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SPONTANEOUS HYPOGLYCEMIA

M2 - Endocrine Sequence

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SPONTANEOUS HYPOGLYCEMIA

Definition:

Hypoglycemia that occurs outside of the setting of diabetes management.

Spontaneous Hypoglycemia

Case #1

Gregor S., a 41-year-old accountant, awoke one morning from uneasy dreams and found himself transformed in his bed into a giant cockroach....or at least feeling “very weird” ...

Recurrent episodes were sporadic but occurred frequently in the mornings and were relieved by breakfast.

The most recent visit occurred two days prior to his clinic visit, when Mrs. S. found her husband happily taking his morning shower...in his pajamas and bathrobe....

Is this hypoglycemia?

Question #1

What is Hypoglycemia?

Spontaneous Hypoglycemia

Clinically relevant hypoglycemia is characterized by:

Whipple's Triad

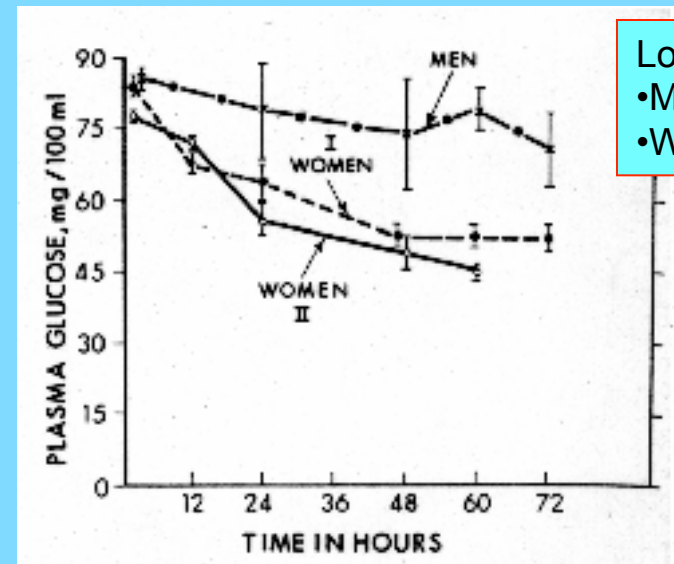
- Characteristic neuroglycopenic symptoms
- Low blood glucose concentration,
- Resolution of symptoms with return of blood glucose concentrations to normal.

Very
Important!

Clinically Significant Hypoglycemia

Why Not Use Just Low Blood Glucose to Define Clinically Relevant Spontaneous Hypoglycemia?

Average plasma glucose concentrations during a 72-hour fast



Lowest average blood glucose:
•Men = 67.5 ± 8.6 mg/dL
•Women = 41.3 ± 13.4 mg/dL

PD-INEL Merimee and Tyson, *NEJM* 291:1275, 1974

Average blood glucose values vary greatly between individuals and between men and women.

Spontaneous Hypoglycemia

Take Home Message #1

A blood glucose concentration of less than 60 mg/dL does NOT necessarily signify disease.

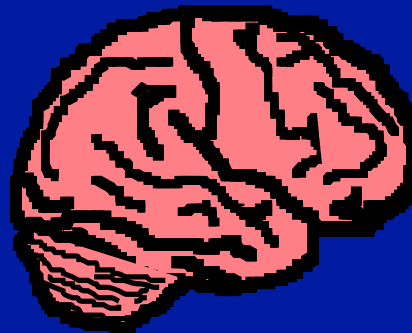
Spontaneous Hypoglycemia

Take Home Message #2

Neuroglycopenia:

- Fatigue
- Headache
- Disorientation
- Slurred speech
- Confusion
- Loss of Consciousness

Disorders involving life-threatening hypoglycemia may present with purely neuroglycopenic symptoms, such as BIZARRE BEHAVIOR....



BUT,

Take Home Message #2

Not all bizarre behavior may be explained by hypoglycemia....

Evaluation of Spontaneous Hypoglycemia

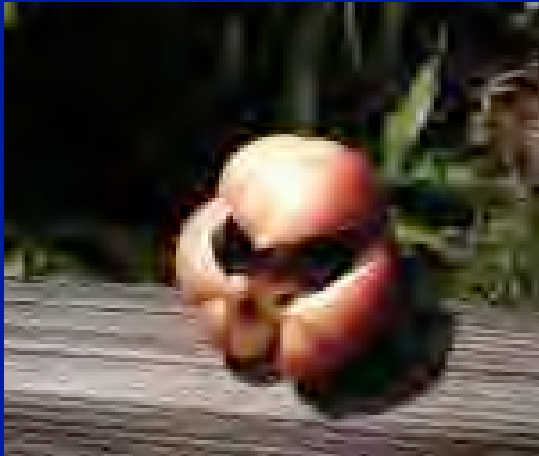
Things to rule out first:


- Drugs and Toxins
- Organ Failure
- Infections and
Chronic
Malnutrition
- Hormonal
Disorders

Spontaneous Hypoglycemia: Drugs and Toxins

1. Increased Circulating Insulin:
 - Insulin
 - Sulfonylureas
 - Pentamidine
2. Depressed Gluconeogenesis:
 - Ethanol
 - “Hypoglycin” from unripe, uncooked Jamaican ackee fruit
3. Unknown mechanism:
 - Aspirin (rare)
 - Sulfonamides (rare)

Jamaican Ackee Fruit



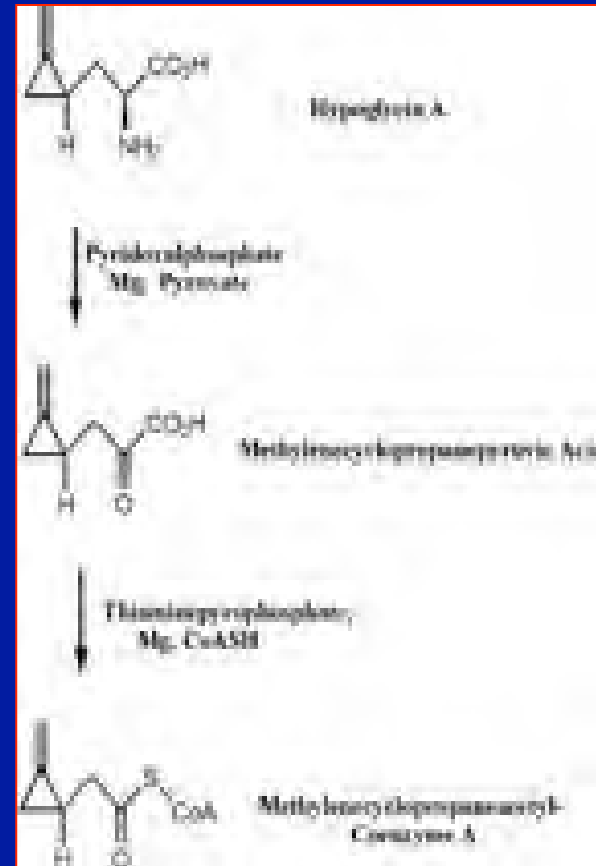
 [DocTaxon](#) (Wikimedia commons)

Ackee fruit



 [barron](#) (Flickr)

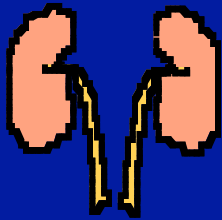
Ackee and saltfish



 [Source Undetermined](#)

Hypoglycin A and MCPA-CoA

Spontaneous Hypoglycemia: Critical Organ System Failure



Kidneys

RENAL FAILURE: #1 cause of hypoglycemia in hospitalized patients- with and without diabetes.

- Decreased clearance of insulin.
- Decreased gluconeogenesis (fr. decreased delivery of alanine from muscle).



Liver

FULMINANT HEPATIC FAILURE:

- Acute fulminant hepatitis, acetaminophen toxicity, Reye's Syndrome.
- Decreased gluconeogenesis and glycogenolysis.
- NOT seen with cirrhosis, chronic hepatitis, liver metastases.



Heart

SEVERE HEART FAILURE:

- Etiology unknown.

Spontaneous Hypoglycemia: Infections and Chronic Malnutrition

Infections

- MALARIA (*P. falciparum*) - occurs occasionally, mostly in association with quinine therapy.
- OVERWHELMING SEPSIS - usually, infections cause hyperglycemia.

Chronic malnutrition

- Mechanism not clear - increased glucose utilization by muscle?

Spontaneous Hypoglycemia: Endocrine Disorders

Adrenal Insufficiency

- Mild hypoglycemia may be seen in adults; however, more severe in children.
- Primary adrenal insufficiency occurring with type 1 diabetes may present with decreased insulin requirements and frequent hypoglycemia.
- Mechanism: Decreased delivery of gluconeogenic precursors to liver and/or decreased synthesis of epinephrine (decreased induction of N-methyl transferase).

Hypothyroidism and “early” diabetes mellitus do **NOT** cause spontaneous hypoglycemia

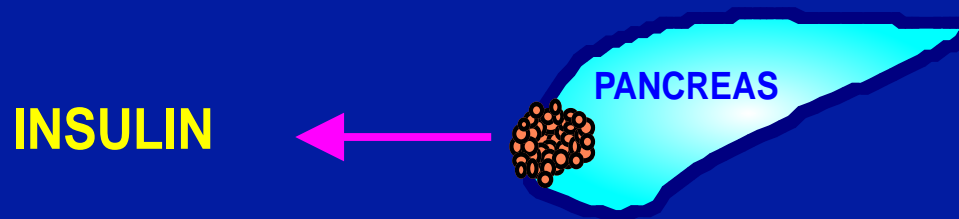
Question #2

Is *FASTING* hypoglycemia present?

Fasting Hypoglycemia

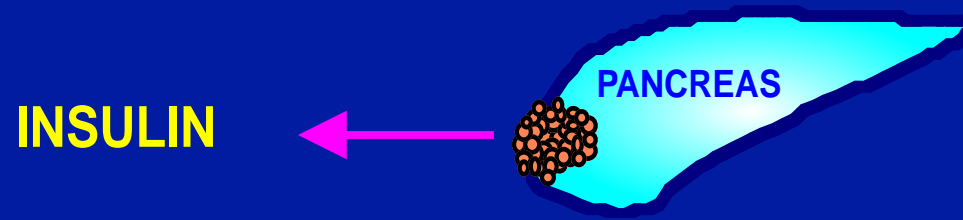
- Insulinoma
 - Insulinoma
 - Insulinoma
 - Non-Islet Cell Tumor Hypoglycemia
 - Autoimmune Hypoglycemia

Insulinoma: The Bad Boy of Spontaneous Hypoglycemia



- Relatively rare: “one in a million” (annual incidence)
- Usually spontaneous, but 10% are multifocal (usually associated with MEN1)
- Usually an adenoma in the pancreas - rarely malignant
- Rarely seen outside of the pancreas (~1%)
- Most are very small (30% are less than 1 cm)
- Classically associated with FASTING hypoglycemia

Insulinoma: The Bad Boy of Spontaneous Hypoglycemia



So why bother with something so rare??

Because if you miss it, it can *KILL* your patient!

Insulinoma

SYMPTOMS OF HYPOGLYCEMIA

“AUTONOMIC”

- Tremulousness
- Palpitations
- Sweating
- Anxiety
- Warmth
- Feelings of “Impending Doom”

NEUROGLYCOPENIC

- Impaired concentration
- Fatigue
- Headache, dizziness
- Slurred speech
- Confusion
- Disorientation
- Coma
- Seizures

Symptoms produced by an insulinoma are generally those of NEUROGLYCOPENIA.



PANCREAS

Spontaneous Hypoglycemia

Case

#1

Remember Gregor S., who was taking a shower in his pajamas?

- Neuroglycopenic symptoms (confusion, bizarre behavior)
- Provoked by fasting
- Relieved with orange juice and breakfast

Spontaneous Hypoglycemia: Diagnosis

The “Gold Standard” for the diagnosis of
insulinoma:

The 72-Hour Fast

Important!



**Basis: Demonstration of
inappropriate endogenous
insulin production in the
presence of clinically relevant
hypoglycemia, i.e., Whipple’s
Triad.**

Spontaneous Hypoglycemia: Diagnosis

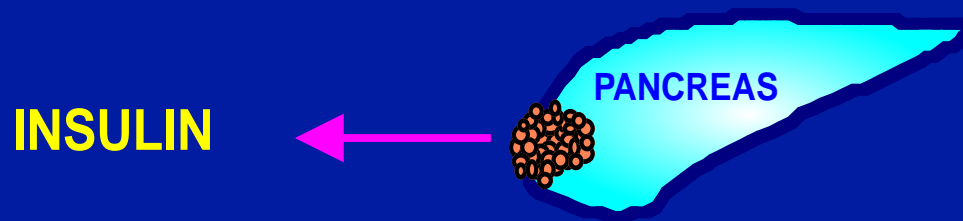
The 72-Hour Fast:

1. Hospitalize patient and fast for up to 72 hrs.
2. Check blood sugars every 2-4 hours.
3. Monitor for hypoglycemic symptoms (esp. neuroglycopenia)
4. In the presence of a low blood glucose, draw at least two sets of labs for :
 - Blood glucose
 - Serum insulin, C-peptide and proinsulin
5. Give glucose (either orally or via IV) and check for resolution of symptoms (i.e., confirming Whipple's Triad)
Sensitivity at 72 hrs >95%

Spontaneous Hypoglycemia: Diagnosis

Glucose Insulin C-Peptide Proinsulin

Insulinoma Low High High High*



*Typically, exceeds 25% of total insulin

Spontaneous Hypoglycemia: Insulinoma versus Surreptitious Insulin Use

Glucose Insulin C-Peptide Proinsulin

Insulinoma Low High High High

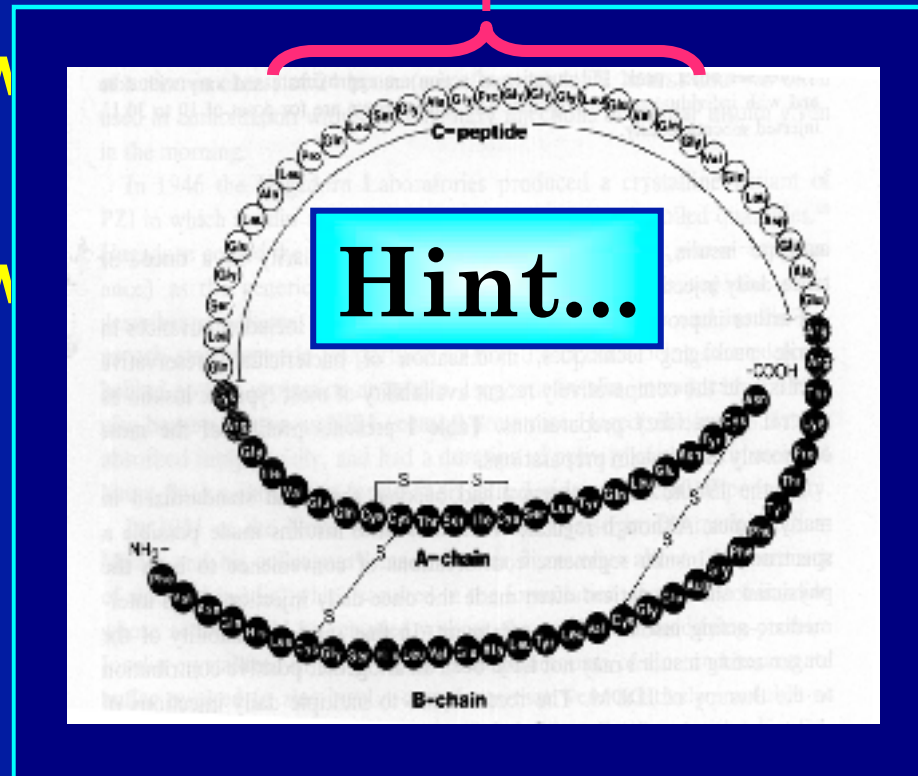
Insulin Low High

Spontaneous Hypoglycemia: Insulinoma versus Surreptitious Insulin Use

Glucose Insulin C-Peptide Proinsulin

Insulinoma **Low**

Insulin **Low**



Spontaneous Hypoglycemia: Insulinoma versus Surreptitious Insulin Use

Glucose Insulin C-Peptide Proinsulin

Insulinoma Low High High High

Insulin Low High Low Low

**With EXOGENOUS insulin administration,
ENDOGENOUS insulin production--and
therefore, C-peptide and proinsulin--is
suppressed**

Spontaneous Hypoglycemia: Insulinoma versus Surreptitious Sulfonylurea Use

	<u>Glucose</u>	<u>Insulin</u>	<u>C-Peptide</u>	<u>Proinsulin</u>
Insulinoma	Low	High	High	High
Insulin	Low	High	Low	Low
Sulfonylurea	Low	High	High	High

Spontaneous Hypoglycemia: Insulinoma versus Surreptitious Insulin Use

	<u>Glucose</u>	<u>Insulin</u>	<u>C-Peptide</u>	<u>Proinsulin</u>
Insulinoma	Low	High	High	High
Insulin	Low	High	Low	Low
Sulfonylurea	Low	High	High	High

How can we tell them apart?

**Serum or Urine
Sulfonylurea
Screen**

Really Weird Causes of Fasting Hypoglycemia

Non-Islet Cell Tumor Hypoglycemia

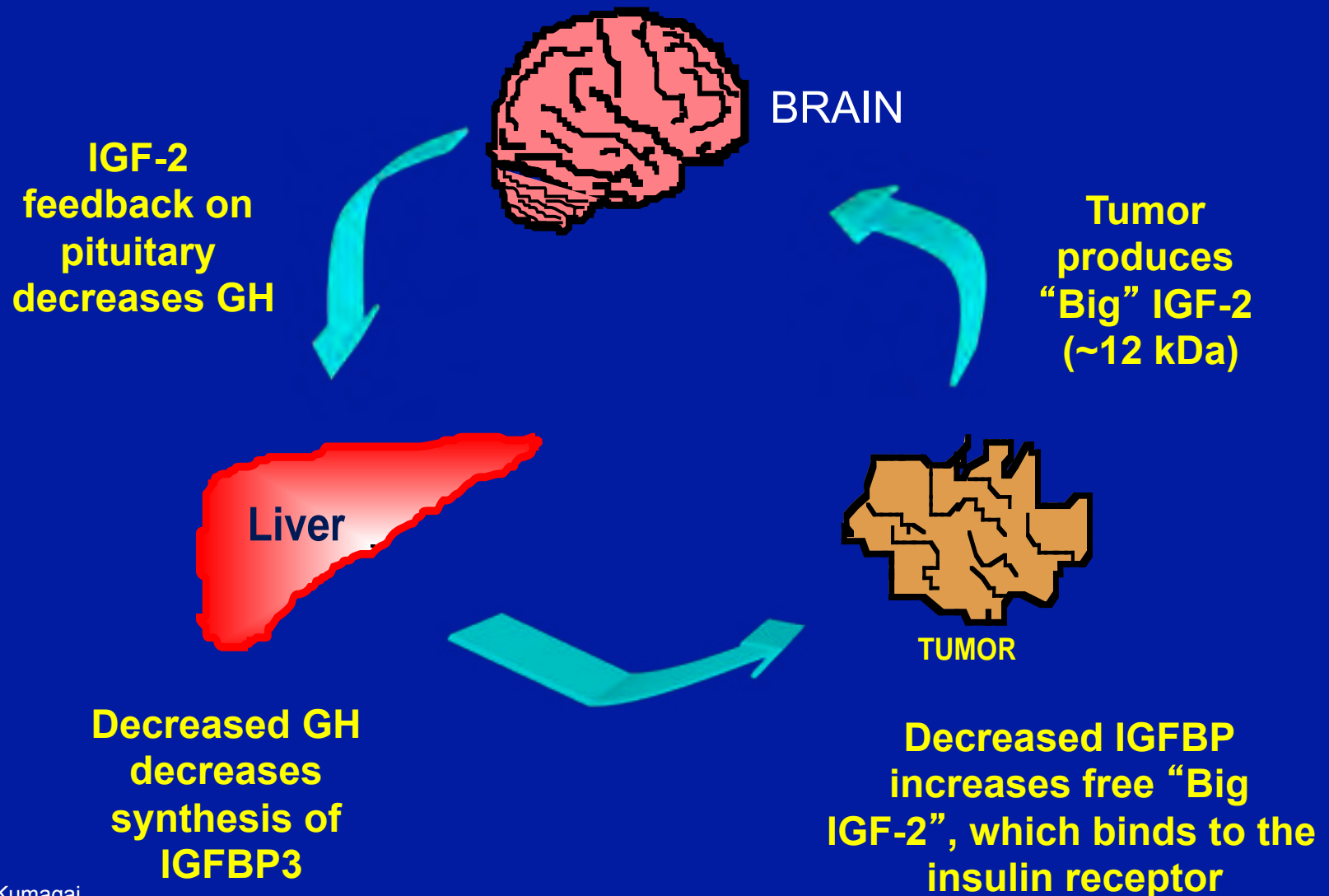
Non-Islet Cell Tumor Hypoglycemia

Remember
these two



- Large mesenchymal tumors (> 2 kg in size) - leiomyosarcomas, mesotheliomas, fibrosarcoma.
- Hepatocellular carcinoma (“hepatoma”), but NOT metastatic disease to the liver.
- Adrenal cortical tumors.
- Carcinoid (bronchus, ileum, pancreas).
- Adenocarcinoma of the lung, stomach or colon.
- Hematologic malignancies - “pseudohypoglycemia”

Non-Islet Cell Tumor Hypoglycemia: Proposed Pathological Mechanisms

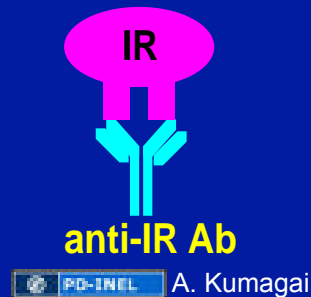


Really Truly Weird Causes of Fasting Hypoglycemia

Anti-Insulin Receptor Antibody Syndrome

Autoimmune Hypoglycemic Syndromes

Anti-Insulin Receptor Antibodies (anti-IR Ab)



- First described in individuals with extreme insulin resistance; however, may be seen in association with type 1 diabetes.
- Characterized by extreme HYPERglycemia (BG > 500) alternating with severe, refractory HYPOglycemia (BG' s < 20), depending on the anti-IR Ab titer.

Extremely rare: less than 100 cases in the literature

Typically causes FASTING hypoglycemia

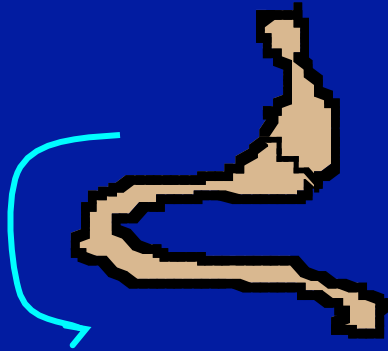
Spontaneous Hypoglycemia

POSTPRANDIAL HYPOGLYCEMIA

- Postgastrectomy Hypoglycemia
 - “Reactive” Hypoglycemia

Postgastrectomy Hypoglycemia

**Rapid transit of
carbohydrate through
shortened stomach**



Shortened stomach
(e.g., post-Billroth II
procedure)

Rapid transit through shortened stomach causes release of insulin secretagogue from GI track. Different than the postgastrectomy “dumping syndrome.”

Spontaneous Hypoglycemia

Case #2

While you are sitting around attempting to digest Thanksgiving dinner, your favorite aunt Ursula, a hulk-like 49-year-old construction worker and crane operator, wipes grease off of her slightly hairy chin and says, “Yo...my doc says that I should lose some weight, but if I don’t eat every couple ‘a hours, I get the ‘dropsies’ ” ...

“Paulie at work says this might be because of low blood sugar, and my doc agrees. So, whadya think?”

Is this hypoglycemia?

Postprandial Hypoglycemia

“REACTIVE” HYPOGLYCEMIA

“The most common diagnosis of a distinctly uncommon disorder”

“Reactive Hypoglycemia”

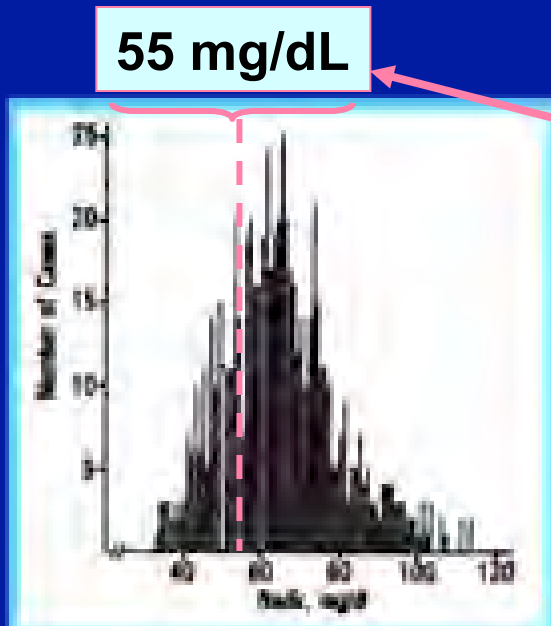
DEFINITION

CLINICAL: Characteristic hypoglycemic symptoms accompanied by low blood glucose concentrations that occur 1-4 hours after eating.

“POPULAR”: Feeling “funny” or “dizzy” after eating.

“Reactive Hypoglycemia” Problems with Diagnosis

Reactive hypoglycemia is frequently “diagnosed” with a modified (5-hour) oral glucose tolerance test.



Distribution of blood glucose values at nadir in 650 subjects during 5hr GTT

PD-INEL Lev-Ran and Anderson *Diabetes* 30:996, 1981

Of the 650 subjects with normal glucose metabolism, 25% had nadir blood glucose values of less than 55 mg/dL.

None had characteristic symptoms.

Bottom Line: The Oral Glucose Tolerance Test should NOT be used in the evaluation of spontaneous hypoglycemia.

“Reactive Hypoglycemia”

Evaluation is based FIRST on the demonstration that postprandial symptoms are associated with low blood glucose, and the symptoms resolve with raising the blood glucose.



 PD-Self [Muhamad Arif](#)
(Wikimeida commons)

Tracking blood glucose levels with and without symptoms at home with a monitor over several days is a good place to start....

When carefully diagnosed, true “reactive” hypoglycemia is a distinctly uncommon clinical disorder.

Spontaneous Hypoglycemia: Important Points

- Whipple's Triad.
- Major characteristics of an insulinoma.
- Diagnostic approach to spontaneous hypoglycemia, including the "Gold standard" for the diagnosis of insulinoma.
- Distinguish between biochemical profiles (glucose, insulin, C-peptide, proinsulin) of an insulinoma, surreptitious insulin use, surreptitious sulfonylurea use and other causes of hypoglycemia.
- Evaluation of suspected postprandial hypoglycemia.

Spontaneous Hypoglycemia

Final Take-Home Message:

Don't forget
'bout
Whipple!!!

Additional Source Information

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Slide 8: Merimee and Tyson, *NEJM* 291:1275, 1974

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Slide 22: A. Kumagai

Slide 26: A. Kumagai

Slide 28: A. Kumagai; Pickup & Williams, 1991

Slide 34: A. Kumagai

Slide 36: A. Kumagai

Slide 38: A. Kumagai

Slide 42: Lev-Ran and Anderson *Diabetes* 30:996, 1981; A. Kumagai

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