HYPOGLYCEMIA

For

4th year Medical Student

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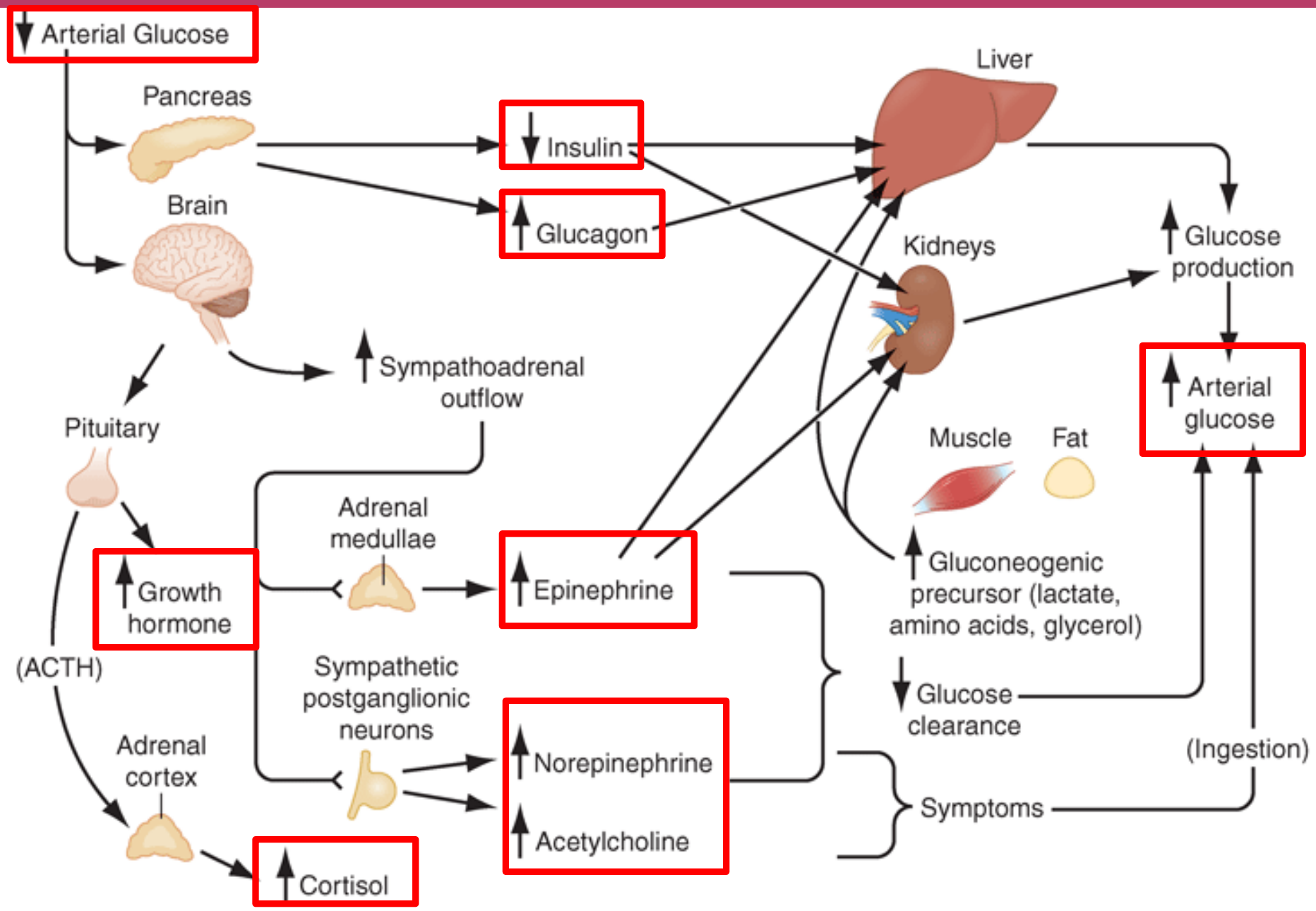
18 July 2014

Outline

- Systemic glucose balance / counterregulation
- Whipple’s triad
- Clinical Manifestations
- Hypoglycemia in diabetes mellitus
- Hypoglycemia in non-diabetes mellitus
- Diagnostic strategy during hypoglycemia
- Treatment

SYSTEMIC GLUCOSE BALANCE

GLUCOSE COUNTERREGULATION



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Physiologic Responses to Decreasing Plasma Glucose Concentrations

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Response	Glycemic threshold (mg/dL)	Glucose counterregulation
↓ Insulin	80-85	Primary glucose regulatory factor/first defense against hypoglycemia
↑ Glucagon	65-70	Primary glucose counterregulatory factor/second defense against hypoglycemia
↑ Epinephrine	65-70	Third defense against hypoglycemia, critical when glucagon is deficient
↑ Cortisol & Growth	65-70	Involved in defense against prolonged hypoglycemia, not critical
Symptoms	50-55	Prompt behavioral defense against hypoglycemia (food ingestion)
↓ Cognition	<50	(Compromises behavioral defense against hypoglycemia)

Whipple's triad

1) Symptoms, signs, or both consistent with hypoglycemia
2) Low plasma glucose concentration
3) Resolution of those symptoms or signs after the plasma glucose concentration is raised

Non-Diabetes : plasma glucose < 55 mg/dl

Diabetes: plasma glucose < 70 mg/dl

Journal of Clinical Endocrinology & Metabolism, March 2009, 94(3): 709-728

Clinical Manifestations

Neurogenic (or autonomic) symptoms

- CNS-mediated sympathoadrenal discharge triggered by hypoglycemia

- Adrenergic symptoms : palpitations, tremor, and anxiety
- Cholinergic symptoms : sweating, hunger, and paresthesias

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Clinical Manifestations

Neuroglycopenic symptoms

- Direct result of central nervous system (CNS) glucose deprivation

- Behavioral changes, confusion, fatigue, seizure, loss of consciousness, and, if hypoglycemia is severe and prolonged, death.

Harrison's Principles of Internal Medicine, 18th Edition

อาการของภาวะน้ำตาลต่ำในเลือด

สายตาพร่า

หัวใจเต้นเร็ว

เหงื่อออกมาก

ตัวสั่น

ฉุนเฉียวง่าย

ปวดหัว

เวียนศีรษะ

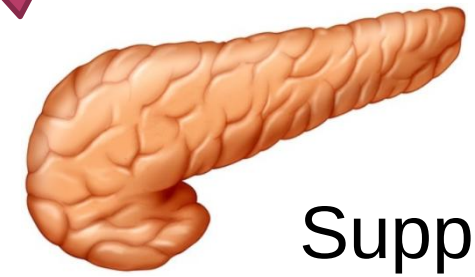
หิวบ่อย

อ่อนเพลีย

กังวล

Normal Physiology

Plasma glucose
< 55 mg/dl



Suppress
Insulin

- Plasma insulin < 3 µU/ml
- C-peptide < 0.6 ng/ml
- Proinsulin < 5.0 pmol/liter

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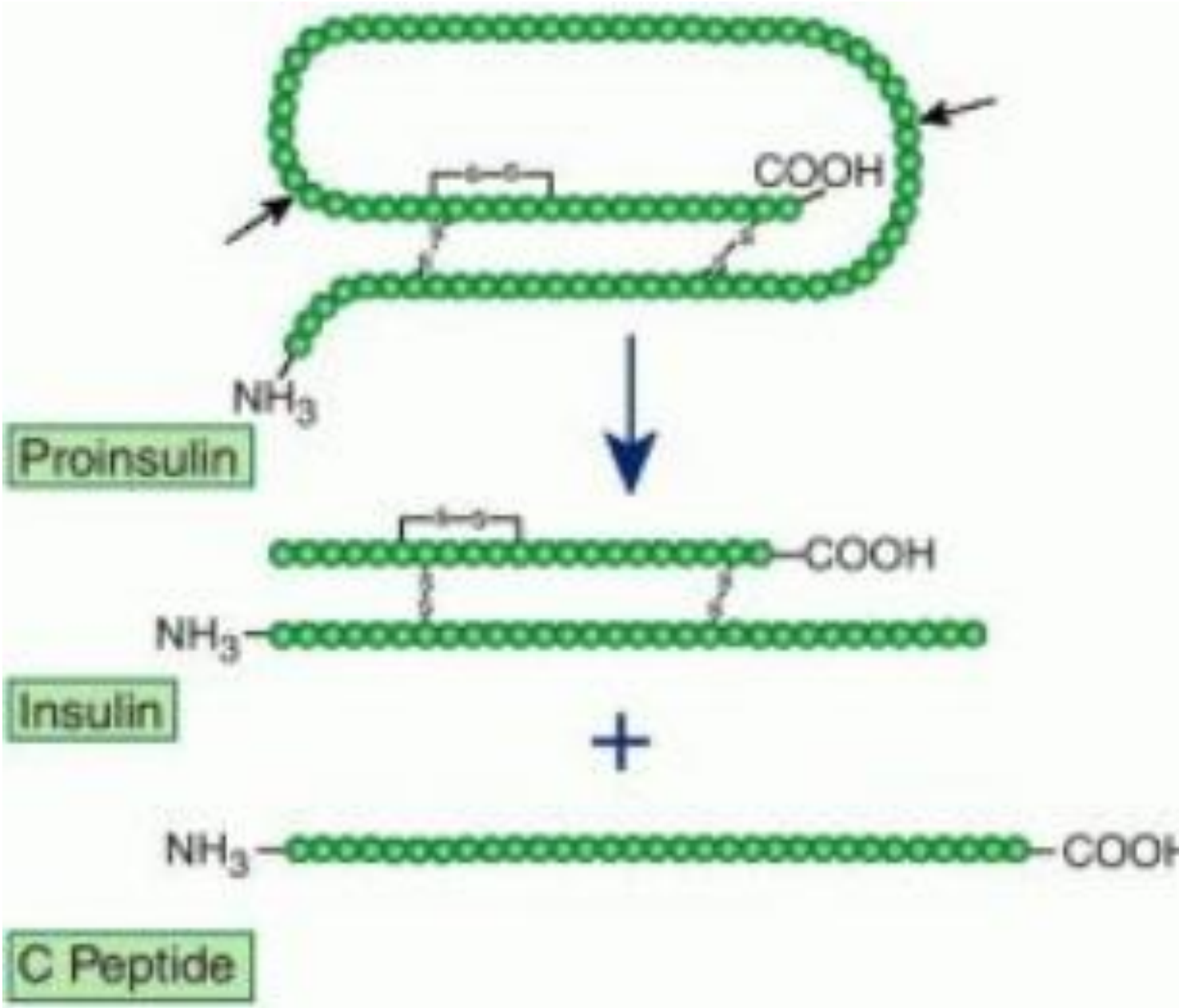
COOH
NH3
Proinsulin
COOH
NH3
Insulin
+
NH3
COOH
C Peptide

HYPOGLYCEMIA IN DIABETES MELLITUS

HYPOGLYCEMIA IN DIABETES MELLITUS

- Suggest that persons with diabetes become concerned about the possibility of developing hypoglycemia when the self-monitored blood glucose concentration is falling rapidly or is no greater than 70 mg/dl (2 | ⊕○○○)

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Risk factors for hypoglycemia in diabetes

(1) Insulin excess (insulin or insulin secretagogue)

: doses are excessive, ill-timed, or the wrong type

(2) Reduced influx of exogenous glucose

e.g. during an overnight fast, missed meals or snacks

(3) Increased insulin-independent glucose utilization

e.g. during exercise

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Risk factors for hypoglycemia in diabetes

(4) Increase sensitivity to insulin

e.g. improved glycemic control, late after exercise, or with increased fitness or weight loss

(5) Reduced endogenous glucose production

e.g. following alcohol ingestion

(6) Reduced insulin clearance; e.g. renal failure

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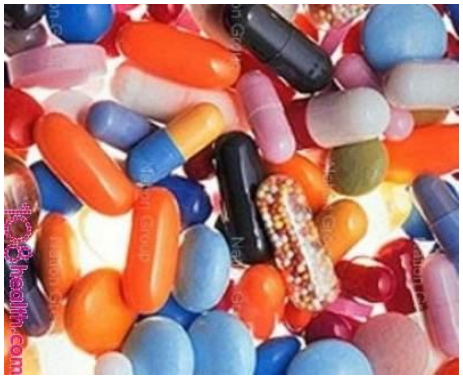
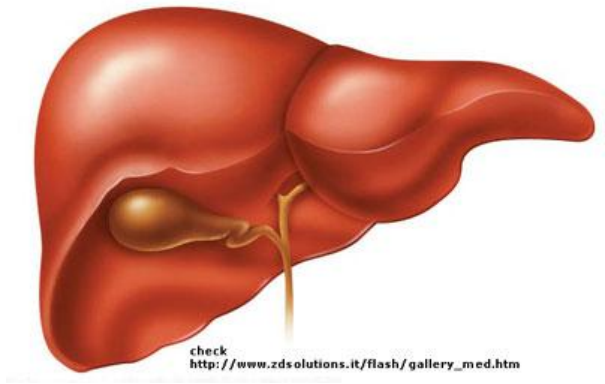
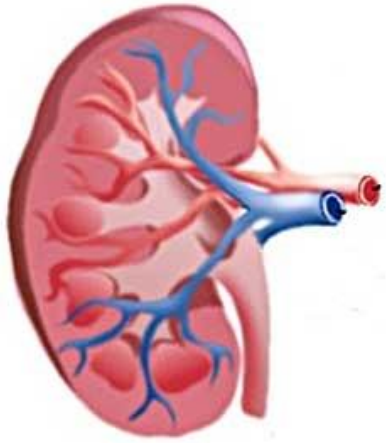
Risk factors for hypoglycemia in diabetes







HYPOGLYCEMIA IN NON- DIABETES

Causes of Hypoglycemia in Adults

Ill or medicated individual

1. Drugs

2. Critical illness

- Hepatic, renal or cardiac failure
- Sepsis
- Inanition

3. Hormone deficiency

- Cortisol
- Glucagon and epinephrine (in insulin-deficient diabetes)

4. **Non–islet cell tumor**

Seemingly well individual

1. Endogenous hyperinsulinism

- **Insulinoma**
- **Functional beta-cell disorders (nesidioblastosis)**
  - Noninsulinoma pancreatogenous hypoglycemia
  - Post–gastric bypass hypoglycemia
- **Insulin autoimmune hypoglycemia**
  - Antibody to insulin
  - Antibody to insulin receptor
- **Insulin secretagogue**

2. Accidental, surreptitious or malicious hypoglycemia

Journal of Clinical Endocrinology & Metabolism, March 2009, 94(3): 709-728

Drugs

- Insulin and insulin secretagogues suppress glucose production and stimulate glucose utilization

- Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia

Journal of Clinical Endocrinology & Metabolism, March 2009, 94(3): 709-728

Moderate evidence

Low evidence

Very low evidence

TABLE 2. Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia (24)

Moderate quality of evidence (⊕⊕⊕◯)
- Cibenzoline
- Gatifloxacin
- Pentamidine
- Quinine
- Indomethacin
- Glucagon (during endoscopy)

Low quality of evidence (⊕⊕◯◯)
- Chloroquineoxaline sulfonamide
- Artesunate/artemisin/artemether
- IGF-I
- Lithium
- Propoxyphene/dextropropoxyphene

Very low quality of evidence (⊕◯◯◯)
- Drugs with >25 cases of hypoglycemia identified
  - Angiotensin converting enzyme inhibitors
  - Angiotensin receptor antagonists
  - β-Adrenergic receptor antagonists
  - Levofloxacin
  - Mifepristone
  - Disopyramide
  - Trimethoprim-sulfamethoxazole
  - Heparin
  - 6-Mercaptopurine
- Drugs with <25 cases of hypoglycemia identified (see Ref. 24)

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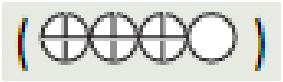
Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia

Moderate quality of evidence 

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- Quinine
- Indomethacin
- Glucagon (during endoscopy)

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Ethanol induced hypoglycemia

- Ethanol blocks gluconeogenesis but not glycogenolysis

Setting 1

- Typically occurs after a several-day ethanol binge during person eats little food, causing glycogen depletion

Setting 2

- Insulin-treated diabetes
  - Gluconeogenesis becomes the predominant route of glucose production during prolonged hypoglycemia
  - Alcohol can contribute to the progression of hypoglycemia

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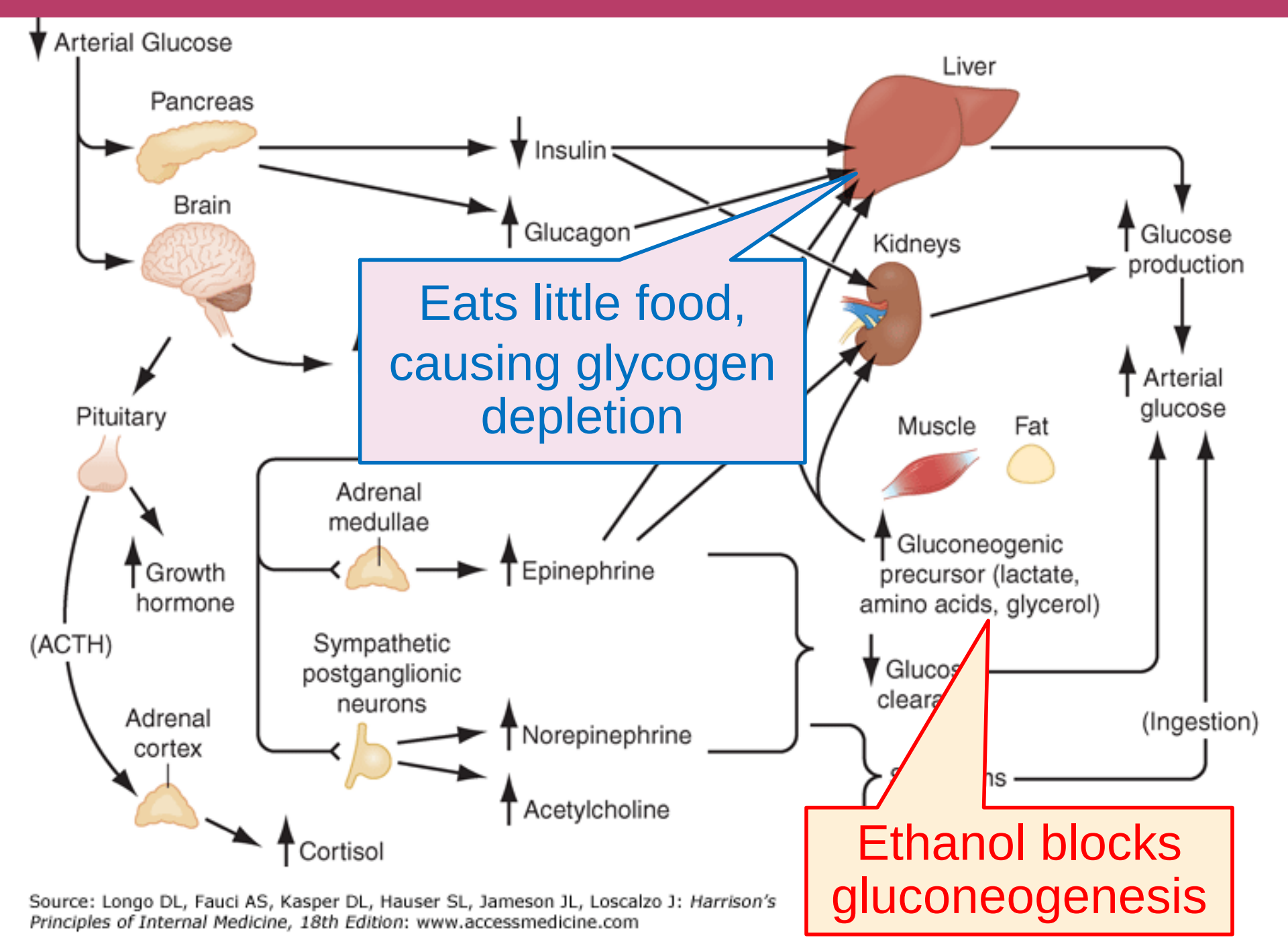

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Critical Illness

- Drugs
- Hepatic failure
- Renal failure
- Cardiac failure
- Sepsis
- Inanition (starvation)

Critical Illness

Hepatic failure

- Rapid & extensive hepatic destruction (e.g. toxic hepatitis) causes fasting hypoglycemia
- Liver is the major site of endogenous glucose production

Renal failure

- Kidneys are a source of glucose production
- Also caused by the reduced clearance of insulin and reduced mobilization of gluconeogenic precursors

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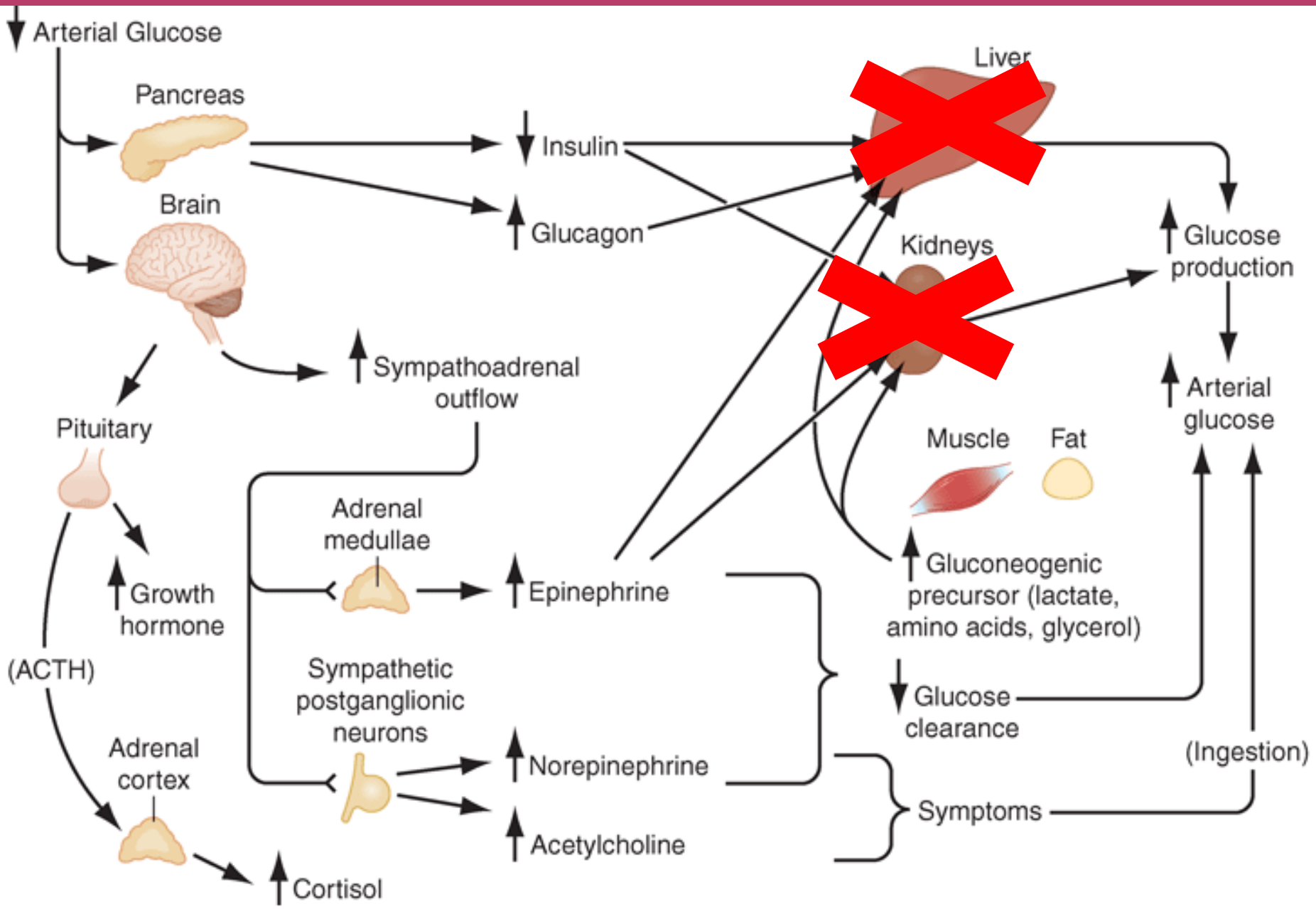

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Critical Illness

Cardiac failure

- Mechanism of hypoglycemia in patients with cardiac failure is unknown.
- It may involve hepatic congestion and hypoxia

Sepsis

- Increased glucose utilization is induced by cytokine
- Cytokine-induced inhibition of gluconeogenesis in the setting of nutritional glycogen depletion, in combination with hepatic and renal hypoperfusion, may also contribute to hypoglycemia

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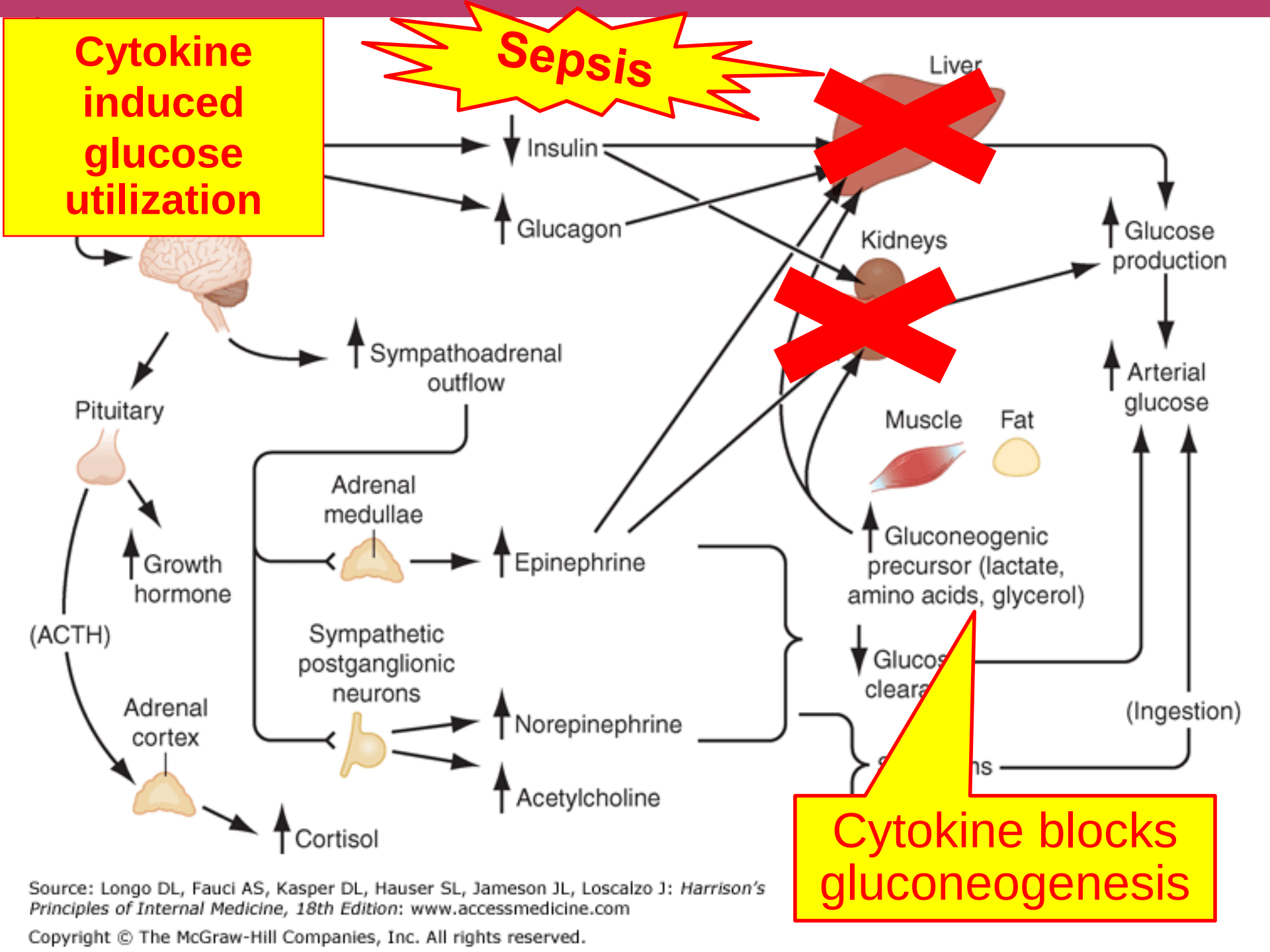

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Critical Illness

Starvation

- Loss of whole-body fat stores and subsequent depletion of gluconeogenic precursors (e.g., amino acids), necessitating increased glucose utilization

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Critical Illness

- Drugs
- Hepatic failure
- Renal failure
- Cardiac failure
- Sepsis
- Inanition (starvation)

Found in → Rapid & extensive hepatic destruction

Decrease glucose production
And reduced clearance of insulin

Unknown mechanism

Increased glucose utilization

Depletion of fat stores
gluconeogenic precursors

Hormone Deficiencies

- **Cortisol and Growth hormone** : Involved in defense against prolonged hypoglycemia, **not critical**

Cortisol

- Occur with prolonged fasting in patients with primary adrenocortical failure (Addison's disease) or hypopituitarism
- Cortisol deficiency : impaired gluconeogenesis and low gluconeogenic precursors, in setting of glycogen depletion

- Growth hormone deficiency can cause hypoglycemia in young children

Growth hormone

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Non–Beta-Cell Tumors

- Feature >>> Fasting hypoglycemia
- Occurs occasionally in large mesenchymal/epithelial tumors
  - Hepatomas, adrenocortical carcinomas, carcinoids

- Glucose kinetic patterns resemble **“hyperinsulinism”**
- Overproduction of an incompletely processed form of **insulin-like growth factor II ("big IGF-II")**
  - Insulin secretion is suppressed appropriately during hypoglycemia

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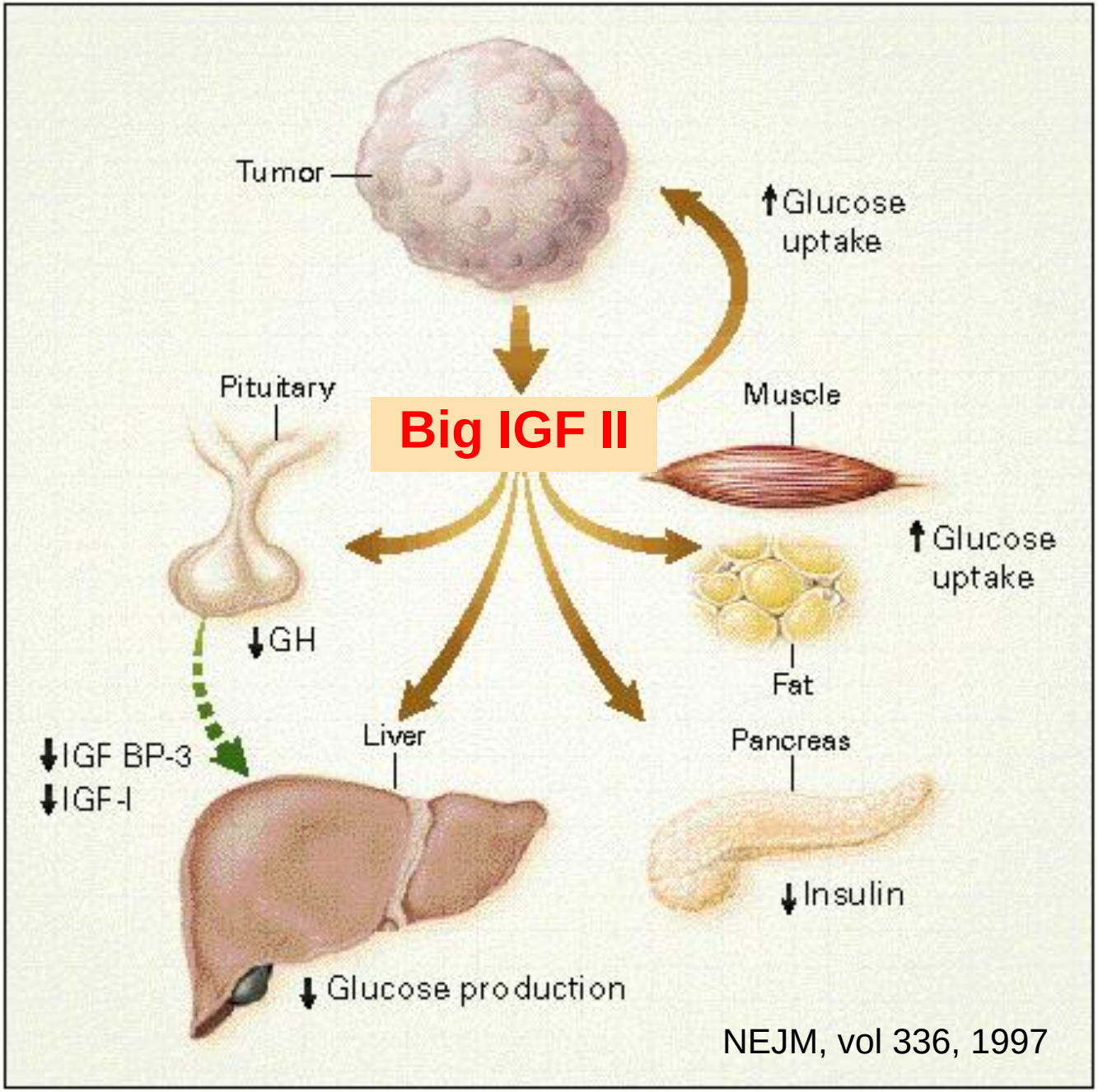
Tumor
↑Glucose uptake
Big IGF II
Pituitary
Muscle
↑Glucose uptake
↓GH
Fat
↓IGF BP-3
↓IGF-I
Liver
Pancreas
↓Insulin
↓Glucose production
NEJM, vol 336, 1997

Endogenous Hyperinsulinism

(1) Primary beta-cell disorder,

-Typically a beta-cell tumor (insulinoma)

-Sometimes multiple insulinomas, or a functional beta-cell disorder with beta-cell hypertrophy or hyperplasia

(2) Antibody to insulin or to the insulin receptor

(3) Beta-cell secretagogue : sulfonylurea

(4) Ectopic insulin → Very rare

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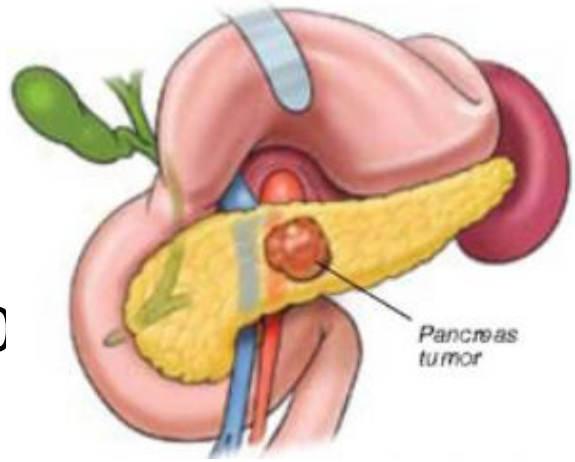
Insulinomas



- Uncommon
- Incidence is estimated to be 1 in 250,000
- >90% are benign
- Potentially fatal hypoglycemia
- Median age at presentation is 50 years in sporadic cases
- >99% of insulinomas are within the substance of the pancreas and usually small (90% <2.0 cm)
- CT or MRI detects ~ 70–80% of insulinomas
- Endoscopic ultrasound has a sensitivity ~90%

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Diagnostic strategy during hypoglycemia

- Plasma glucose
- Insulin
- C-peptide
- Proinsulin

Document Whipple's triad

- Symptoms & signs with hypoglycemia
- Low plasma glucose concentration
- Resolution of symptoms or signs after plasma glucose concentration is raised

- ß-hydroxybutyrate concentrations
- Screen for circulating oral hypoglycemic agents

Cortisol

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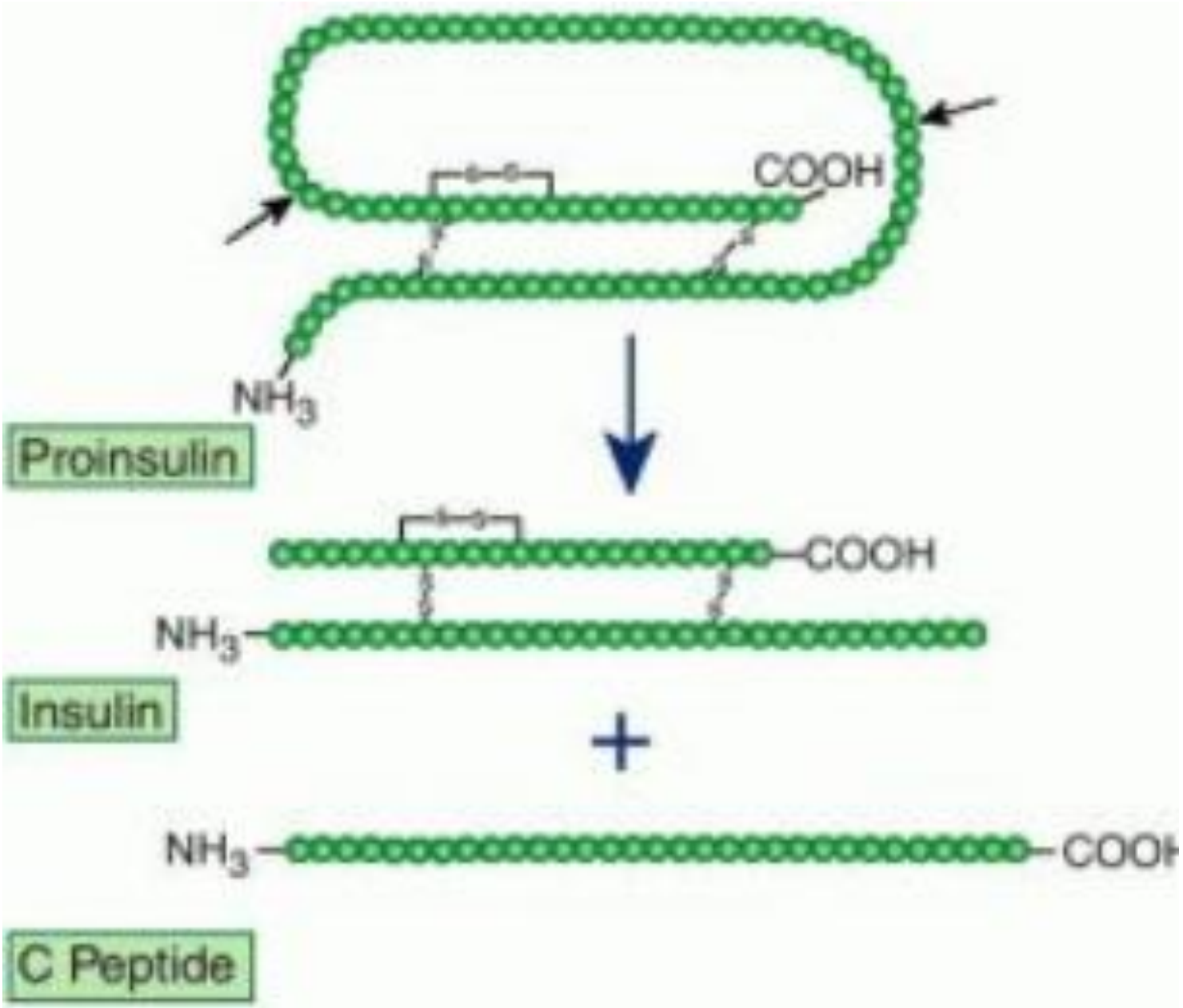
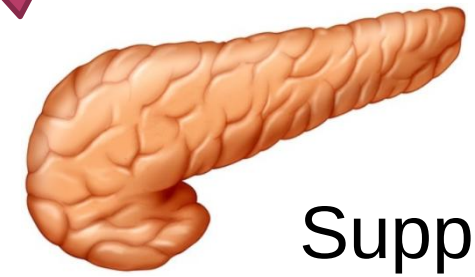

COOH
NH3
Proinsulin
COOH
NH3
Insulin
+
NH3
COOH
C Peptide

Normal Physiology

Plasma glucose
< 55 mg/dl



Suppress
Insulin

- Plasma insulin < 3 µU/ml
- C-peptide < 0.6 ng/ml
- Proinsulin < 5.0 pmol/liter

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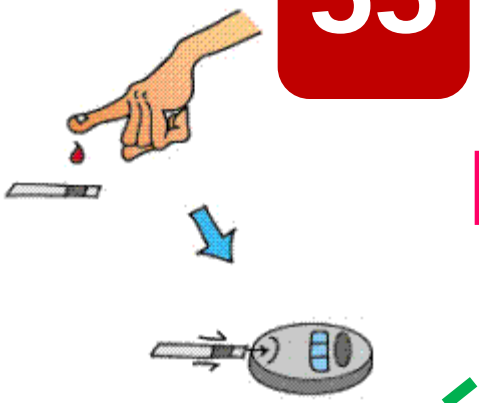
Diagnostic strategy and treatment during hypoglycemia in non DM

Whipple's triad



Plasma glucose

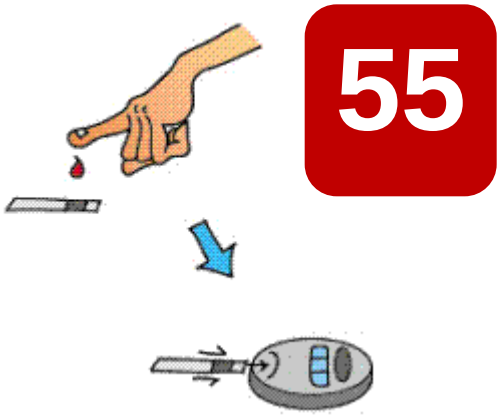
Clot blood

Treat

Plasma glucose <55 mg/dL

- **Insulin**
- **C-peptide**
- **Cortisol**
- **Other**

Diagnostic strategy and treatment during hypoglycemia in non DM



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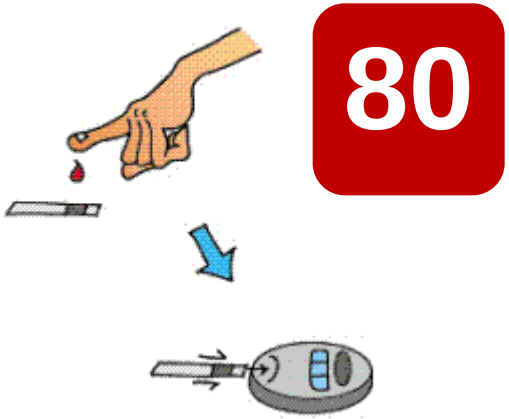

Symptoms, signs, or both	Glucose (mg/dl)	Insulin (μU/ml	C-peptide (nmol/liter)	Proinsulin (pmol/liter)	β-Hydroxy -butyrate (mmol/liter)	Glucose increase after glucagon (mg/dl)	Circulating oral hypo-glycemic	Antibody to insulin	Diagnostic inter-pretation
No	< 55	< 3	< 0.2	< 5	> 2.7	< 25	No	No	Normal
Yes	< 55	» 3	< 0.2	< 5	≤ 2.7	> 25	No	Neg (Pos)	Exogenous insulin
Yes	< 55	≥ 3	≥ 0.2	≥ 5	≤ 2.7	> 25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	< 55	≥ 3	≥ 0.2	≥ 5	≤ 2.7	> 25	Yes	Neg	Oral hypo-glycemic agent
Yes	< 55	» 3	» 0.2[a]	» 5[a]	≤ 2.7	> 25	No	Pos	Insulin autoimmune
Yes	< 55	< 3	< 0.2	< 5	≤ 2.7	> 25	No	Neg	IGF[b]
Yes	< 55	< 3	< 0.2	< 5	> 2.7	< 25	No	Neg	Not insulin (or IGF)-mediated

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Urgent Treatment

If patient is able to take oral treatment

- Oral treatment with glucose tablets or glucose-containing fluids, candy, or food is appropriate
- Initial dose is 20 g of glucose

If patient is unable to take oral treatment

- Intravenous glucose (25 g) should be given and followed by a glucose infusion guided by serial plasma glucose

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Prevention of Recurrent Hypoglycemia

- Prevention of recurrent hypoglycemia requires an understanding of the hypoglycemic mechanism.
- Offending drugs can be discontinued or their doses reduced.
- Hypoglycemia caused by a sulfonylurea can persist for hours, or even days.

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Prevention of Recurrent Hypoglycemia

- Cortisol and growth hormone can be replaced if they are deficient.
- Surgical resection of an insulinoma is curative
- Medical therapy with **diazoxide or octreotide** can be used if resection is not possible and in patients with a nontumor beta-cell disorder.

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Prevention of Recurrent Hypoglycemia

- Partial pancreatectomy may be necessary in the latter patients.
- Failing these treatments, frequent feedings and avoidance of fasting may be required.
- Administration of uncooked cornstarch at bedtime or even an overnight intragastric infusion of glucose may be necessary in some patients.

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