± 1.2 (19)[3]

[1] Mean ± SEM.
[2] Number of observations indicated in parentheses.
[3] $P < 0.05$ when the sick and recovered groups were compared.

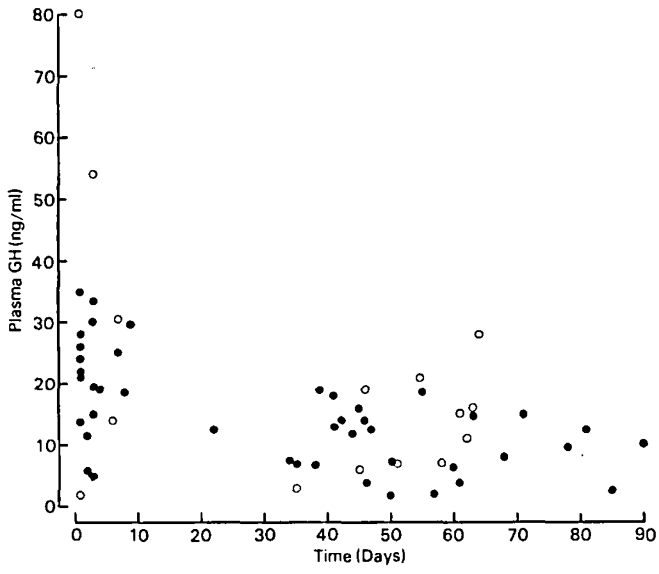

Fig. 2. Scattergram showing fasting GH levels in plasma plotted against length of stay in hospital of malnourished infants. ●: Boys. ○: Girls.

Intravenous Glucose

Too few glucose determinations were made after the intravenous glucose load to allow an estimate of the disappearance rate of glucose (k) to be made in each case. The mean levels of glucose show that glucose tolerance improved on recovery (Table II). From the mean levels an approximate glucose disappearance rate for the sick children (SC) was k_t 1.0% min^{-1} and for the recovered children (RC), 1.6% min^{-1}. Levels of FFA were significantly higher in SC at all times except in the 60-min sample. No significant change was seen in either group after the glucose load. Administration

of intravenous glucose had no effect on α-aaN levels, and, although these levels tended to be higher in RC, the difference was significant only at 30 min. There was no insulin response to glucose in the SC whereas a rise occurred at 3 min in RC. Levels of insulin in RC were significantly higher than those in SC at 10 and 30 min, but fell to fasting levels at 60 min. In both SC and RC levels of GH rose after glucose administration. The rise in GH levels observed in RC at 3 min was significantly greater than that seen in SC ($P < 0.025$); and the subsequent fall was slower, returning to fasting levels at 30 min in the SC but remaining significantly above the fasting level in the RC at 60 min.

Intravenous Glucagon

The intravenous injection of glucagon had no clinical effect on any child. Levels of glucose rose to a plateau by 30 min in the SC and to a peak at 30 min in RC (Table III). The maximal rise in glucose levels after glucagon administration was significantly greater in RC than in SC. In RC, levels of glucose fell significantly from 30 to 60 min. Levels of FFA were higher in SC throughout the test. In both groups, glucagon caused a rise between 0 and 10 min, which was not significant, followed by a gradual fall at 30 and 60 min. The fall in FFA level between 10 and 60 min was significant in both groups. Levels of α-aaN were similar in both groups and did not change after intravenous glucagon. There was no significant rise in levels of insulin in either group at any time after the injection of glucagon. Also, neither the sum of the rises above the fasting level nor the maximal rise in the test was significant. Levels of GH were higher throughout the test in SC. In both groups there was a rise in GH levels after injection of glucagon reaching a maximal elevation at 10 min with a subsequent fall to fasting levels by the end of the test.

Effect of Five Venepunctures

The effect of five venepunctures alone, on the concentrations of metabolites and hormones measured, was studied in six recovered fasting children. The change from fasting levels of each of the variables during the 60-min period is shown in Table IV. The high

Table II. Metabolic and hormonal response of malnourished infants to intravenous glucose injection

Levels of metabolite or hormone in plasma	Condition	Time, min, before or after glucose challenge, 0.5 g/kg body wt				
		0	3	10	30	60
Glucose, mg/100 ml	Sick	72 ± 6[1] (10)[2]	333 ± 19 (10)	253 ± 15 (10)	190 ± 16 (10)	150 ± 17 (10)
	Recovered	71 ± 4 (10)	275 ± 15 (10)[3]	208 ± 13 (10)[3]	142 ± 8 (10)[3]	94 ± 4 (10)[3]
FFA, μmoles/liter	Sick	617 ± 131 (10)	586 ± 132 (10)	585 ± 135 (10)	573 ± 150 (10)	481 ± 126 (10)
	Recovered	192 ± 38 (10)[3]	166 ± 39 (9)[3]	207 ± 35 (10)[3]	170 ± 55 (10)[3]	202 ± 66 (10)
α-Amino nitrogen,	Sick	2.2 ± 0.1 (10)	2.4 ± 0.2 (10)	2.4 ± 0.3 (10)	2.2 ± 0.2 (10)	2.4 ± 0.3 (10)
mmoles/liter	Recovered	3.2 ± 0.5 (10)	3.0 ± 0.4 (9)	3.2 ± 0.4 (10)	3.2 ± 0.4 (10)	2.7 ± 0.3 (10)
Insulin, μU/ml	Sick	7 ± 1 (10)	11 ± 3 (10)	9 ± 1 (10)	8 ± 1 (9)	10 ± 2 (10)
	Recovered	10 ± 2 (10)	36 ± 8 (9)[3]	19 ± 3 (10)[3]	17 ± 3 (10)[3]	11 ± 2 (10)
GH, ng/ml	Sick	24.8 ± 8.6 (8)	29.3 ± 7.4 (10)	31.2 ± 7.0 (10)	21.8 ± 4.5 (9)	21.1 ± 6.2 (10)
	Recovered	6.9 ± 1.3 (10)	17.6 ± 2.9 (9)	11.4 ± 3.0 (10)[3]	12.4 ± 3.7 (10)	11.0 ± 2.1 (10)

[1] Mean ± SEM.
[2] Number of observations indicated in parentheses.
[3] $P < 0.05$ when the recovered and sick groups were compared.

Table III. Metabolic and hormonal response of malnourished infants to intravenous glucagon injection

Levels of metabolite or hormone in plasma	Condition	Time, min, before or after glucagon challenge, 0.1 mg/kg body wt				
		0	3	10	30	60
Glucose, mg/100 ml	Sick	62 ± 5[1] (9)[2]	75 ± 6 (9)	92 ± 8 (9)	116 ± 10 (9)	118 ± 10 (9)
	Recovered	75 ± 3 (9)[3]	103 ± 8 (9)[3]	123 ± 9 (9)[3]	167 ± 10 (9)[3]	138 ± 15 (9)
FFA, μmoles/liter	Sick	807 ± 125 (9)	864 ± 150 (9)	896 ± 156 (9)	678 ± 128 (9)	593 ± 113 (9)
	Recovered	289 ± 69 (9)[3]	337 ± 79 (9)[3]	384 ± 79 (9)[3]	221 ± 51 (9)[3]	150 ± 62 (9)[3]
α-Amino nitrogen,	Sick	2.9 ± 0.2 (9)	3.1 ± 0.2 (8)	3.0 ± 0.2 (9)	3.1 ± 0.3 (9)	2.7 ± 0.2 (7)
mmoles/liter	Recovered	3.3 ± 0.2 (9)	3.1 ± 0.2 (9)	3.1 ± 0.2 (9)	2.7 ± 0.3 (9)	2.5 ± 0.3 (9)
Insulin, μU/ml	Sick	7 ± 2 (9)	11 ± 2 (9)	12 ± 4 (9)	13 ± 6 (9)	11 ± 3 (9)
	Recovered	12 ± 2 (9)[3]	17 ± 4 (9)	15 ± 3 (9)	17 ± 2 (9)	16 ± 2 (9)
GH, ng/ml	Sick	24.5 ± 4.5 (9)	34.8 ± 7.2 (8)	45.4 ± 9.7 (9)	35.4 ± 5.1 (9)	27.0 ± 5.0 (8)
	Recovered	10.7 ± 1.8 (9)	24.0 ± 4.6 (9)	29.1 ± 3.6 (9)	13.9 ± 2.0 (9)[3]	10.6 ± 1.1 (9)[3]

[1] Mean ± SEM.
[2] Number of observations indicated in parentheses.
[3] $P < 0.05$ when the well and sick groups are compared.

Table IV. Change from fasting levels of metabolites and hormones in six infants who had recovered from infantile malnutrition

Level of metabolite or hormone	Fasting level	Change from fasting level at time, min			
		3	10	30	60
Glucose, mg/100 ml	61 ± 10[1]	+2 ± 2[1]	+5 ± 2	+5 ± 2	+6 ± 3
FFA, μmoles/liter	685 ± 262	+18 ± 32	+72 ± 75	+130 ± 64	+147 ± 71
α-Amino nitrogen, mmoles/liter	3.1 ± 0.3	−0.1 ± 0.2	+0.2 ± 0.3	0 ± 0.2	−0.1 ± 0.3
Insulin, μU/ml	7 ± 1	+2 ± 1	+7 ± 4	+4 ± 3	+4 ± 2
GH, ng/ml	10.3 ± 3.8	+4 ± 1.6[2]	+8.6 ± 1.9[2]	+1.9 ± 1.3	−0.9 ± 0.8

[1] Mean ± SEM.
[2] Change is significant ($P < 0.05$).

mean fasting level of FFA in this group was due to measurements of 1730 and 1235 μmoles/liter in two infants whose intake had been temporarily reduced. The only significant change from fasting levels was in GH, which was raised at 3 and 10 min. Figure 3 shows a comparison of the rise in plasma GH levels in RC due to venepuncture alone compared with that due to injection of glucose or glucagon. It was concluded that intravenous glucose did not cause a greater rise in GH levels than venepuncture alone, but that glucagon did cause a rise in GH levels greater than that due to venepuncture.

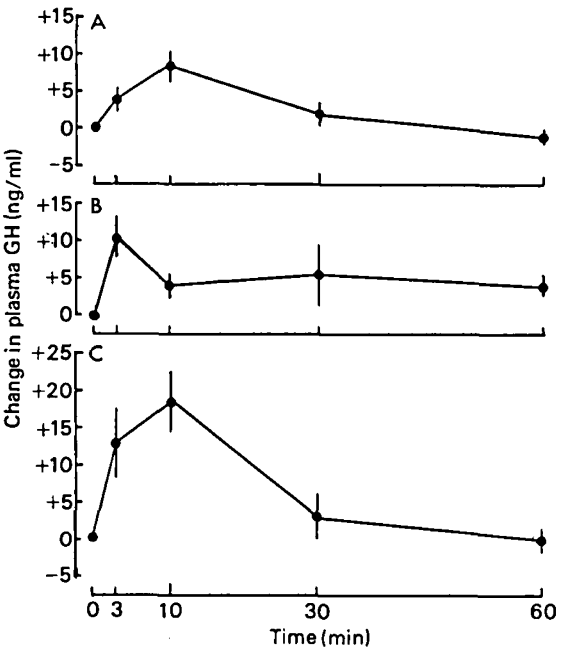

Fig. 3. Mean ± SEM change from fasting level of GH in plasma in infants who had recovered from malnutrition. *A:* Six infants who had venepunctures only. *B:* Ten infants who received intravenous glucose. *C:* Nine infants who received intravenous glucagon. Further details are given in the text.

Discussion

When initial glucose- and glucagon-loading tests were performed, the infants were still undernourished since they were receiving dilute milk feeds, but when the second tests were performed each child was near his expected weight for height and had passed his peak growth rate.

Despite the normality of fasting levels of glucose a deficiency in glucose homeostasis was revealed by glucagon. Glucagon caused a smaller rise in glucose levels in plasma in SC than in RC, which was probably due to decreased hepatic glycogen since glycogenolysis is known to be normal in infants with similar problems [1]. Impaired utilization of glucose in the SC was seen after glucose injection and in the glucose levels 30 and 60 min after glucagon. High levels of FFA and GH and the absence of a β-cell response to hyperglycemia contributed to this impairment.

The high levels of FFA in the SC are similar to those seen in patients with kwashiorkor [12]. In patients with marasmus, Lewis *et al.* [12] found raised FFA levels also, whereas Hadden [7] reported low levels of FFA. In this study, the fasting FFA levels in the four infants ill with marasmus were greater than the mean of the group, being 738, 920, 1000, and 1409 μmoles/liter. High levels of FFA are associated with increased FFA flux [13], which may also be due to the high GH [31] and low insulin levels in plasma.

By studying the same children twice, it was possible to demonstrate a significant rise in insulin levels in plasma to normal fasting levels on recovery. This did not indicate a return to normal β cell function, as revealed by results of both the glucose and glucagon tests. Because of the dual nature of the stimulus to release of insulin by glucagon, it was possible that the failure to demonstrate a significant rise in insulin was due to differences in the timing of the response of the β cell in different infants. This was excluded by finding that the maximal insulin rise or the sum of the

insulin rises above the fasting level was not significant. The insulin response to intravenous glucose showed that clinical recovery was associated with improvement in β cell function.

Because of the persistence of what appeared to be high levels of GH in RC, an analysis of all estimations of fasting GH was made. The scattergram (Fig. 2) shows that, although some of the highest values were in girls, there was no clear-cut sex difference. Between the 4th and 12th weeks the range of levels varied little. It is not possible to state whether the mean fasting GH level at this time was normal since the fasting GH level in normal infants aged 1 year is not known. The interpretation of the GH response to glucose or glucagon is complicated in that the design of the investigations required repeated venepunctures and venepuncture in children has been shown to cause a rise in GH levels [9]. Control measurements of metabolites and hormones in six recovered children showed that venepunctures caused significant rises in GH levels at 3 and 10 min. The rise in GH level after glucose was similar to that seen after venepunctures alone (Fig. 3), suggesting that the GH response to glucose was an artefact caused by venepuncture. In contrast, the GH response to glucagon was greater than that due to glucose or venepuncture, and, allowing for the stimulation by venepunctures after the injection of glucagon, it was apparent that glucagon itself caused a rise in GH levels. It follows that secretion of GH, although stimulated by malnutrition, can be further increased by either the stress of venepuncture or a glucagon challenge.

The malnourished infant resembles the starving normal adult in having low levels of insulin and high levels of GH, and the hypothesis that insulin is the prime signal responsible for fuel control is apt for infancy as well as for adults [5]. The possible permanence of subnormal secretion of insulin makes it important to study these children yet again to clarify whether infantile malnutrition can predispose to adult diabetes mellitus.

Undernutrition or malnutrition in adults as in infants causes similar changes in GH levels. Fasting [26], anorexia nervosa [14], renal failure [32], and protein-losing enteropathy [23] are all associated with elevated levels of circulating GH. Of more direct relevance to infantile malnutrition may be the fact that babies born small for their gestational age, who are thought to have been malnourished *in utero,* have high levels of GH [11], while babies born to diabetic mothers, who may have been overnourished *in utero,* have low levels of GH at birth [30].

Malnutrition of the severity observed in the present study does not result in hyposecretion of GH, as has been suggested by others [17–19].

Summary

Measurements of levels of glucose, FFA, α-amino nitrogen (α-aaN), insulin, and growth hormone in the plasma of malnourished infants revealed low fasting levels of insulin and high levels of FFA and growth hormone on admission to the hospital. After recovery, fasting levels of insulin and FFA became normal and growth hormone levels fell but probably remained above normal. Insulin secretion was stimulated by glucose in the recovered children (RC) but not in the sick children (SC). Glucagon was ineffective in causing insulin release in either group. Secretion of growth hormone was stimulated by glucagon or the stress of venepuncture in both sick and recovered infants.

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33. "Insulin binding reagent" and ox insulin (potency 21.6 U/mg) were kindly given by Dr. B. A. L. Hurn, The Wellcome Laboratories, Beckenham, England.
34. Human growth hormone, MRC new preparation R4, was kindly given by Dr. A. Stockell-Hartree, Department of Biochemistry, University of Cambridge, England.
35. The author thanks Professor J. C. Waterlow for his encouragement throughout this study and Miss M. Ceballos for excellent technical assistance.
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38. Accepted for publication January 14, 1970.

