ABNORMAL PANCREATIC ENDOCRINE FUNCTION IN REYE'S SYNDROME SURVIVORS AND THEIR RELATIVES: A PRELIMINARY REPORT

(Reye's Syndrome survivors, insulin, glucagon)

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SUMMARY

To explore the possibility that children who develop Reye's syndrome may be metabolically unique, we examined the ability of survivors to respond to endogenous and exogenous metabolic stimuli. Our preliminary results indicate the presence of abnormal insulin and glucagon responses under fasted and stimulated states. Specifically, higher fasting insulin and glucagon values were found in Reye's survivors than their siblings or normal control children. (Insulin levels ± SEM in uU/ml, 21.1 ± 1.86 for Reye's survivors, 15.4 ± 2.31 for siblings and 10.8 ± 1.30 for normal control children. Significance of difference between Reye's survivors and normal control children = $p < .001$. Glucagon levels ± SEM in pg/ml, 416 ± 46.7 for Reye's survivors and 178 ± 32.4 in siblings, $p = < .001$. Only one sibling had high fasting insulin values (mean 28 uU/ml) and two had fasting glucagon values above 200 pg/ml. Elevated levels of both hormones were not found in any sibling. Higher insulin and glucose responses to oral glucose were seen in 3 of 4 survivors during an OGTT. Higher mean integrated insulin areas above baseline were observed in Reye's survivors and their siblings compared to controls ($p < .001$. After l-arginine infusion, a clearly discernible double peak in the glucagon response was seen in 2 survivors, 1 sibling and 3 parents examined, a response not observed in the peripheral venous circulation but only reported in portal vein samples. These observations indicate that responses to a variety of pancreatic endocrine stimuli are altered in Reye's survivors and their families.

SPECULATION

In Reye's syndrome, high levels of circulating glucose substrates and metabolic fuels such as, alanine, lactate, pyruvate, glycerol, non-esterified fatty acids, acetoacetate and β-hydroxybutyrate, are reported (15,37) frequently in the presence of normal plasma glucose concentrations. The regulation of the flux of these substrates is highly influenced by the hormones, insulin and glucagon. Insulin is particularly important in the inhibition of release of such substrates from peripheral stores. Animal and human studies in various hyperinsulinemic states in which hyperglucagonemia is also seen have shown significant reduction in insulin-receptor binding. The possibility is raised that the relative hyperinsulinism expressed by children who have survived Reye's syndrome may have been present before their acute disease and may have contributed to the metabolic manifestations of the acute disorder.

Reye's syndrome is a rare pediatric complication of common viral illnesses such as influenza and varicella (4). While epidemics of influenza afflict vast numbers of people throughout the entire age spectrum of man, Reye's syndrome as a sequel to influenza is limited to less than 1/10th of a percent of children who have influenza (4). This epidemiological feature suggests that age and a susceptibility factor must both be present to selectively produce Reye's syndrome. The latter possibility is further supported by increasing evidence of familial clustering and recurrences of this syndrome (1,10,12, 13,17,18,22,27-30,31,34,35).

We have searched for a predisposing factor in these children long after they had recovered from their acute Reye's episodes. Because several glucose substrates are elevated in the plasma during the acute disease even in the absence of hypoglycemia in many cases, we chose to examine the ability of survivors to maintain caloric homeostasis under a variety of stimuli.

The results of our preliminary studies indicate that these children maintain homeostasis in the presence of increased insulin and glucagon concentrations in the peripheral circulation under fasting conditions and in response to various stimuli. This altered state of metabolic responsiveness was also found in some but not all parents and siblings examined raising the likelihood that genetic factors may be involved in these findings.

METHODS

Informed consent was obtained from all participating adults and parents of minors.

This study was conducted on the parents and siblings of seven unrelated children who had Reye's syndrome. Five of the six children who survived were also studied and are designated survivors #1-5. The sixth child was excluded because of the recent occurrence of his illness. The seventh child succumbed and the diagnosis was supported by autopsy findings.

Criteria for the diagnosis of Reye's syndrome include clinical evidence of a progressive encephalopathy following a viral-like prodromal illness, normal spinal fluid, evidence of hepatic dysfunction in the absence of hyperbilirubinemia and absence of trauma or exposure to toxins (14). Staging of the acute disorder was according to Lovejoy, et al (19).

Of the five Reye's survivors studied, oral glucose tolerance tests (OGTT) were done in four subjects (#1-4), arginine stimulation in two (#2,3), and epinephrine, glucagon and insulin tolerance studies were performed in four (#1-4). In one survivor, #5, repeated fasting samples, only, were examined. Each child had fully recovered from the acute syndrome as judged by his return to normal activity and normalization of a wide battery of liver function tests, including the SGOT, SGPT, LDH, alkaline phosphatase, prothrombin, serum proteins and blood ammonia.

The interval of time between the acute episode and the initial study was 2.5 years, 2.5 years, four months, 3 years, and 1 year for subjects, #1,2,3, 4, and 5, respectively. Their mean age was 10.4 years if all 5 are included and 12.4 if subject #5 is excluded at the time of these studies. The glucose tolerance test was repeated 12 months later in two subjects, #2 and #3. Similar findings were found. The body habitus of these subjects was normal as indicated by the height and weight percentiles for each of the four who were studied in detail (#1, 25 percentile (%) for height (h) and weight (w), #2 75% h and w, #3 50% h and 90% w, #4 90% h and 75% w). A summary of their clinical findings at the time of their acute episode is presented in Table 1.

Eight unaffected siblings were studied, 3 of whom were siblings of the fatal case of Reye's syndrome, #7. Fasting blood samples were collected in seven for determinations of insulin, glucagon and glucose. An OGTT was performed in six including 3 siblings of patient #7 and an arginine infusion study was performed in the sibling of survivor #3. The siblings on whom an OGTT was performed had weight percentiles at or below their height percentiles. None was obese. The ages of these siblings in years were 7 8/12 (sibling of #2), 13 2/12 (#3), 13 (#4), 3 (#5), 6½ (#6), and 5, 8 and 10 years for the fatal case #7 at the time of this study.

Twelve parents were studied including the mothers of #1, #3, and both parents of #2, #4, #5, #6, and #7. Fasting blood samples were obtained from each (n=12), an OGTT was performed on the mother of #3 and the parents of #2, #6, and #7 (n=7) and an arginine stimulation test was done on the mother of #3 and the parents of #2 (n=3). Of the seven on whom an OGTT was performed, 4 were slightly obese (fathers of #2 & 6, mothers of #3 & 7) and 3 were lean.

Normal controls are from our previously reported series (3,4) as well as additional unrelated pediatric subjects, siblings, and adult laboratory workers. Adult controls are separated into lean and obese categories. Control children were not obese. The mean ages and ranges for the control children were as follows: normal children, 9.1 years (6.3 - 13.3 years); chemical diabetics with increased insulin 10.2 years (5.1 - 13.8 years); chemical diabetics without increased insulin 9 years (7 - 10.3 years).

Preparation for the OGTT included instructions to parents to insure a high carbohydrate diet for three days prior to admission. To our knowledge, only one subject, father of #6, could not adhere to the high carbohydrate intake due to symptoms of reactive hypoglycemia. Subjects were admitted for each tolerance test the afternoon prior to the study except in one family (parents and sibling) who were studied on an outpatient basis. After an overnight fast, 1.75 grams of glucose per kilogram body weight was given after preparation of the patient. For the arginine infusion, 0.5 grams per kilogram body weight of l-arginine hydrochloride, not to exceed 30 grams, was given intravenously over a 30-minute period. For each study an intravenous needle was placed in a peripheral arm vein which was kept open with 1/3 normal saline. Three ml of blood was withdrawn from the cannulated vein and discarded before the sample for analysis was collected. During the study period, the subject was allowed to engage in quiet play activities in bed.

Blood for insulin and glucagon was collected in heparinized tubes. For glucagon determinations, 500 units of a kallikrein-trypsin inhibitor, Trasylol (R), was added per ml of blood immediately upon collection of the blood. Insulin was determined as total immunoreactive material in plasma which reacts with porcine insulin antisera as determined by the double-antibody radioimmunoassay as described by Morgan and Lazarow (20). Proinsulin was determined by the difference between total immunoreactive material in plasma to porcine insulin antisera before and after treatment with the insulin-specific protease as previously described (3). Glucagon was determined by the radioimmunoassay method as described by Unger (33) and Faloona (22). Glucose was determined by the autoanalyzer method.

RESULTS

Mean fasting values ± S.E.M. for insulin and glucagon for the various groups are presented in Figures 1 and 2.

An analysis of variance was made. The average variance within groups (S_p^2) and the variance between groups (S_m^2) for insulin were 24.5470 and 78.4515, respectively. $F = S_m^2 / S_p^2 = 3.1960$. The F value at the 95% confidence limit was 3.03 and was 4.76 at the 99% confidence limit (degrees of freedom, d_f, for the variance between means was 3 and the d_f for the variance between groups was 23). Thus, the difference of mean fasting insulin levels between groups is significant. By multiple range testing the difference between survivors and control children was significant at the 99% confidence limit.

For glucagon, S_p^2 was 13.235.32, S_m^2 was 79.658.69 and F was 6.0186. The F value at the 99% confidence limit was 4.61 (d_f for variance between means was 3 and d_f for variance between groups was 27).

Thus, Reye's survivors have significantly higher fasting plasma insulin levels than control children and higher fasting glucagon levels than unaffected siblings of Reye's syndrome subjects.

Of seven siblings examined, only one had high insulin values with a mean value of 28 μU/ml. The remaining six siblings had fasting values comparable to control children. With respect to glucagon, two of the seven siblings had fasting values above 200 pg/ml. Both had normal fasting insulin levels. Three of seven siblings had increased fasting insulin or glucagon levels but none had elevations of both hormones as described for the Reye's survivors.

When the stimulatory effect of glucose on insulin secretion is studied during OGTT, the response of survivors as a group was different from control children. The mean integrated insulin area above baseline was higher in Reye's survivors (8,868 μU/ml/min x 10^{-3} ± S.E.M. 1106) compared to normal children (4,792 μU/ml/min x 10^{-3} ± S.E.M. 621); $p < .001$. The mean value obtained for siblings was also significantly elevated (mean 9,749 μU/ml/min x 10^{-3} ± S.E.M. 1894); $p < .001$. (See Figure 3).

Heterogeneous responses to oral glucose were exhibited by parents. In nine of twelve, responses were essentially normal. One asymptomatic mother who is obese demonstrated glucose intolerance, manifested by hyperglycemia (glucose values: 110,141,176,214,209,213,207,159 and 155 mg/100 ml at 0,15, 30,45,60,90,120,180, and 240 minutes respectively) and hyperinsulinemia (insulin values: 16,85,109,160,172,204,238,169, and 140 μU/ml for the corresponding times). Another mother who is lean and asymptomatic had hyperglycemia (glucose values: 80,167,177,170,190,210,220, and 184 mg/100 ml from 0-180 min.) and hypoinsulinemia (insulin values: 8,21,19,19,2,15,14, and 22 μU/ml for the corresponding times). One symptomatic father who is slightly obese had hyperglycemia (glucose values: 97,245,245,207,187,129,111 mg/100 ml at 0-120 min.) and corresponding insulin values of 8,62,93,103,75,16, and

8 μU/ml. Severe symptoms are reported by this father who is a physician who describes diaphoresis and syncope following a high carbohydrate intake. The 3-day dietary preparation for the OGTT was only partially carried out due to the continued development of symptoms. Thus, the response of parents to oral glucose was abnormal in three of twelve individuals examined and ranged from excessive to inadequate beta cell responses each individually associated with either peripheral insulin insensitivity or insulin dependence.

Peak insulin values were higher in three of four survivors and four of five siblings than control children. The highest peak insulin concentrations, 277 and 258 μU/ml, were found in siblings. One parent had a peak value higher than that observed in obese adults. The mother of #7 had an insulin concentration of 238 μU/ml which occurred 120 minutes after the ingestion of glucose.

Proinsulin, which is present in plasma and contributes to immunoreactive insulin, has much less biologic activity than insulin (16). The contribution of proinsulin to the increase in total insulin was examined in two survivors, #2 and #3, their respective siblings and their parents.

Proinsulin levels after glucose were much more variable in Reye's survivors and one of two siblings than in controls. The three parents had lower fasting values than control adult values and peaks were reached at earlier times than in controls. These studies do not implicate proinsulin as a major component of the total immunoreactive insulin found in their peripheral plasma.

Suppression of α cell activity was seen in every subject except one (mother of #3). An early rise in immunoreactive glucagon was seen 15-30 minutes after glucose ingestion in survivors #2 and #3, their respective siblings, the siblings of #7, the mothers of #2 and #3 and the father of #6. The mean maximal fall in glucagon in survivors was 59.5 pg/ml, S.E.M. ± 21.1, comparable to 50 ± 9 (SEM) reported for normals by Muller, et al (21).

Insulin and glucagon responses to l-arginine stimulation were examined in subjects #2 and #3, the sibling of #3, the parents of #2 and the mother of #3. Subjects #2 and #3 had maximal insulin increments of 145 and 78 μU/ml compared to values of thirty reported for normal children (26). A large increment for insulin was also seen in the one sibling tested. Of striking occurrence is a clearly discernible double peak in the glucagon response of l-arginine infusion, a finding considered only observed in portal vein samples and not expressed in the peripheral venous circulation (23,24). This biphasic pattern is not exhibited by control adults studied at this center (Figure 4).

DISCUSSION

A complexity of metabolic derangements accompanies Reye's syndrome, each of which evokes its own compensatory change. These derangements and counter-regulatory metabolic events interfere with attempts to delineate cause and effect and, as a consequence the etiology of this disease remains unknown.

Our approach to Reye's syndrome has been influenced by our surmise that a number of metabolic processes which utilize the second messenger system appear to be affected including gluconeogenesis, lipolysis, proteolysis and neuronal transmission (15). Based on this prejudice, we have extended our studies to survivors long after they had recovered from their acute illness. Our findings indicate the presence of an altered state of responsiveness to metabolic stimuli involving the glucostatic hormones, insulin, and, particularly, glucagon, which are found in high concentrations under both fasting and stimulated states in children who have survived Reye's syndrome. These hormones generally promote opposing effects in the regulation of normal fuel homeostasis. Since stimulation of one hormone generally evokes a counter regulatory response from the other, the primary or compensatory nature of the hyperglucagonemia or the hyperinsulinemia cannot readily be determined.

Hormonal regulation of gluconeogenesis serves to ensure the maintenance of glucostasis during fasting and is primarily centered on peripheral tissues, according to Exton et al (6), to control the release of substrates for glucose production by the liver through the influence of glucagon (7). With respect to its action on hepatic glucose balance, glucagon is believed to be far more potent than insulin on a molar basis (32). Ratios of insulin to glucagon in the peripheral plasmas of normal humans after an overnight fast is 3.8 at which time the liver is producing glucose at a substantial rate, exhibiting a glucagon effect, whereas ratios of 0.4 are found during starvation and 16 on glucose infusion (32). Fasting insulin to glucagon ratios in survivors are substantially under adult values, averaging 0.85, 1.73, 1.04, and 0.91 in subjects #1 to #4, respectively. Estimates of half-maximum concentrations of glucagon converted to pg/ml for activation of several physiologically important metabolic processes are 175 pg/ml for glycogenolysis, 350 pg/ml for gluconeogenesis and 1750 for both ureagenesis and ketogenesis (25). Since portal vein concentrations are about 2.6 times higher than peripheral levels (9), and the mean fasting glucagon concentration in the peripheral circulation in these subjects is 400 pg/ml, it might be expected that gluconeogenesis was fully activated after an overnight fast. The concentrations of the body fuels which are ordinarily determined by the interaction of insulin on the one hand and glucagon and other catabolic hormones on the other, appear to be normal under fasting conditions except for glucose in these subjects. Repeated fasting samples on survivors revealed higher fasting glucose levels in survivors than reported for controls and are in accord with the low insulin to glucagon ratios found in these children.

The infusion of l-arginine as a test of alpha cell function results in a dramatic rise in plasma glucagon and a parallel rise in plasma insulin. A greater rise in plasma glucagon is reported in juvenile diabetics without a change in insulin levels (21). In normal man, portal vein glucagon levels change in a biphasic manner during arginine infusion, but the separation of the two phases is not observed in peripheral plasma even when plasmas are sampled at frequent intervals (2,24). The early maximal glucagon rise during an arginine infusion reflects primarily the acute component of alpha cell secretion in analogy to the early insulin response to glucose, while the later rise reflects an integration of residual first phase plus second phase alpha cell secretion. Comparison between diabetic subjects and controls shows no distinguishable difference in area or slopes during the acute phase of alpha cell secretion, whereas the 5-30 minute slopes and areas are increased in diabetes (23). Both insulin and glucagon responses in Reye's syndrome survivors and their families to intravenous arginine are increased. In addition, the glucagon response is strikingly biphasic in the peripheral plasma in contrast to normal individuals. Since the glucagon in the peripheral plasma represents that which has escaped metabolism by the liver and kidney or excretion into bile, several factors in addition to the alpha cell response may contribute to this finding including diminished degradation of glucagon by the liver. Since large glucagon and gut glucagon may be immunoreactive with reduced biological activity, characterization of the glucagon components is indicated. Such studies are in progress. We have already examined the contribution of proinsulin to the total immunoreactive insulin or plasma in Reye's survivors and their families. Thus far, proinsulin does not appear to contribute significantly to the total immunoreactive insulin fraction of plasma in these patients.

Our findings in survivors of Reye's syndrome and their families indicate the presence of heterogenous types of abnormalities of pancreatic endocrine function as reflected by the increased concentrations of insulin and glucagon under fasted and stimulated states in the peripheral venous circulation. What role this abnormality plays in the development of Reye's syndrome cannot be determined. It is interesting, however, that marked changes in the concentrations of the plasma fuel components which are influenced by these hormones are found in Reye's syndrome. Hormone concentrations in the untreated, acutely affected subject are increased but not in excess of other catabolic states of metabolic stress (11). The levels reported for these two hormones in untreated, acutely affected subjects resemble those we report here for survivors who are clinically well. If the hormone concentrations found in survivors were present before the Reye's episode, the levels reported for the acutely affected subjects are unduly low. The possibility must also be considered that the atypical hormone profiles exhibited by survivors is the result of Reye's syndrome. The presence of similar abnormalities in some unaffected siblings would make this highly unlikely, although the possibility that these siblings sustained a subclinical form of Reye's syndrome cannot be excluded. The possibility that an environmental factor contributes to this phenotype would be excluded by the presence of these findings in some, but not all, family members. Several types of abnormalities have been described in siblings and parents, but in none of the parents or siblings were both insulin and glucagon levels increased under fasting conditions. Of three siblings with increased hormone levels in the fasting state, two involved glucagon alone and one involved insulin alone. Of the four parents with high glucagon levels, two had very low insulin levels in the fasted state and two had normal levels. The consistent abnormality observed in the five survivors in the study was elevation of glucagon and insulin under fasting conditions. We propose this biochemical phenotype may be a contributing factor to the exaggerated catabolic state which characterizes the acute syndrome.

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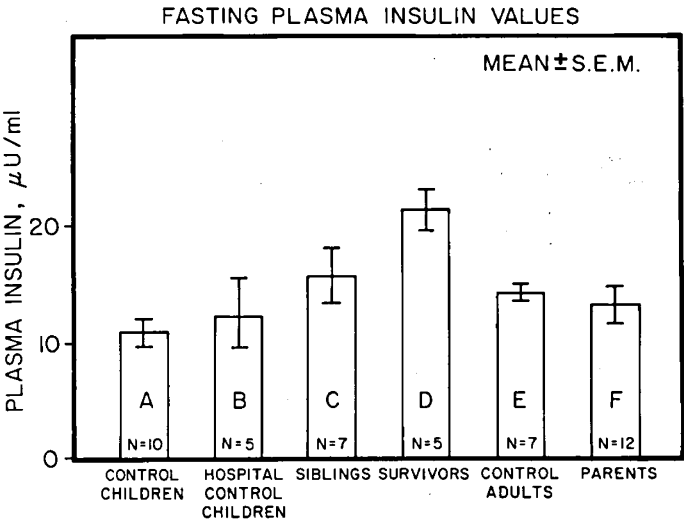

Figure 1

Fasting Plasma Insulin Values

Legend: Plasma samples collected after an overnight fast, mean ± SEM, insulin concentrations.

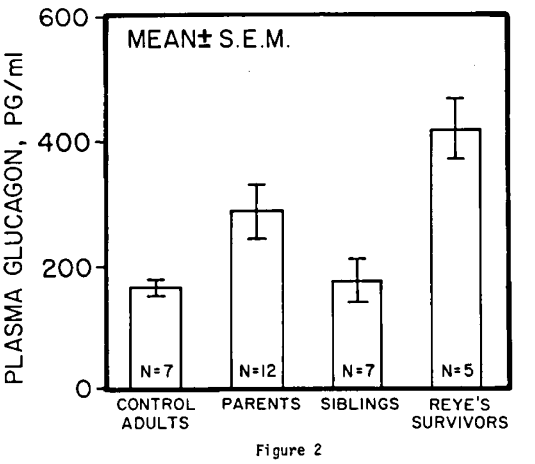

Figure 2

Fasting Plasma Glucagon Values

Legend: Plasma samples collected after an overnight fast, mean ± SEM, glucagon concentrations.

Table I

CLINICAL FINDINGS DURING ACUTE DISEASE

SUBJECT	#1	#2	#3	#4	#5
Age, years	5.5	8.8	14.5	12.0	2.0
Sex	M	F	M	F	F
Prodrome	URI,vomiting	URI,vomiting	URI,mania	URI,vomiting	vomiting+
Stage at Dx	II-III	II-III	II-III	III-IV	III
Fever	0	0	0	105°F	102°F
Hepatomegaly	0	+	+	0	+
SGOT (4-40 units/ml)*	1080	1140	1080	1250	570
SGPT (4-35 units/ml)	672	440	1013		350
LDH (30-110 units/ml)	348	360	1119	1000	
CPK (5-80 units/ml)		140	500	3000	
Alkaline PO_4'ase (1-30 units/ml)	3.6		5.2	315	
NH_3 (18-48 mcg/100 ml)	100	61	286	98	137
Prothrombin (100%)	87%	75%	72%	30%	83%
Glucose (60-105 mg/100 ml)	107	100	107	100	45
Bilirubin, total(0.3-1.0mg/100ml)	1.5	1.0	1.1	1.0	0.2
BUN (8-20 mg/100 ml)	6.7	17.5	32.2	39	23
Salicylate (0 mg/100 ml)			5.4		
CSF					
glucose	66	73	70	65	32
protein	13	<20	12.9	54	15
cells	7rbc, 9 lymphs	0	0	bloody	7 rbc
culture	neg.	neg.	neg.	neg.	neg.
pressure	increased	normal	normal	normal	normal
Interval between acute illness and present studies, years	2.5	2.5	0.3	3.0	1.0

*Normals are listed parenthetically

+ hematemesis

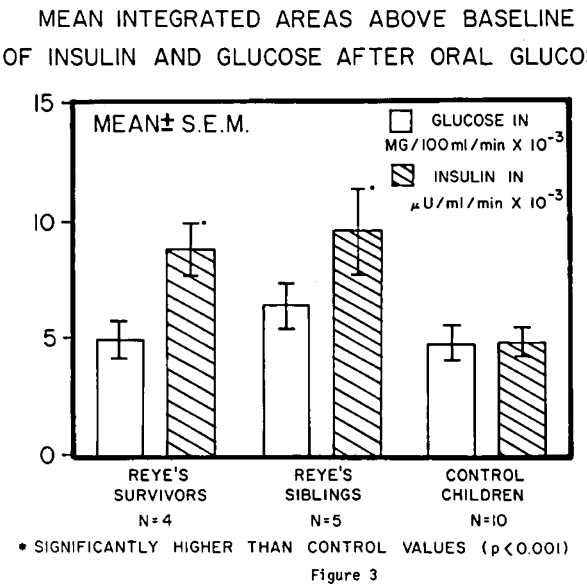

Figure 3

Insulin and Glucose Responses After Oral Glucose

Legend: Mean integrated areas above baseline of insulin and glucose.

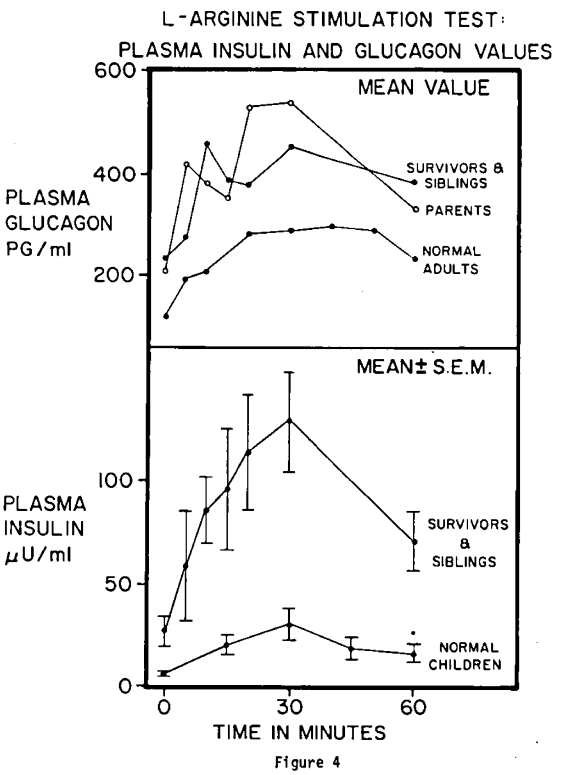

Figure 4

L-arginine Stimulation Test:
Plasma Insulin and Glucagon Responses

Legend: Mean values for plasma glucagon depicted in upper panel. Mean values ± SEM for plasma insulin in lower panel.

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