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STUDIES OF CHILDREN WITH KETOTIC HYPOGLYCEMIA¶

The work of Ulstrom and his associates,[1,2] has described many of the features of ketotic hypoglycemia, a syndrome of sporadic hypoglycemia associated with ketosis in children. These investigators have described the following characteristics: hypoglycemia rarely occurred before 18 months of age; it usually occurred after poor dietary intake; acetonuria was present; this kind of hypoglycemia was seen in children who were small for their age and who had low birth weights, and it was associated with a depletion of hepatic glycogen stores. Most of their patients had normal intelligence and apparently outgrew the tendency to develop hypoglycemia by the time they reached adolescence. Blood sugar responses to glucose, glucagon, epinephrine, tolbutamide, leucine and ACTH were considered to be normal. However, when 14 of their 30 patients were given a ketogenic diet they developed symptomatic hypoglycemia within 24 hours, and then failed to respond to glucagon. In contrast, the control group did not become symptomatically hypoglycemic during the three days of an identical diet. On the other hand, Senior and Loridan[3] have reported that both their patients with ketotic hypoglycemia and their control subjects became hypoglycemic in response to the ketogenic diet.

Despite these studies and those of other workers,[4-8] the etiology and pathogenesis of this condition remain unknown and the diagnosis difficult to make. Frequently this diagnosis is made when acetonuria and hypoglycemia coexist. However, as acetonuria has been reported in patients with several types of sporadic hypoglycemia and appears to be a nonspecific feature, its presence in the hypoglycemic child is insufficient to make the diagnosis of ketotic hypoglycemia. In order to achieve a better understanding of the etiology and pathogenesis as well as to improve the diagnostic criteria, we have undertaken a systematic evaluation of changes in blood

sugar, serum insulin, growth hormone, and free fatty acid levels following several different stimuli. This approach should assist in the definition and diagnosis of ketotic hypoglycemia.

During the past five years, 19 children with several different kinds of hypoglycemia have been studied in the Yale Children's General Clinical Research Center. The parents of all of these children were interviewed by the social worker. A recurrent theme in these interviews was parental anxiety about possible mental retardation in the children. Parents attributed this fear to predictive statements made by physicians at the time of the initial hypoglycemic episode.

All parents had responded to such predictions with heightened attention to the child's developmental accomplishments. Some had been prompted to offer intense stimulation and optimal learning experiences to promote development. Others, however, had subjectively experienced a sense of emotional withdrawal and detachment from the child akin to a partial mourning experience. Since early development can be adversely influenced by such parental detachment, and since reports concerning the effects of ketotic hypoglycemia on neurological and intellectual development have been conflicting,[1,2,6] it was evident that systematic evaluation of the development of these children was urgently needed.

MATERIALS AND METHODS

Patients studied

The pertinent historical and physical findings of eight patients with ketotic hypoglycemia* are shown in Table 1. At the onset of the investigation all of the children who had been referred to the senior author because of hypoglycemia were studied. However, only the eight patients whose findings fit most of the following criteria were considered to have ketotic hypoglycemia: hypoglycemia associated with acetonuria, low birth weight, perinatal stress, relative short stature, marked variability in 12-hour fasting blood sugar levels, a rapid utilization of glucose despite normal levels of serum immuno-reactive insulin, and the occurrence of hypoglycemia within 24 hours after the start of the ketogenic diet (at which time most patients do not respond to glucagon stimulation). Five were males. Four of the eight mothers were 34 years of age or older when their children were born. During five of the pregnancies these mothers had experienced pre-eclampsia, toxemia or another significant illness. Five of the eight children

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*The studies were discussed in detail with each of the parents prior to admission by the senior author (J.G.) and later by the Research Social Worker (A.McC.). Signed consent was then obtained before the child entered the Clinical Research Center.

TABLE 1. PERTINENT HISTORICAL, PHYSICAL AND ELECTROENCEPHALOGRAPHIC FINDINGS IN CHILDREN WITH KETOTIC HYPOGLYCEMIA

Patient	Sex	Maternal age	Pregnancy history	Perinatal stress	Birth weight (gms.)	Age at diagnosis (mos.)	Percentile Ht./Wt.	Cataracts	EEG
J.H.	M	37	Normal	Breech delivery, Intracranial bleeding, Pneumonia-Apnea-Flaccid	2010	11	97/70	No	Normal
M.H.	F	26	Normal	None	3544	11	10/3	No	Normal
A.B.	F	21	Pre-eclampsia	Cyanosis-jaundice, Symptomatic hypoglycemia	2400	18	25/5	No	Normal
J.J.	M	28	Persistent hematuria, Pneumonia	Precipitous delivery @ 7 mos., Sub & epidural bleeding-Anoxia	2800	8	5/10	No	Abnormal
M.L.	F	38	Hypertension	Anoxia-Cyanosis-Pneumonia, Respir. dis. syn.	1950	18	10/10	Yes	Abnormal
A.K.	M	39	Normal triplets	Breech delivery, Jaundice-Respir. dis. syn.	1635	21	3/3	Yes	Abnormal
C.C.	M	34	Toxemia	Cyanosis-Apnea-Symptomatic hypoglycemia	3200	38	3/5	No	Abnormal
P.L.	M	28	Spotting @ 6 weeks, Hypertension 9 mos.	Anoxia-Symptomatic hypoglycemia	2273	35	50/75	No	Abnormal

weighed less than 2,500 grams at birth and seven of the eight patients experienced a great deal of stress during the neonatal period. Three had symptomatic hypoglycemia.

When the patients were studied, (at 8-38 months of age), seven were below the 50th percentile and five were below the 10th percentile for height. Cataracts were present in two and four had abnormal electroencephalograms.

Urinalysis, complete blood count, hepatic function, renal function, and endocrine function (ACTH and Metapirone tests, PBI, and RAI) were normal.

Metabolic studies

All tolerance tests were started after a 12-hour fast period, and after at least three days of a diet consisting of an average of: 1500 calories; 150 gm. carbohydrate; 70 gm. protein and 70 gm. fat.

The glucose tolerance test was carried out using one gram of glucose per kilogram of body weight in a 20% solution administered intravenously in 3-5 minutes. Glucose utilization (K_T) was calculated using the method of Bowie, *et al.*[6] The leucine tolerance test utilized 150 mg. d-1 leucine per kg. dissolved in warm water and given orally within 2-5 minutes. Insulin tolerance was tested using a rapid intravenous infusion of 0.1U crystalline insulin per kg.

During the study, each patient was given the ketogenic diet designed by Colle and Ulstrom[1] for one to two days, depending on his response. This diet consists of the following: 1200 calories per 1.73 square meter of body surface per day, 67% of the calories as fat, 16% as carbohydrate, and 17% as protein. Three meals each with an equal caloric content, were fed each day and bloods were sampled prior to each meal and at four hourly intervals.

Glucagon tolerance tests were carried out at the following times: at the completion of the glucose tolerance test, at the completion of the insulin tolerance tests, and at that point in the course of the ketogenic diet when symptoms (extreme irritability, altered speech, impending or frank seizure activity) warranted a discontinuation of the diet. This test utilized 0.03 mg. glucagon per kg. as an intramuscular injection.

Blood glucose was measured using glucose oxidase.[7] Immuno-reactive insulin (IRI) was determined by the double antibody radioimmunoassay.[8] Growth hormone (HGH) was determined by a similar double antibody radioimmunoassay.[9] Free fatty acids (FFA) were determined using the method of Dole.[10]

Developmental studies

The developmental evaluation of the children being reported included:

1) Parent interviews conducted separately by developmental examiner and social worker in which detailed medical, developmental, and social histories were elicited.

2) Formal examination by the developmental examiner utilizing the Revised Yale Developmental Test. This is a composite test with items drawn from the Gesell, the Hetzer-Wolf Baby Test, the Merrill Palmer and Stanford-Binet Scales. The test's results yield:

   1) a score expressing developmental age and developmental quotient;

   2) a profile of scores in the separate sectors of gross motor, fine motor, adaptive, language, and personal-social development;

   3) an analysis of specific functions within the five major areas. Among these are functions such as perception, memory, imitation, development of object relations, ability to solve problems;

   4) observation of mother-child interaction in the structured test situation.

Escalona,[11,12] Knobloch,[13,14] Provence and others[15,16] have demonstrated that the examination can effectively identify those infants who will later manifest neurological and intellectual deficits and those who will not.

By the latter half of the first year, experienced developmental examiners with basic knowledge of pediatrics and infant neurology can rule out most of the common developmental disorders and establish the capacity for development within the normal range.

TABLE 2. TWELVE-HOUR FASTING VENOUS BLOOD SUGAR LEVELS IN PATIENTS WITH KETOTIC HYPOGLYCEMIA

Patient	Fasting blood sugar (mg/100 ml.)						Max-Min
J.H.	33	53	70	78	91	97	66
M.H.	49	57	61	61	77	109	60
A.B.	61	61	76	78	79	108	47
J.J.	29	59	67	71	82	90	61
M.L.	22	44	65	65	66	79	57
A.K.	54	68	71	74	76	92	38
C.C.	59	59	66	80	80	98	39
P.L.	50	50	59	71	76	77	27

RESULTS
Metabolic studies

Twelve-hour fasting blood sugar levels* (*Table 2*). Each value in this table represents a 12-hour fasting blood sugar taken after at least three days of good dietary intake (described above). The blood sugar levels have been arbitrarily listed in ascending order. The final column of the Table (labeled Max-Min) represents the difference between the highest and the lowest 12-hour blood sugar value for each of the patients. Worthy of note is the great variability seen in the values of individual patients in all but possibly one (P.L.) of these children. The variations in 12-hour blood sugar values for these patients (Max-Min) ranged from 27 to 66 mg% and averaged 49.4 ± 4.8 (S.E.M.).

TABLE 3. BLOOD SUGAR AND SERUM INSULIN LEVELS DURING A TWENTY-FOUR HOUR FAST IN PATIENTS WITH KETOTIC HYPOGLYCEMIA

		Hours					
		4	*8*	*12*	*16*	*20*	*24*
Patient	*Test*						
J.H.	Sugar*			33	48	24	31**
	Insulin†						
M.H.	Sugar	67	56	61	49	38	20
	Insulin					0	0
A.B.	Sugar	84	82	61	64		
	Insulin						
J.J.	Sugar	64	65	82	49	45**	
	Insulin						
M.L.	Sugar	87	67	65	23	36	28
	Insulin				0	0	0
A.K.	Sugar	68	71	71	67	63	63
	Insulin						
C.C.	Sugar	76	68	59	56	23	18**
	Insulin						0
P.L.	Sugar	50	55	50	19**		
	Insulin	4	1	1	1		

* mg/100 ml.
† μU/ml.
** Seizure activity.

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* Although glucose was measured using the glucose oxidase method, the term, "blood sugar" will be used throughout the paper in order to maintain a consistency with previously published data.

Twenty-four hour fast (Table 3). Blood sugar and IRI values obtained at four-hour intervals during a 24-hour fast are noted in this table. Six of these patients developed hypoglycemia ·(blood sugar less than 50 mg%) after 20 hours; four developed a marked change in sensorium (extreme irritability, altered speech, impending or frank seizure activity), and four cases in which insulin was measured at the time blood sugars were low, also had IRI levels that were low.

Glucose and glucagon tolerance test (Tables 4 and 5). Blood sugar, IRI and FFA responses were as expected in all patients for the first 60 minutes following the glucose load. However, three of the seven patients had hypoglycemic blood sugar levels five hours after the infusion. All of the patients responded with elevated blood sugars when glucagon was given at the end of the glucose tolerance test. Rates of glucose utilization for each patient following the glucose load (K_T) are noted in Table 5. These values ranged from 2.57 to 3.15 and averaged 2.94 ± 0.11 (S.E.M.). Patient A.K. did not have this test.

Leucine tolerance test (Table 6). Not one of the eight patients developed hypoglycemia during the test and in no instance was the IRI level excessive in response to the leucine load.

Insulin and glucagon tolerance test (Table 7). Two hours after infusion of insulin blood sugar levels were markedly below fasting values in four of the patients. Despite this, the patients tested responded to glucagon with notably elevated blood sugars. (One patient, A.K., did not have this test.) HGH and FFA also responded as expected. HGH levels increased at least twofold in response to insulin in each patient and in no case was there an excessive level of HGH at any time throughout the test.

Ketogenic diet (Table 8). All eight patients developed hypoglycemia within 20 hours after the onset of the diet, and in every case acetonuria was noted. All of the patients developed a significant change in sensorium ·(as described above) within 28 hours at which time the test was discontinued and glucagon was administered. Although glucagon stimulation was followed by a rise in blood sugar in only two of the patients, seizure activity was not persistent and glucose administration was not required in any of the eight patients.

Developmental studies

Table 9 demonstrates that three children had entirely normal development, two manifested mild, specific developmental deviations, possibly re-

TABLE 4. BLOOD SUGAR, INSULIN AND FREE FATTY ACIDS FOLLOWING GLUCOSE AND GLUCAGON TOLERANCE TESTS IN PATIENTS WITH KETOTIC HYPOGLYCEMIA

Patient	Test	IV Glucose tolerance test												IM glucagon tolerance test		
		0'	2.5'	5'	15'	30'	60'	90'	120'	3hr	4hr	5hr	6hr	15'	30'	60'
J.H.	BS	70		367	289	203	77	73	76	83	46	36	36	118	148	106
	IRI	5		38	55	23										
	FFA	407		320	247	204	204									
M.H.	BS	57	445	334	289	208	96	47	47	43	31	15	22			
	IRI	0	40	15	15	12	5	1	0							
	FFA	920	1006	920	865	632	259	1006	1236							
A.B.	BS	79		480	469	292	143		48	47	32	52	64	98	102	50
	IRI	1		18	25	18										
	FFA	1318		1433	1051	649										
J.J.	BS	29		353	224	144	60	21	12	39	44	33	15	42	56	50
	IRI	2		50	48	15	0									
	FFA	920		575	489	374	316									
M.L.	BS	66	407	338	205	96	50	55	68	67	67	67	62	105	119	100
	IRI	2	78	60	48	10	0									
	FFA	316	361	331	301	301	271									
C.C.	BS	80	440	405	314	203	99	52	68	65	69	68	59	122	125	81
	IRI	6	40	35	23	8	3									
	FFA	600	490	465	325	300	300									
P.L.	BS	71	397	493	342	217	80	58	58	60	68	72	70	140	171	134
	IRI	9	99	85	65	67	9									
	FFA	740	795	640	400	240	110									

BS = Blood sugar (mg/100 ml.)   IRI = Serum insulin (μU/ml.)   FFA = Free fatty acids (μEq/L)

TABLE 5. RATES OF GLUCOSE UTILIZATION FOLLOWING GLUCOSE LOAD
IN PATIENTS WITH KETOTIC HYPOGLYCEMIA

Patient	K_t (% per min.)
J.H.	3.01
M.H.	2.67
A.B.	3.01
J.J.	2.77
M.L.	3.15
C.C.	3.57
P.L.	3.15
Mean + SEM	2.94 ± 0.11

TABLE 6. BLOOD SUGAR AND INSULIN LEVELS FOLLOWING LEUCINE LOADING
IN PATIENTS WITH KETOTIC HYPOGLYCEMIA

Patient	Test	0'	15'	30'	45'
J.H.	Sugar*	97	82	82	82
	Insulin†	2	1	1	8
M.H.	Sugar	77	66	58	60
	Insulin	5	14	9	4
A.B.	Sugar	78	85	74	66
	Insulin	6	7	7	3
J.J.	Sugar	67	58	58	57
	Insulin	18	32	25	16
M.L.	Sugar	65	70	67	64
	Insulin	12	0	0	0
A.K.	Sugar	92	73	72	67
	Insulin	18	8	11	9
C.C.	Sugar	98	71	63	65
	Insulin	1	22	17	10
P.L.	Sugar	77	76	72	73
	Insulin	9	70	13	5

* mg/100 ml.
† μU/ml.

TABLE 7. BLOOD SUGAR, GROWTH HORMONE AND FREE FATTY ACIDS FOLLOWING
INSULIN AND GLUCAGON TOLERANCE TESTS IN PATIENTS
WITH KETOTIC HYPOGLYCEMIA

Patient	Test	IV Insulin tolerance test						IM Glucagon tolerance test			
		0'	15'	30'	45'	60'	120'	15'	30'	45'	60'
J.H.	Sugar*	78	39	38	43	55	70	109	116	122	108
	HGH**	6	10	13	7	6	2				
	FFA†	611	320		189		698				
M.H.	Sugar	57	19	27	38	42	40	67	71	71	55
	HGH	0	18	20	13	12	7				
	FFA	832	655	683	699		1192				
A.B.	Sugar	108	98	92		89	87	124	144	151	127
	HGH	4	4	12		6	6				
	FFA	1240	1490	859		1081	989				
J.J.	Sugar	59	32	13	16	24	31	76	108	71	
	HGH	3	9	7	18	20					
	FFA	1299	592	559							
M.L.	Sugar	44	10	10	10		21	47	67		
	HGH	7	19	17	20		20				
	FFA	777	426	397	455		412				
C.C.	Sugar	80	28	24	62	55	78	100	114	82	69
	HGH	2	1	2	2	26	12				
	FFA	530	260	195	195	215	320				
P.L.	Sugar	76	43	29	40	48	58	86	79	76	61
	HGH	3	5	5	10	18	4				
	FFA	640	350	210	120	310	560				

* mg/100 ml.
** mµg/ml.
† µEq/L

lated to adverse environmental influences, and three showed specific signs of
CNS dysfunctions. All children, however, functioned intellectually within
the normal range.

No clear association between developmental status, EEG findings and
seizure history could be demonstrated (Table 10). Seven children experi-
enced perinatal stress, but there is clear evidence of associated CNS damage
in only three. Precise data concerning the relative severity of the stress ex-
perienced by the impaired and intact children have not been available.

TABLE 8. BLOOD SUGAR, URINARY ACETONE AND SEIZURE ACTIVITY FOLLOWING
KETOGENIC DIET AND GLUCAGON TOLERANCE TEST IN PATIENTS
WITH KETOGENIC HYPOGLYCEMIA

| | | | | | | | | | *Glucagon tolerance test (Blood sugar— mg/100 ml.)* | | | |
| | *Ketogenic diet (blood sugar—mg/100 ml.)* | | | | | | | | | | | |
Patient	0'	4hrs.	8hrs.	12hrs.	16hrs.	20hrs.	24hrs.	28hrs.	15'	30'	45'	60'
J.H.	91	61	70	45	12	22		*15**	51	67	80	73
M.H.	54	42	24	*22	*13	*14**			35	50		65
A.B.				65	35	*25**			25	25	26	25
J.J.	90	61	103	*17	*15**				17	22		28
M.L.	79	74	79	*34	*16**				24	30		22
A.K.	54	48	46	*41	*23**				30	29		29
C.C.	83	87	76	*69	*58	*31**			35	34	33	32
P.L.	78	78	70	*66	*118	*30	*28		39	40	39	37

* Acetonuria.
** Seizure activity.

DISCUSSION

Senior and Loridan[3] found that their patients with ketotic hypoglycemia, as well as their control patients, developed hypoglycemia in response to the ketogenic diet. This finding questions the very existence of this disease entity and therefore makes mandatory more precision of definition and diagnosis. In addition to the patients presented in this study, three other patients were given the ketogenic diet: one normal boy, one adolescent boy with an insulinoma and one three-year old girl with Beckwith's Syndrome. None of these children developed hypoglycemia within 48 hours after starting the diet.

Eight of the 19 children with sporadic hypoglycemia who have been referred to the senior author during the past four years have fulfilled our criteria for ketotic hypoglycemia. Therefore, we suggest that although ketotic hypoglycemia may be associated with other conditions,[17] it is a distinct disease entity and may represent the largest group of children with sporadic hypoglycemia. The present study verifies the following findings of Ulstrom, et al.[1,2]: the patients present with hypoglycemia and acetonuria; the children are usually small for their age and most had low birth weights; hypoglycemia occurs within 24 hours after the start of the ketogenic diet

at which time most patients fail to respond to glucagon stimulation. In addition, this study suggests that a stormy perinatal course, a marked variability in blood sugar levels during a 12-hour fast, and a rapid utilization of glucose despite normal to low levels of IRI are often present.

Five of these eight children had difficult gestational courses and seven had inordinate amounts of perinatal stress. Even though our sample is quite small, our experience indicates that this neonatal stress may well be an important stimulus for the development of subsequent ketotic hypoglycemia. Any suggestion of a mechanism whereby such stress stimulates the subsequent episodes of hypoglycemia would be highly speculative and therefore unwarranted at this time.

This concept of neonatal stress-induced hypoglycemia may gather together several types of hypoglycemia now classified separately: children born to toxemic mothers; children small for dates; cold-injured newborns; and children with ketotic hypoglycemia. At first consideration this compilation may appear to contradict our thesis that ketotic hypoglycemia is a distinct entity. However, we suggest that each of these conditions may actually be ketotic hypoglycemia, the only difference being the specific type of neonatal stress in each case.

There was a marked variability of the blood sugar responses to the 12-hour fast. As noted in Table 2, the maximum minus minimum 12-hour fasting blood sugar values for the eight patients ranged from 27 to 66 mg. per 100 ml. with a mean ($\pm$ S.E.M.) of 49.4 $\pm$ 4.8 mg. per 100 ml. Control data are not available. However, data presented by Danowski[18] for 17 children, 9-15 years of age, showed that the maximum minus the minimum values ranged from 0 to 46 mg. per 100 ml. with a mean ($\pm$ S.E.M.) of 10.9 $\pm$ 2.6. Although the data reported by Danowski were obtained from older children, they suggest that the variability demonstrated here may represent an abnormality in the control mechanisms governing blood sugar homeostasis. In addition, comparable inability to maintain normal blood sugar levels was noted when our patients were fasted 24 hours, at which time six of the eight became hypoglycemic, although insulin levels were low in the four patients where measurements were made.

Glucose tolerance testing revealed a very rapid utilization of the infused glucose ($K_T = 2.95\%$ per minute) without any evidence of inappropriately elevated IRI or of abnormal FFA levels. Although control data are meager and less than ideal, Danowski[18] has presented IV glucose tolerance data for 27 normal children 2-16 years of age. The (K_T) value was 1.26 percent per minute for Danowski's patients. This contrasted with values of 1.67 to 1.80 percent per minute for adults[19,20,21] and 1.03 for infants.[6]

TABLE 9. DEVELOPMENTAL FINDINGS

Patient category	Patient	Age at exam. (in mos.)	Signs of CNS impairment	Intellectual level	Description of findings
Normal development	M.H.	#1 22 #2 29	None	Average to above	Excellent language and problem solving skills
	P.L.	#1 46	None	Average to above	Fully average intellectual functioning
	C.C.	#1 40	None	Average to above	Intense anxiety
	A.B.	#1* 19	Uncertain—Slight delay in gross motor development. Good muscle tone and strength. No overt abnormal signs on neurological exam.	Average	Gross motor delay possibly related to maternal deprivation.
Mild developmental deviation of uncertain etiology	J.J.	#1 26 #2 59	Uncertain—Slight deficits in visuo-motor & specific language functions requiring reasoning and abstract thought.	Average	Intellectual functioning within the average range. Unevenness in language may be related to environmental factors.

					CNS impairment
A.K.	#1	8	*Definite*—mild visuo-motor difficulty, gross motor awkwardness, impulsiveness & short attention span.	Average	Average intelligence with possible mild central nervous system dysfunction.
	#2	23			
	#3	35			
J.H.	#1	50	*Definite*—deficit in visuo-motor function and poor number concepts.	Average to above	Mild specific central nervous system impairment in child of fully average intellectual ability. Intense anxiety.
	#2	64			
M.L.	#1	57	*Definite*—deficits in specific visuomotor, language, adaptive functions and marked unevenness of development.	Dull-normal	Diffuse central nervous system impairment in child of at least dull-normal intelligence. Difficulties intensified by visual defect and environmental factors

* To be re-evaluated.

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TABLE 10. RELATIONSHIP BETWEEN DEVELOPMENTAL FINDINGS, PERINATAL EVENTS, EEG AND SEIZURE HISTORY

Patient category	Patient	Perinatal abnormalities			EEG	Seizure history
		Gestational	*Parturitional*	*Neonatal*		
Normal development	M.H.	None	None	Dermoid cyst. B.W. 3544	Nor.	None
	P.L.	Spotting @ 6 wks. Hypertension 9 mos.	None	Anoxia & symptomatic hypoglycemia. B.W. 2273	Nor.	Neonatal 2 11/12 years 3 6/12 years
	C.C.	Pre-eclampsia	Difficulty extracting shoulders	Apnea, cyanosis & symptomatic hypo-glycemia. B.W. 3200	Abn.	Neonatal 3 years 3 4/12 years
Mild developmental deviation of uncertain etiology	A.B.	Pre-eclampsia. Spotting @ 39 wks.	None	Cephalohematoma, cyanosis, jaundice, hypotonia, & symptomatic hypoglycemia. B.W. 2400	Nor.	?Neonatal ?1 7/12 years (pale & unresponsive—ff. several days vomiting & 12 hr. fast)
	J.J.	Persistent hematuria. Pneumonitis & premature delivery 7th month.	Precipitate delivery (5 min. labor)	Subdural & epidural bleeding, anoxia & poor muscle tone. B.W. 2800	Abn.*	8 mos. 1 4/12 years 2 2/12 years 4 9/12 years

Mild specific CNS impairment					
A.K.	Triplets (2nd)	Double footling breech	R.D.S. jaundice. B.W. 1635	?Abn.	1 9/12 years
J.H.	Delivery 1 mon. premature	Breech	R.D.S. with apnea and "twitching", pneumonitis. B.W. 2010	Nor.	?Neonatal 8 mos. 4 2/12 years
M.L.	Hypertension. Delivery 2 wks. premature	Meconium stained fluid	R.D.S. with anoxia, cyanosis and pneumonia. Apgars: 1/2 & 5/3. B.W. 1950	Abn.*	1 10/12 years 2 8/12 years 3 6/12 years 4 8/12 years

* Compatible with primary seizure disorder.

Although various suggestions have been made, the pathogenesis of ketotic hypoglycemia remains uncertain. Ulstrom, *et al.*[1,2] have suggested that this type of hypoglycemia represents a failure to make one or more adaptations necessary to convert from a carbohydrate-burning to a fat-burning economy. Kogut, *et al.*[5] have suggested that in patients with ketotic hypoglycemia, hyperketonemia fails to stimulate an increase in insulin secretion, thus failing to regulate hepatic ketone production and failing to preserve liver glycogen. However, there is no evidence that ketones ever stimulate IRI in man.[22,23]

Senior and Loridan[8] demonstrated that the rates of glycerol disposal were the same in their patients with ketotic hypoglycemia and in their control patients. They concluded that there was no abnormality in gluconeogenesis and postulated that children who developed this type of hypoglycemia have a relatively greater demand for fuel by the brain. Unfortunately, in considering the pathogenesis of ketotic hypoglycemia, it is important to note that glycerol provides only about 5% of the substrate for gluconeogenesis;[24] this study neither allows us to disregard a failure of gluconeogenesis nor does it give convincing evidence of the importance of increased glucose utilization by the brain.

These hypoglycemic patients demonstrate three findings which we cannot explain on the basis of any single mechanism: they have an increased utilization of blood sugar following glucose infusion; they have marked variation in their 12-hour fasting blood sugar levels and they usually do not respond to glucagon after becoming hypoglycemic in response to the ketogenic diet. These findings were not associated with: increased levels of serum IRI; abnormalities in plasma concentrations of FFA or a deficiency of serum HGH. In addition, from our experience and that of others[1,2,5] there seems little doubt that the tendency to develop this type of hypoglycemia lessens with age. Although the mechanism responsible is still unknown, this type of hypoglycemia may well be due to neonatal stress which induces a transient abnormality in the control of the "counter-regulatory principles" involved with blood sugar homeostasis. As defined by Freinkel and Metzger,[25] these principles antagonize glucose utilization in the periphery and activate hepatic glycogenolysis or gluconeogenesis or both.

There is little evidence that ketotic hypoglycemia either produces or is associated with mental retardation. Kogut, *et al.*[5] identified three of 13 ketotic children with I.Q.s or D.Q.s below 80, and three in the dull-normal range. However, no information is given concerning other potential influences upon the intellectual function of these children. In contrast, Ulstrom, *et al.*[1,2] reported normal intellectual development in 30 children with ketotic hypoglycemia. Our study revealed entirely normal intellectual

function in seven of eight children and dull-normal function in only one. There was clear evidence of specific neurological dysfunction in three children, and possible mild, specific dysfunction in two others. However, since the incidence of such perceptual-motor handicaps in the general population has not been established, it cannot be stated that this finding is significantly associated with ketotic hypoglycemia.

Kogut, *et al.*[5] have suggested the use of a specific diet and the daily testing for acetonuria in their patients with ketotic hypoglycemia. They also teach these parents how to estimate blood glucose levels with Dextrostix.® Although this approach may be warranted in some patients with frequent, severe episodes of hypoglycemia, we feel the condition is generally mild and warrants no further treatment other than: parental reassurance, the avoidance of prolonged fasts, the avoidance of excess dietary fats, and the need for breaking fasts with a low-fat content food. No medication is necessary. If concern about the child's development is expressed, careful evaluation should be arranged. Predictions without such evaluation serve no useful purpose.

SUMMARY

A study of eight children with ketotic hypoglycemia has made the diagnostic criteria for that condition more precise. These include the following: sporadic hypoglycemia associated with acetonuria; low birth weight; perinatal stress; relative short stature; marked variability in 12-hour fasting blood sugar levels; a rapid utilization of glucose despite normal levels of serum immunoreactive insulin; and the occurrence of hypoglycemia within 24 hours after the start of the ketogenic diet, at which time most patients do not respond to glucagon administration. The etiology and pathogenesis are discussed. In addition, developmental studies in these eight patients fail to demonstrate an association of ketotic hypoglycemia with mental retardation.

REFERENCES

1. Colle, E. and Ulstrom, R. A.: Ketotic hypoglycemia. *J. Pediat.*, 1964, *64*, 632-651.
2. Sauls, H. S. and Ulstrom, R. A.: Hypoglycemia. Brennemann-Kelley, *Practice of Pediatrics.* Vol. 1, 1967, Chap. 40, 1-68.
3. Senior, B. and Loridan, L.: Gluconeogenesis and insulin in the ketotic variety of childhood hypoglycemia and in control children. *J. Pediat.*, 1969, *74*, 529-539.
4. Cornblath, M. and Schwartz, R.: *Disorders of Carbohydrate Metabolism in Infancy.* Philadelphia, W. B. Saunders Co., 1966.
5. Kogut, M. D., Blaskovics, M., and Donnell, G. N.: Idiopathic hypoglycemia: a study of twenty-six children. *J. Pediat.*, 1969, *74*, 853-871.
6. Bowie, M., Mulligan, P. B., and Schwartz, R.: Intravenous glucose tolerance in the normal newborn infant: the effects of a double dose of glucose and insulin. *Pediatrics*, 1963, *31*, 590-598.

7. Watson, D.: Enzymatic determination of glucose and easily hydrolyzable glucose esters in blood. *Analyt. Biochem.*, 1962, *3*, 131-144.
8. Soeldner, J. S. and Slone, D.: Critical variables in the radio-immunoassay of serum insulin using the double antibody technique. *Diabetes*, 1965, *14*, 771-779.
9. Boden, G. and Soeldner, J. S.: A sensitive double antibody radio-immunoassay for human growth hormone: levels of HGH following rapid tolbutamide infusion. *Diabetologia*, 1967, *3*, 413-421.
10. Dole, V. P.: A relation between non-esterified fatty acids in plasma and the metabolism of glucose. *J. clin. Invest.*, 1956, *35*, 150-154.
11. Escalona, S. K.: Use of infant tests for predictive purposes. *Bull. Meninger Clinic*, 1950, *14*, 117-128.
12. Escalona, S. K. and Moriorty, A.: Prediction of school age intelligence from infant tests. *Child. Dev.*, 1961, *32*, 597-605.
13. Knobloch, H. and Pasamanick, B.: Predicting intellectual potential in infancy. *Amer. J. Dis. Child.*, 1963, *106*, 43-51.
14. Knobloch, H. and Pasamanick, B.: Developmental behavioral approach to neurological examination in infancy. *Child Dev.*, 1960, *33*, 181-198.
15. Provence, S. A. and Lyston, R. C.: *Infants in Institutions.* New York, International Universities Press, 1963.
16. Provence, S. A. and Ritvo, S.: Effects of deprivation on institutionalized infants: disturbance of relationships to inanimate objects. *The Psychonalytic Study of the Child.* New York, International Universities Press, 1961.
17. Snow, R., Sacks, M. O., and Cornblath, M.: Ketotic hypoglycemia in a Russell Dwarf. *J. Pediat.*, 1966, *69*, 121-125.
18. Danowski, T. S.: Fasting blood sugar levels and glucose tolerance tests in non-diabetic and diabetic children. Ch. 8. in, *Diabetes Mellitus.* Baltimore, The Williams and Wilkins Co., 1957.
19. Cleempoel, H., Conrad, V., and Bastenie, P. A.: Carcinoma of the Islets of Langerhans. *Lancet*, 1955, *2*, 801-803.
20. Silverstone, F. A., Solomons, E., and Rubricius, J.: The rapid glucose tolerance test in pregnancy. *J. clin. Invest.*, 1961, *40*, 2180-2189.
21. Lundbaek, K.: Intravenous glucose tolerance as a tool in the definition and diagnosis of diabetes mellitus. *Brit. Med. J.*, 1962, *1*, 1507-1513.
22. Fajans, S. S., Floyd, J. C., Jr., Knopf, R. F., and Conn, J. W.: A comparison of leucine and acetoacetate induced hypoglycemia in man. *J. clin. Invest.*, 1964, *43*, 2003-2008.
23. Senior, B. and Loridan, L.: Direct regulatory effect of ketones on lipolysis and on glucose concentrations in man. *Nature*, 1968, *219*, 83-84.
24. Cahill, G. F., Jr., Herrera, M. G., Morgan, A. P., Soeldner, J. S., Steinke, J., Levy, P. L., Reichard, G. A., Jr., and Kipnis, D. M.: Hormone-fuel interrelationships during fasting. *J. clin. Invest.*, 1966, *45*, 1751-1769.
25. Freinkel, N. and Metzger, B. E.: Oral glucose tolerance curve and hypoglycemias in the fed state. *N. Engl. J. Med.*, 1969, *280*, 820-828.