MEDICAL GRAND ROUNDS

Parkland Memorial Hospital

24 March, 1966

CLINICAL HYPOGLYCEMIA SYNDROMES AND THE NON-GLUCOSE PHYSIOLOGIC STIMULATORS OF INSULIN SECRETION

CLASSIFICATION OF ORGANIC TYPES OF HYPOGLYCEMIA

I INCREASED INSULIN SECRETION - HYPERINSULINISM

- A) Insulinoma - βeta-cell Tumors
- B) Leucine-Induced Hypoglycemia of Infancy and Childhood
- C) Ketotic Hypoglycemia of Childhood
- D) Milk Sickness -"Trembles" (?)

II HEPATIC - Impaired production, storage or release of glucose

- A) Liver Disease
  - 1) Hepatic necrosis - severe liver disease
  - 2) Hepatic venous congestion - CHF
  - 3) Iatrogenic - sudden cessation of IV glucose
- B) Ethanol-Induced
- C) Enzymatic Defects
  - 1) Glycogen Storage Disease

    VonGierke - G-6-phosphatase deficiency
    Forbes - Debrancher enzyme deficiency
    Hers - phosphorylase deficiency
  - 2) Glycogen - synthetase deficiency
  - 3) Hereditary Fructose Intolerance - deficiency of phosphofructaldolase
  - 4) Galactosemia - deficiency of galactose-1-phosphate uridyl transferase

III ENDOCRINE DISORDERS

- A) Adrenal insufficiency
- B) Panhypopituitary disease
- C) Growth Hormone deficiency
- D) Catecholamine deficiency
- E) Glucagon deficiency
- F) Myxedema severe (?)

IV NON-PANCREATIC TUMORS

- A) Fibrosarcoma
- B) Carcinoma
- C) Mesothelioma
- D) Hepatoma
- E) Adrenal carcinoma

V MISCELLANEOUS

- A) CNS lesions (?)
- B) Severe starvation

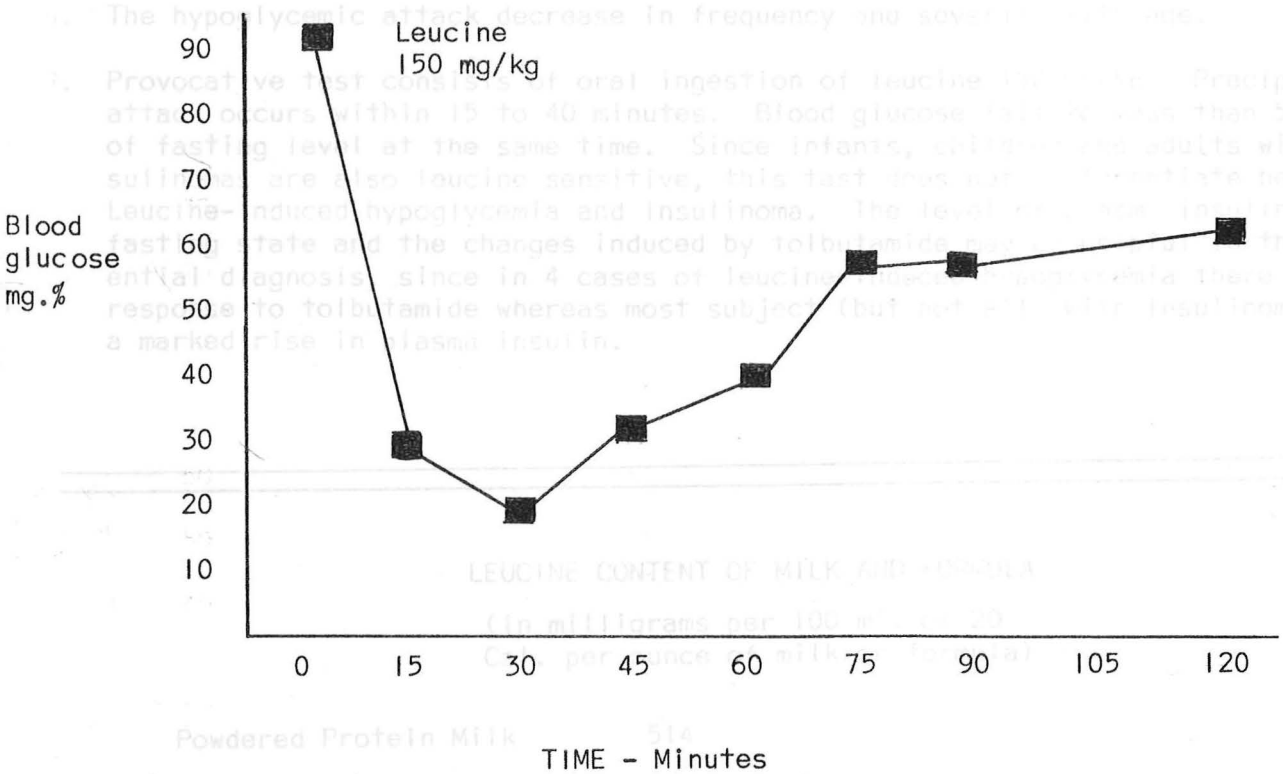
VI FACTITIOUS - SURREPTITIOUS

- A) Insulin
- B) Oral Hypoglycemia Agents

Case I. [redacted]

This four month old infant was admitted to [redacted] on [redacted], 1965 for pneumonia and work-up of hypoglycemic episodes which started on [redacted], 1965. She was first admitted to [redacted] for a 7 day period following a convulsive seizure associated with a blood sugar of 32 mg/100 ml on the first of [redacted], 1965. Work-up failed to reveal any apparent cause of hypoglycemia but a leucine tolerance test was not done. After her pneumonia cleared, a leucine tolerance test (150 mg/kg by mouth) was performed. The results are shown below.

She was discharged on [redacted], 1965 on a frequent feeding high carbohydrate regimen, milk being the only source of protein. Follow-up at the metabolic clinic at [redacted] reveals that she has been asymptomatic since discharge.



CLINICAL CHARACTERISTICS OF LEUCINE-INDUCED HYPOGLYCEMIA OF INFANTS

1. Onset of attacks before 2 years of age; most start by 4 months of age.
2. A higher incidence is recorded in male infants.
3. Infants usually appear well nourished and without physical abnormalities unless brain damage has occurred as a consequence of hypoglycemia.
4. Convulsions are the presenting symptoms of the hypoglycemia in 80 percent of the cases.
5. Hypoglycemic manifestations vary from hyperirritability and disturbed mentation to convulsions or sudden coma.
6. Attacks may occur on fasting. Although fasting hypoglycemia is present symptomatic hypoglycemia occurs less commonly before breakfast than after a meal of protein containing large amounts of leucine (milk, eggs, fish, meat)
7. The pattern of recurrent seizures, drowsiness or stupor shortly after a meal should arouse suspicion of leucine-induced hypoglycemia. [Other causes of hypoglycemia in infants precipitated by food include Galactosemia (milk) and Hereditaty Fructose Intolerance (fruit, sweets)]
8. The hypoglycemic attack decrease in frequency and severity with age.
9. Provocative test consists of oral ingestion of leucine 150 mg/kg. Precipitated attack occurs within 15 to 40 minutes. Blood glucose fall to less than 50 percent of fasting level at the same time. Since infants, children and adults with insulinomas are also leucine sensitive, this test does not differentiate between Leucine-Induced hypoglycemia and insulinoma. The level of plasma insulin in the fasting state and the changes induced by tolbutamide may be helpful in the differential diagnosis, since in 4 cases of leucine-induced hypoglycemia there was no response to tolbutamide whereas most subject (but not all) with insulinomas show a marked rise in plasma insulin.

LEUCINE CONTENT OF MILK AND FORMULA

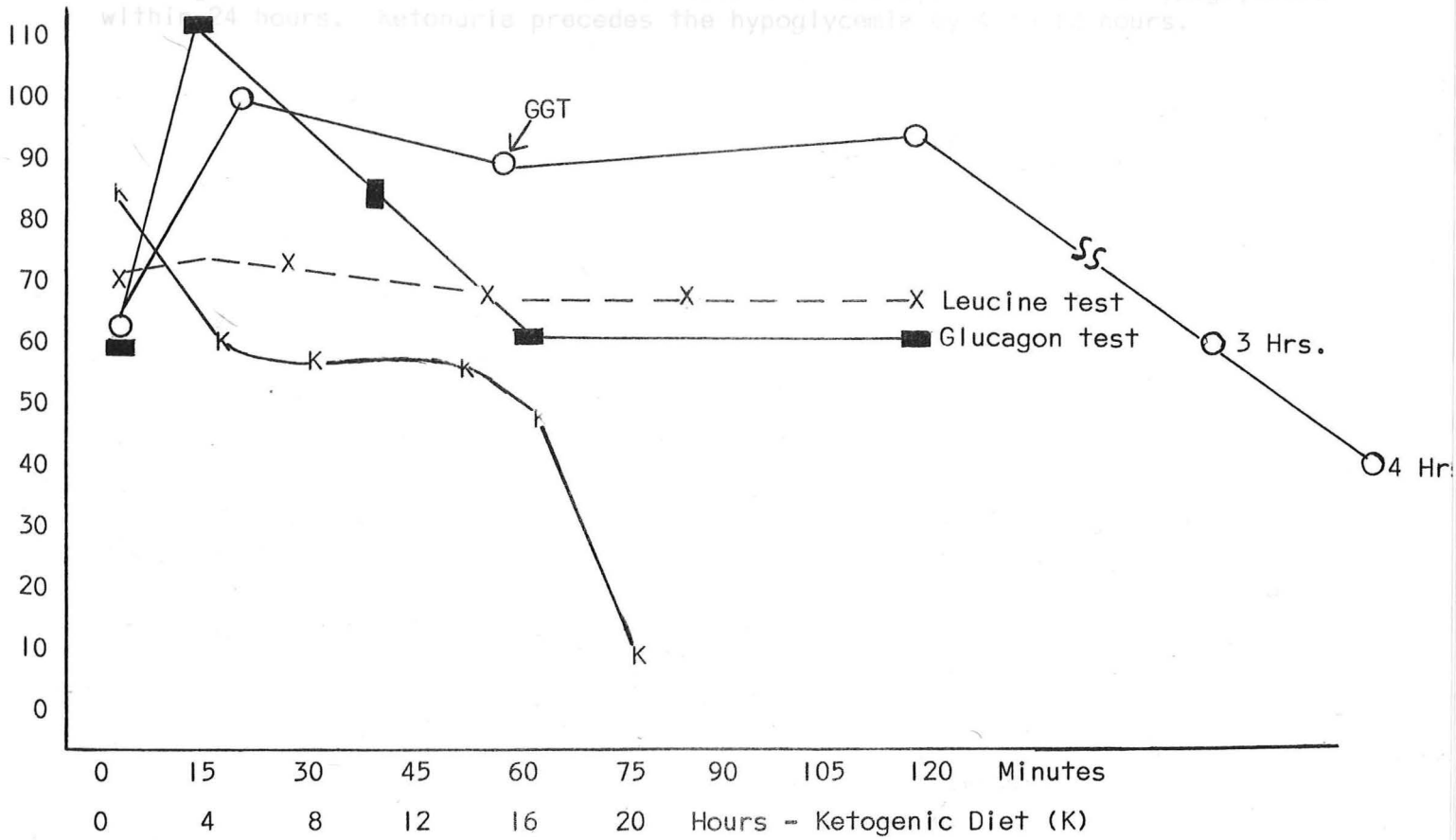
(In milligrams per 100 ml. of 20 Cal. per ounce of milk or formula)

Powdered Protein Milk	514
Cow	356
Lactum	295
Mull-Soy	220
Similac	181
Human	161
S-M-A	157

Case II. From Colle and Ulstrom (Ref. 62)

This child who weighed 5 pounds, 8 ounces at birth had his first convulsive episode at the age of two years. The spell was characterized by crying, disorientation and limpness. A second spontaneous episode with a blood sugar of 26 mg.% occurred after a 12 hour fast. He was hospitalized at the [redacted] at age two and one-half years. No fasting hypoglycemia was found. During the ensuing year, two severe attacks occurred. He was re-admitted when three and one-half years of age, at which time the association of ketosis and symptoms of hypoglycemia was established.

Oral glucose tolerance test, leucine response test and glucagon tests were normal. Tests of adrenal cortical function were normal. Eight hours after being placed on a ketogenic diet the urine was positive for acetone. By 20 hours the blood glucose fell to 15 mg. %.



CLINICAL CHARACTERISTICS OF KETOTIC HYPOGLYCEMIA

1) Attacks rarely start before the age of one and one-half years.

2) Hypoglycemic episodes are manifested by disturbances in mentation, motor dysfunction and convulsions.

3) The attacks are episodic in nature and the child appears in good health between attacks.

4) Attacks are precipitated by non-specific gastrointestinal disturbances or other illness which preclude normal food intake. Attacks may occur if fasting extends beyond 12-15 hours for any reason.

5) Ketonemia, ketonuria precede and accompany the hypoglycemia.

6) On a normal diet fasting blood sugar levels are normal between attacks and remain so after a 12 hour fast. At that time epinephrine and glucagon tests are normal.

7) A glucose tolerance test does not induce hypoglycemia. Leucine tolerance test is negative.

8) Attacks decrease in frequency as the child grows older.

9) A ketogenic diet produces clinical attacks with CNS dysfunction and hypoglycemia within 24 hours. Ketonuria precedes the hypoglycemia by 4 to 12 hours.

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HYPOGLYCEMIC SYNDROMES ASSOCIATED WITH DISORDERS OF NON-GLUCOSE STIMULATIONS OF INSULIN SECRETION

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KETOTIC HYPOGLYCEMIA

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