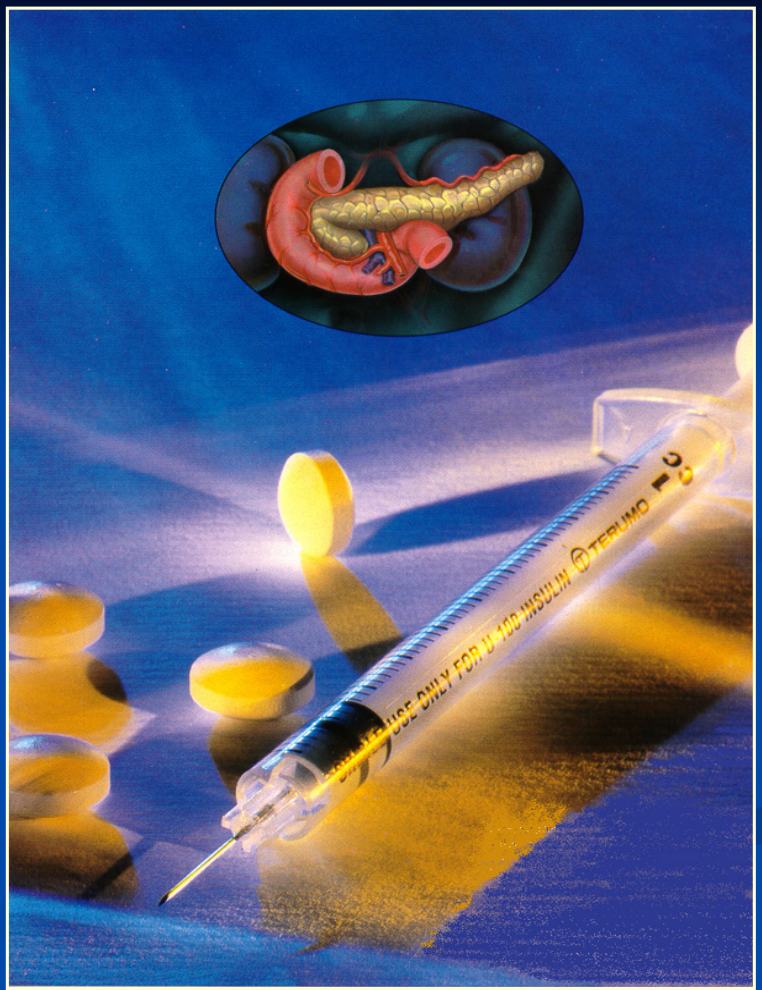
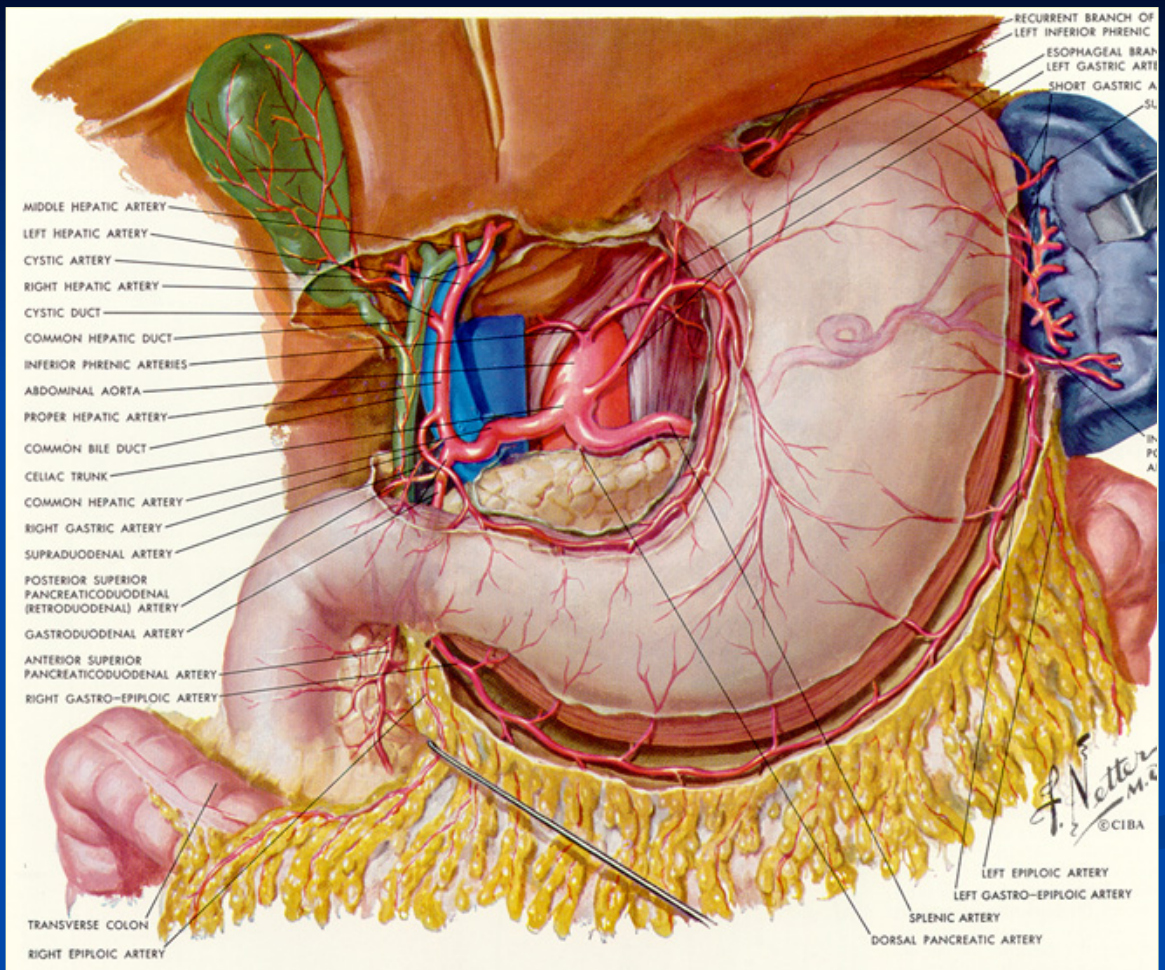
Management & Treatment of Diabetes Mellitus

Southern California University of Health Sciences



ANATOMY


RECURRENT BRANCH OF
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COMMON HEPATIC DUCT
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COMMON BILE DUCT
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TRANSVERSE COLON
RIGHT EPIPLOIC ARTERY
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LEFT GASTRO–EPIPLOIC ARTERY
SPLENIC ARTERY
DORSAL PANCREATIC ARTERY
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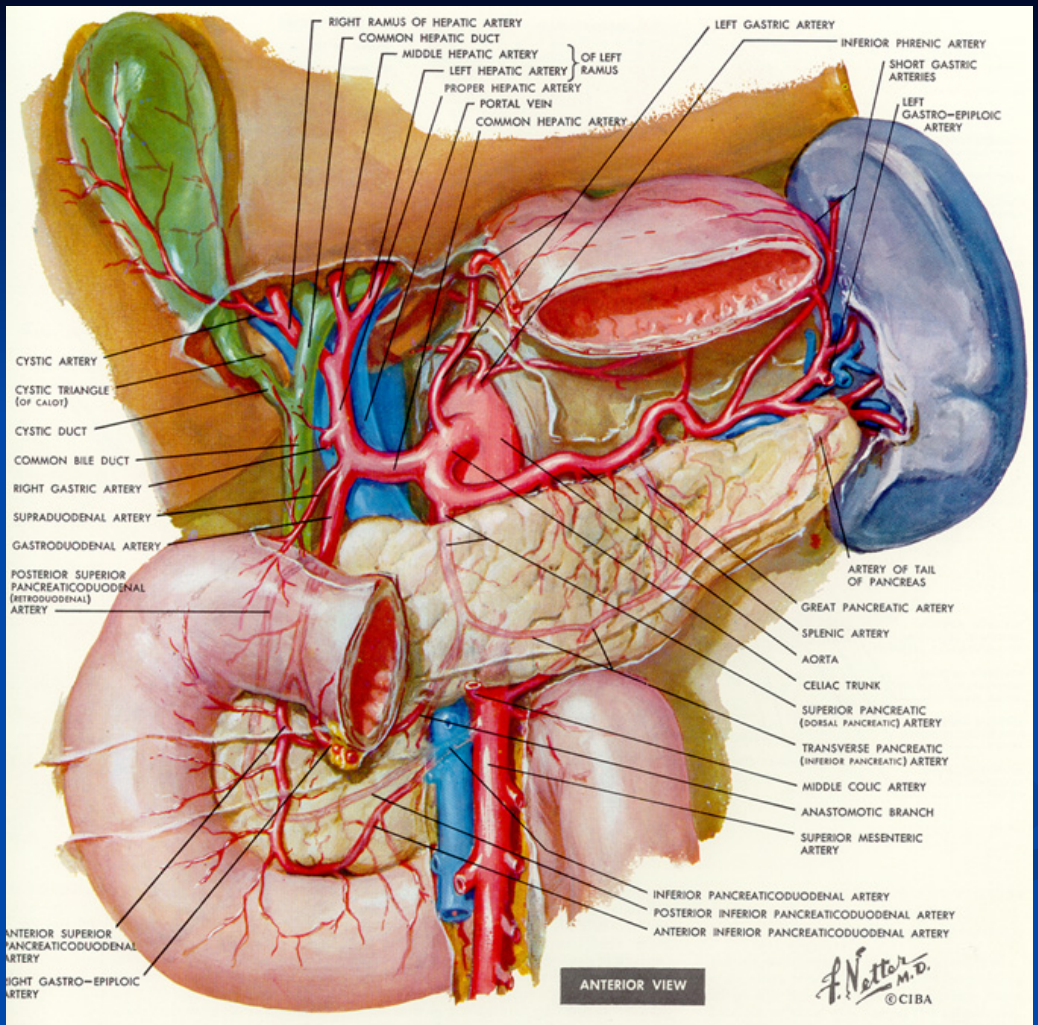
ANATOMY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COMMON HEPATIC ARTERY
LEFT GASTRIC ARTERY
INFERIOR PHRENIC ARTERY
SHORT GASTRIC ARTERIES
LEFT GASTRO-EPIPLOIC ARTERY
CYSTIC ARTERY
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COMMON BILE DUCT
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CELIAC TRUNK
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POSTERIOR INFERIOR PANCREATICODUODENAL ARTERY
ANTERIOR INFERIOR PANCREATICODUODENAL ARTERY
ANTERIOR SUPERIOR PANCREATICODUODENAL ARTERY
RIGHT GASTRO-EPIPLOIC ARTERY
ANTERIOR VIEW
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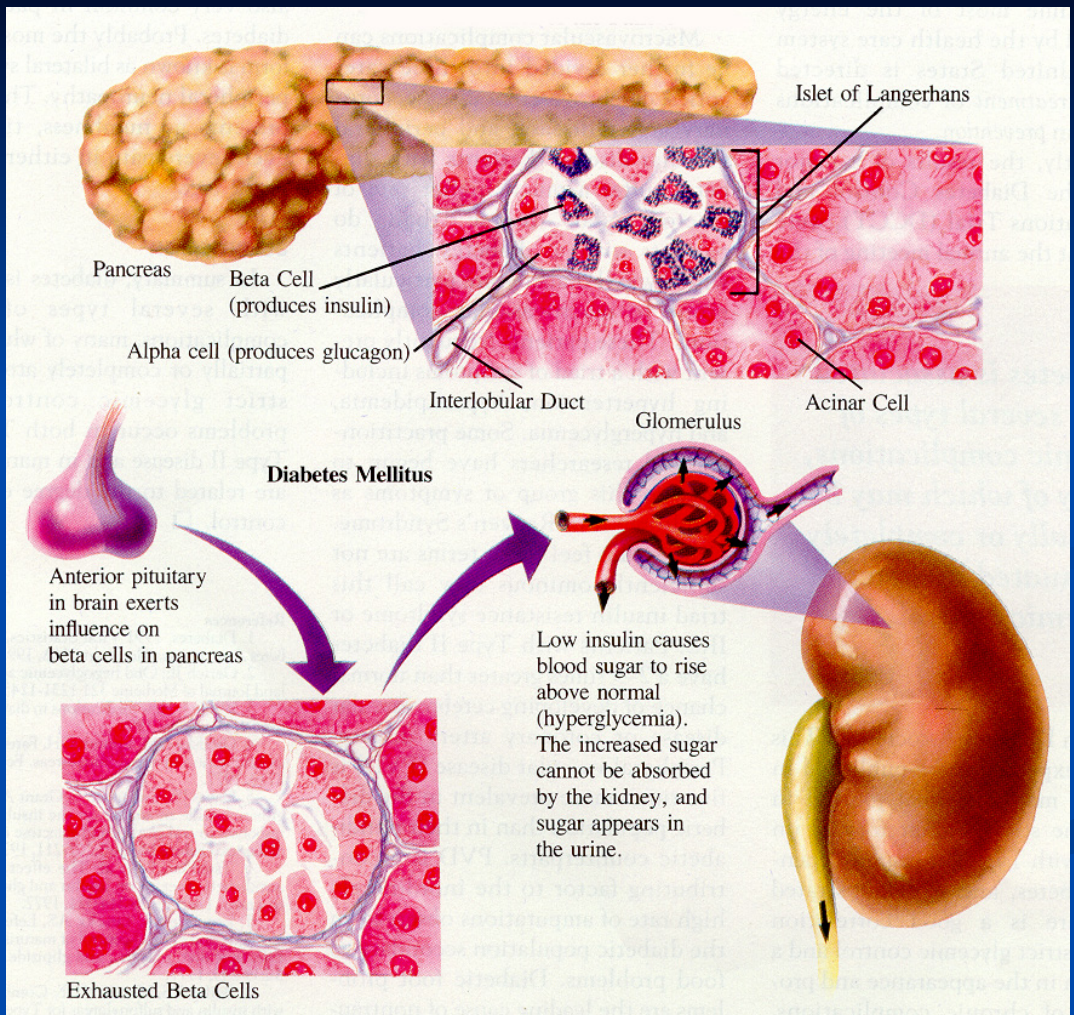
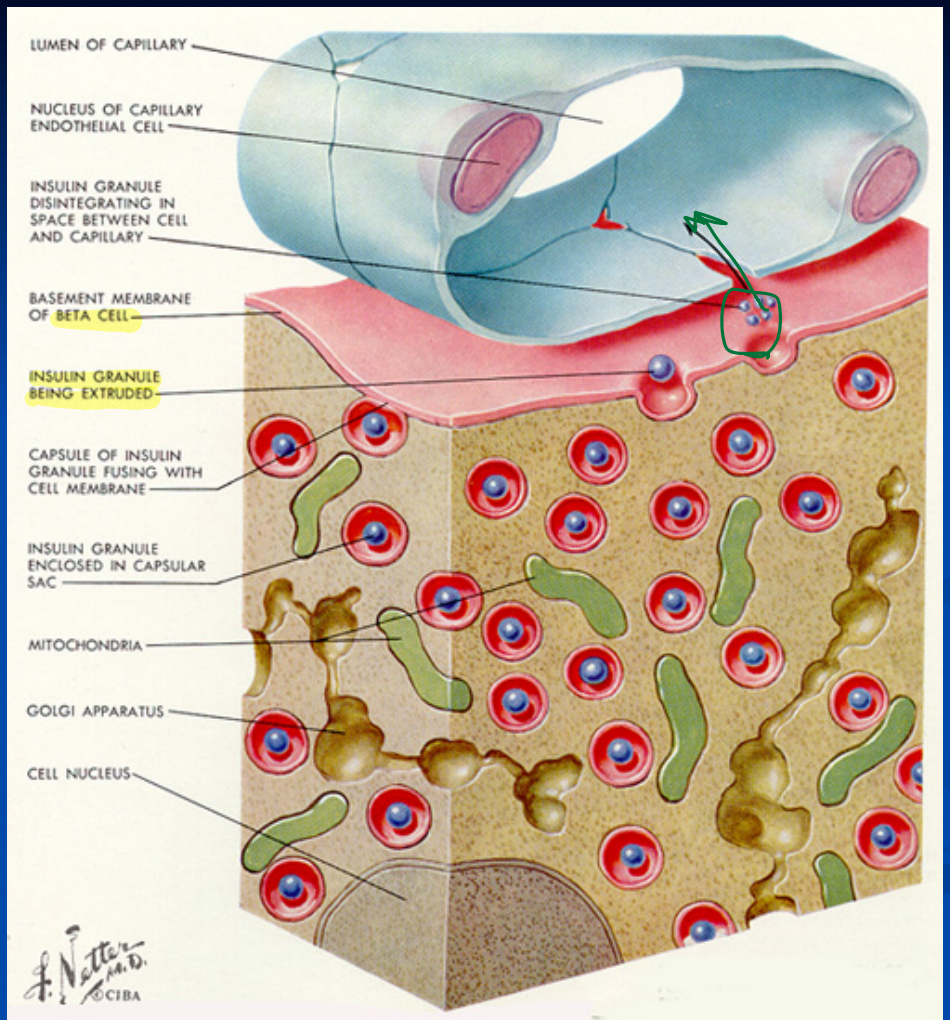
PHYSIOLOGY


Islet of Langerhans
Pancreas
Beta Cell
(produces insulin)
Alpha cell (produces glucagon)
Interlobular Duct
Acinar Cell
Glomerulus
Diabetes Mellitus
Anterior pituitary in brain exerts influence on beta cells in pancreas
Low insulin causes blood sugar to rise above normal (hyperglycemia). The increased sugar cannot be absorbed by the kidney, and sugar appears in the urine.
Exhausted Beta Cells

PHYSIOLOGY


LUMEN OF CAPILLARY
NUCLEUS OF CAPILLARY ENDOTHELIAL CELL
INSULIN GRANULE DISINTEGRATING IN SPACE BETWEEN CELL AND CAPILLARY
BASEMENT MEMBRANE OF BETA CELL
INSULIN GRANULE BEING EXTRUDED
CAPSULE OF INSULIN GRANULE FUSING WITH CELL MEMBRANE
INSULIN GRANULE ENCLOSED IN CAPSULAR SAC
MITOCHONDRIA
GOLGI APPARATUS
CELL NUCLEUS
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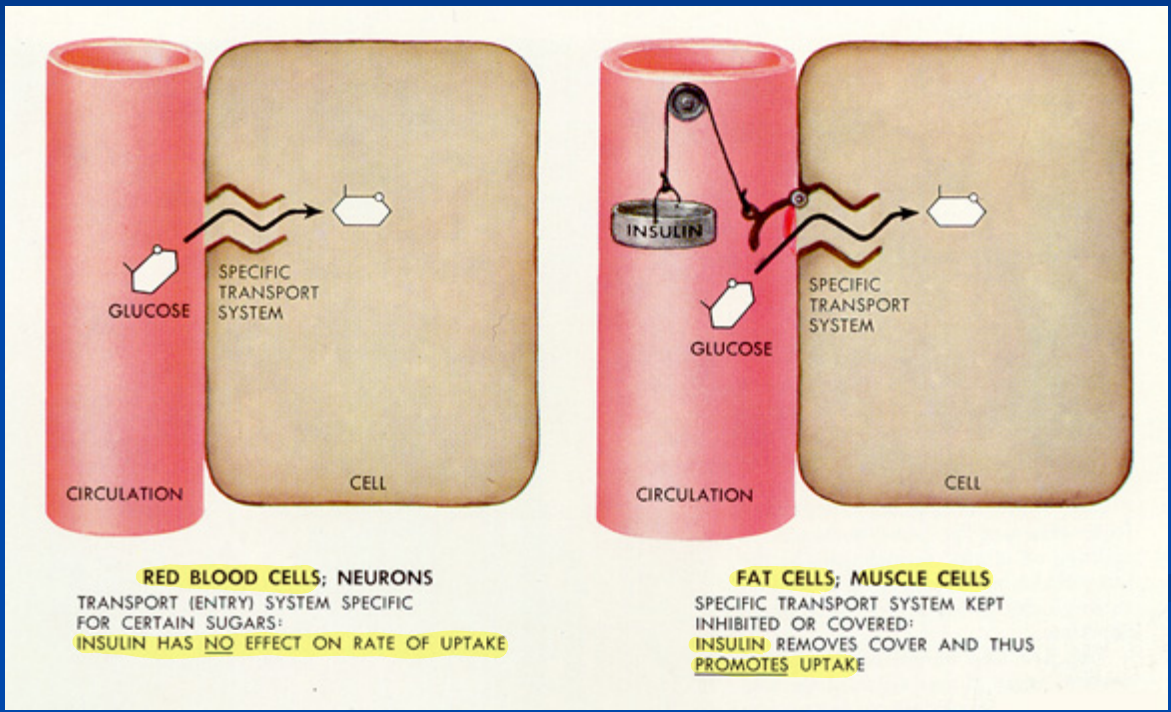
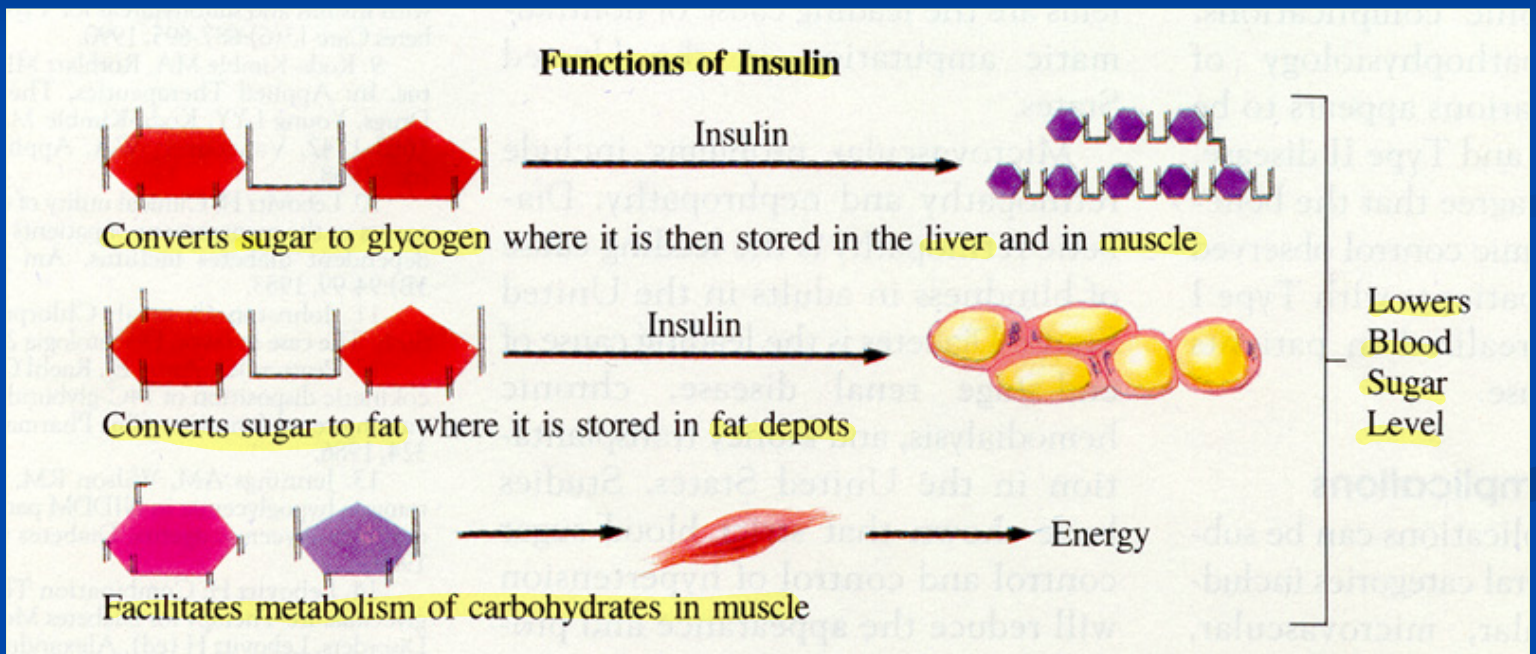
FUNCTION OF INSULIN



RED BLOOD CELLS; NEURONS
TRANSPORT (ENTRY) SYSTEM SPECIFIC FOR CERTAIN SUGARS:
INSULIN HAS NO EFFECT ON RATE OF UPTAKE

FAT CELLS; MUSCLE CELLS
SPECIFIC TRANSPORT SYSTEM KEPT INHIBITED OR COVERED:
INSULIN REMOVES COVER AND THUS PROMOTES UPTAKE

FUNCTION OF INSULIN



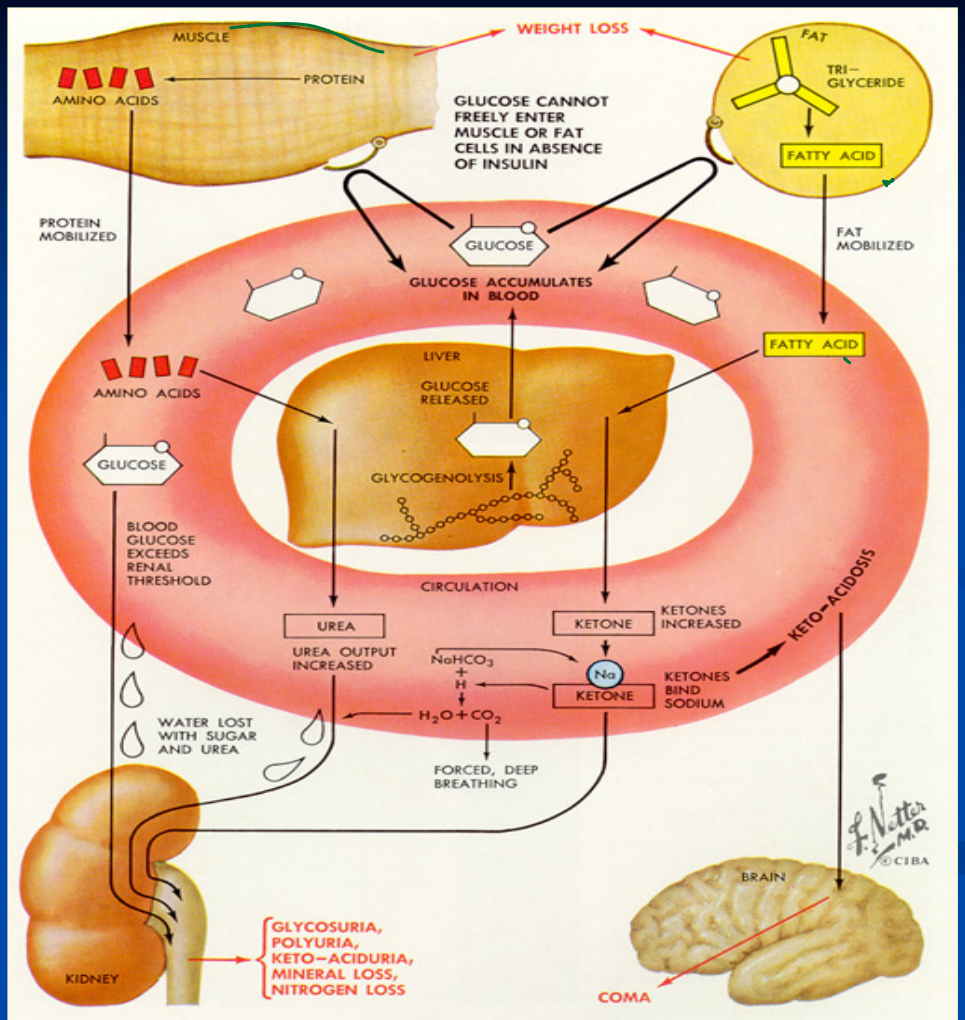
I. General Considerations

A. Type I ("Juvenile Onset" or IDDM)

- IDDM results from autoimmune destruction of beta cells
- inability to secrete insulin
- --> ketone formation --> DKA

Diabetic Ketoacidosis (DKA)

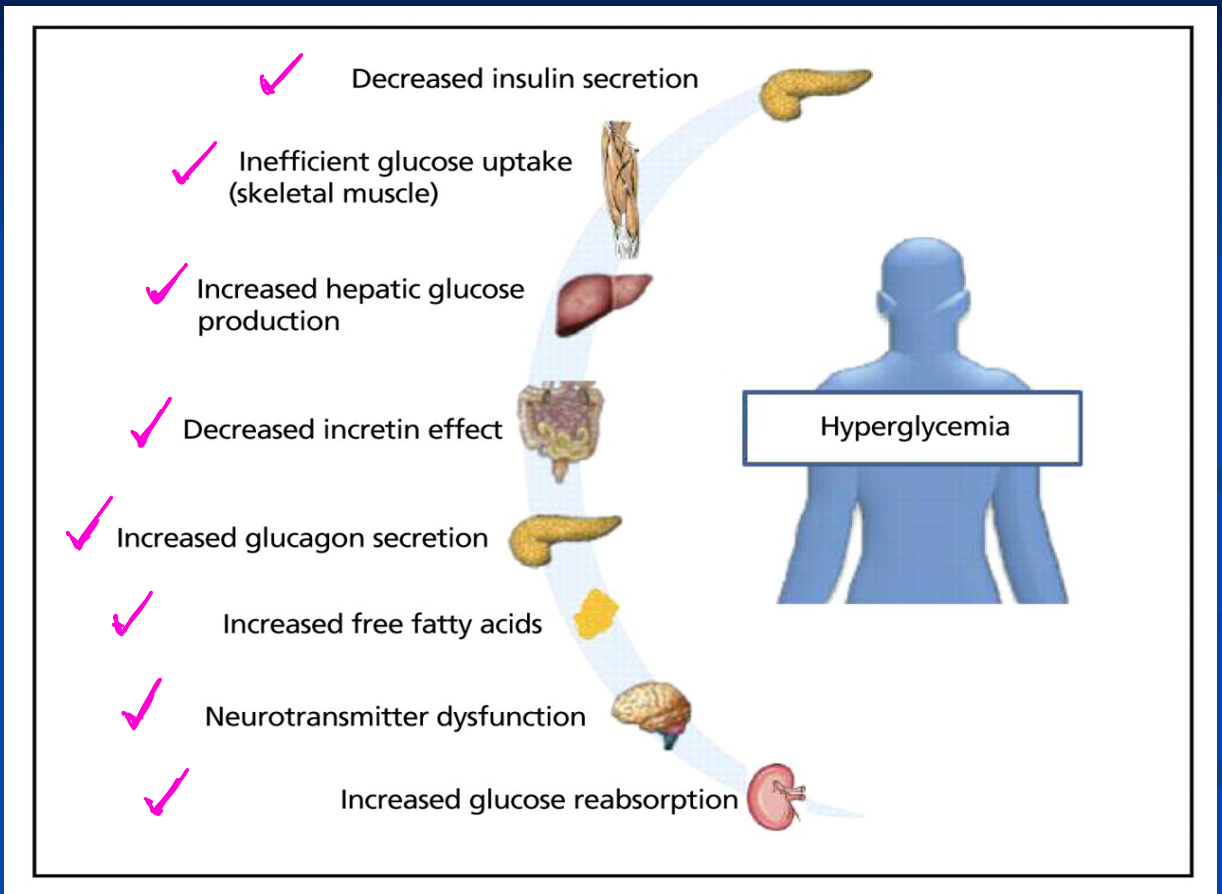
- ✓ Fatty acids are converted to glucose by the liver, releasing ketones into the bloodstream → DKA
- ✓ DKA is a life-threatening medical emergency



B. Type II ("Adult Onset" or NIDDM)

- NIDDM results from resistance to insulin and impaired response of beta cell to glucose ---> hyperglycemia
- sufficient endogenous insulin is usually present to prevent ketoacidosis

B. Type II DM (cont.) ✓ Pathogenesis of Type II DM



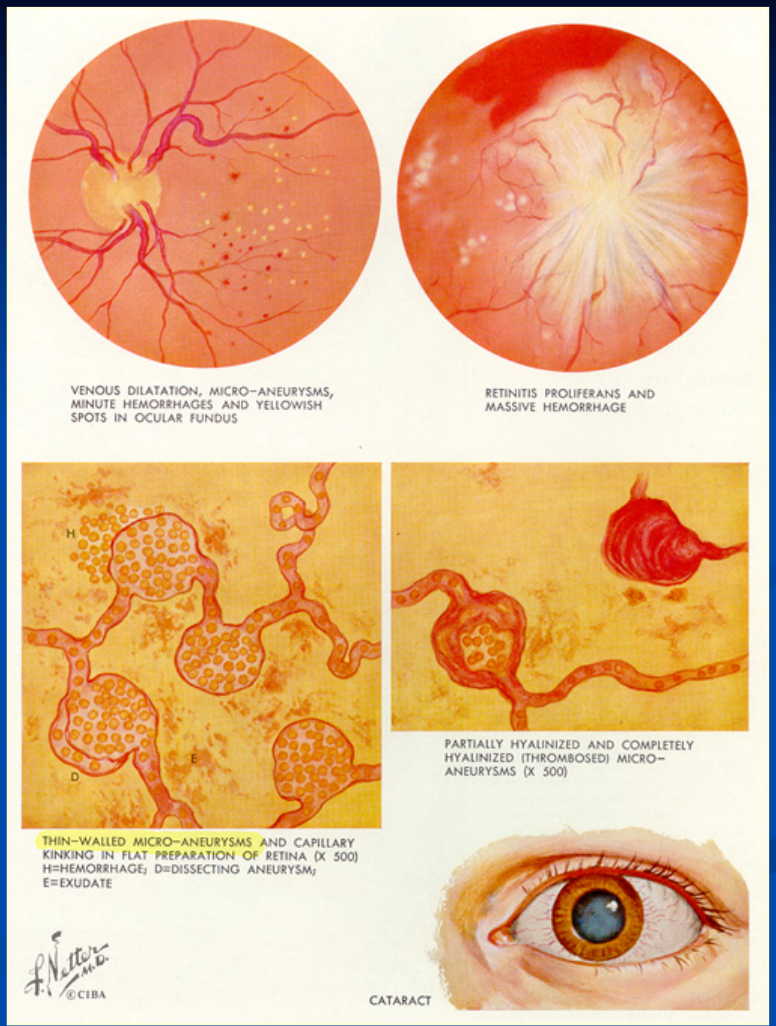
C. Complications of Diabetes

- polydipsia, polyuria, polyphagia, nocturia, hypoglycemia, fatigue, and blurred vision
- DKA --> Type I Diabetes
- Non-Ketotic coma --> Type II Diabetes

(2) Chronic Complications

(a) Microvascular

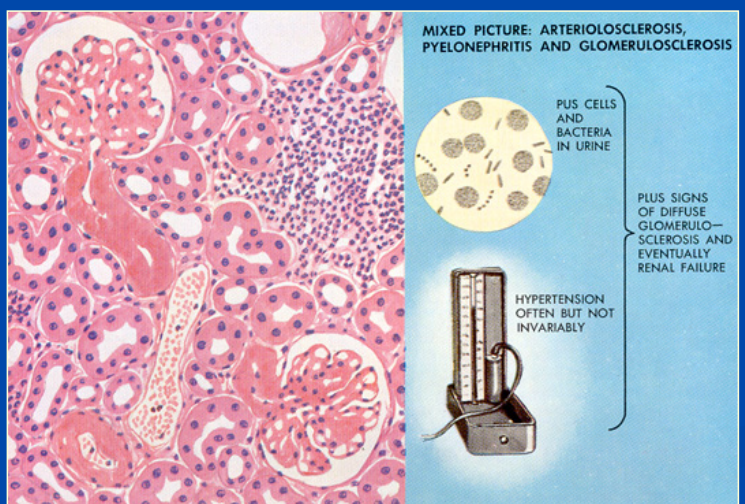
- diabetic retinopathy

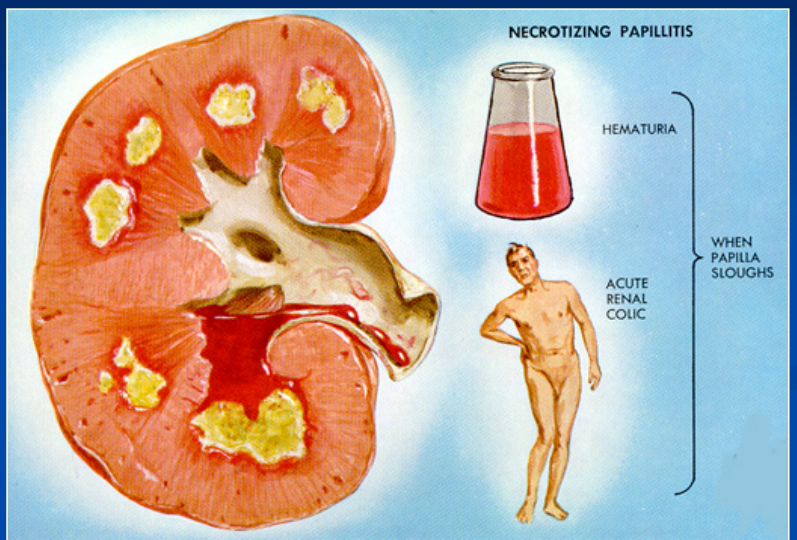


(2) Chronic Complications

b. kidney disease

- glomerulosclerosis
- pyelonephritis

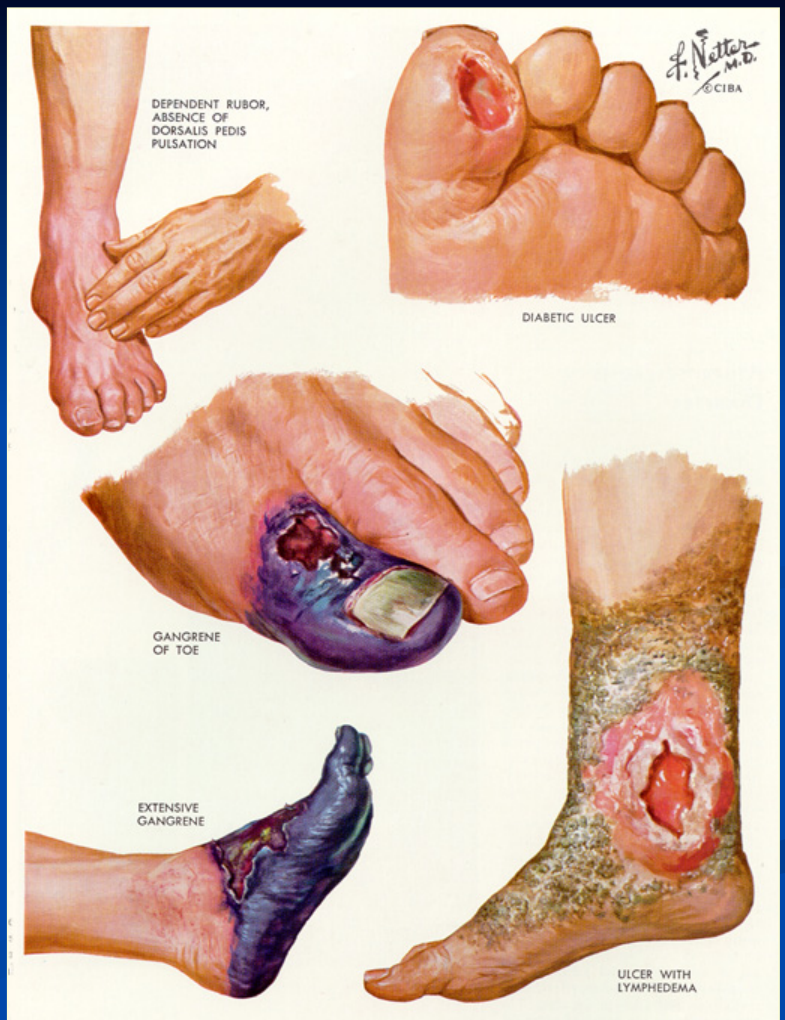




- necrotizing papillitus

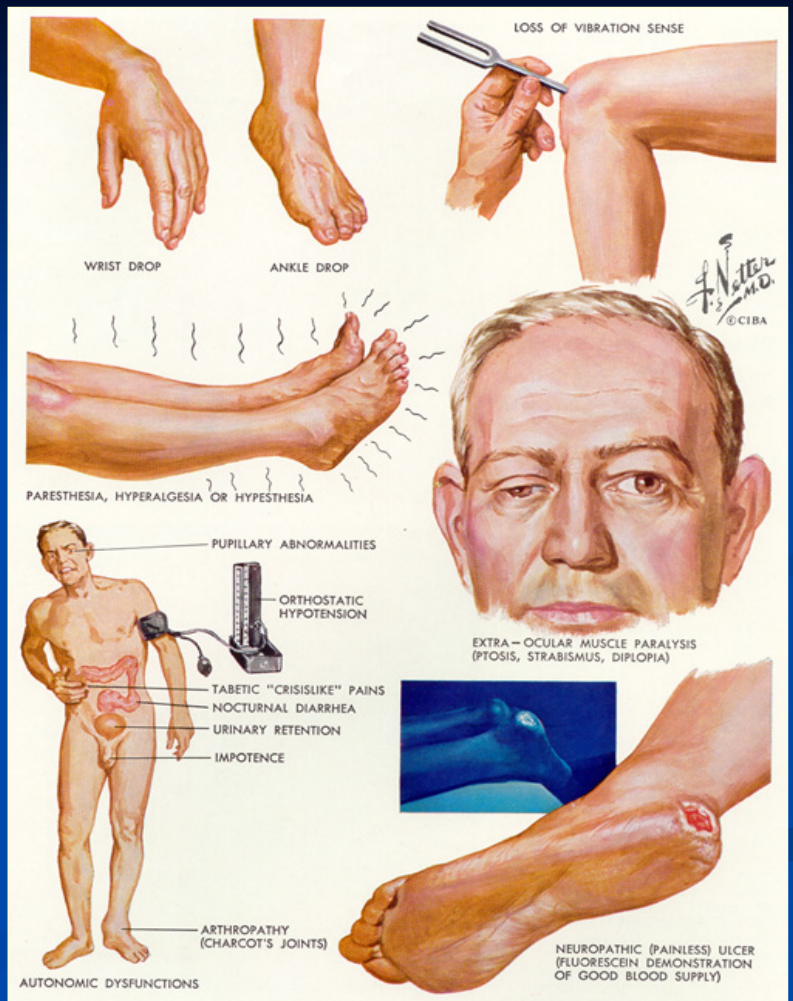
(b) Macrovascular

- cerebrovascular disease
- cardiovascular disease
- peripheral vascular disease



(c) Neuropathy

- orthostatic hypotension
- numbness and/or pain in extremities
- gastroparesis
- diabetic foot disease



III. Criteria for Diagnosis of PRE-DIABETES & DIABETES

Criteria for the Diagnosis of PREDIABETES
A1C ≥5.7%, but <6.5% **OR** Fasting plasma glucose ≥100 mg/dL (fasting is no food for at least 8 hours), but <126 mg/dL **OR** Two-hour plasma glucose ≥140 mg/dL during an oral glucose tolerance test, but <200 mg/dL
Criteria for the Diagnosis of DIABETES
A1C ≥6.5% **OR** Fasting plasma glucose ≥126 mg/dL (fasting is no food for at least 8 hours) **OR** Two-hour plasma glucose ≥200 mg/dL during an oral glucose tolerance test **OR** Symptomatic patients with a random plasma glucose ≥200 mg/dL

IV. Treatment of Diabetes

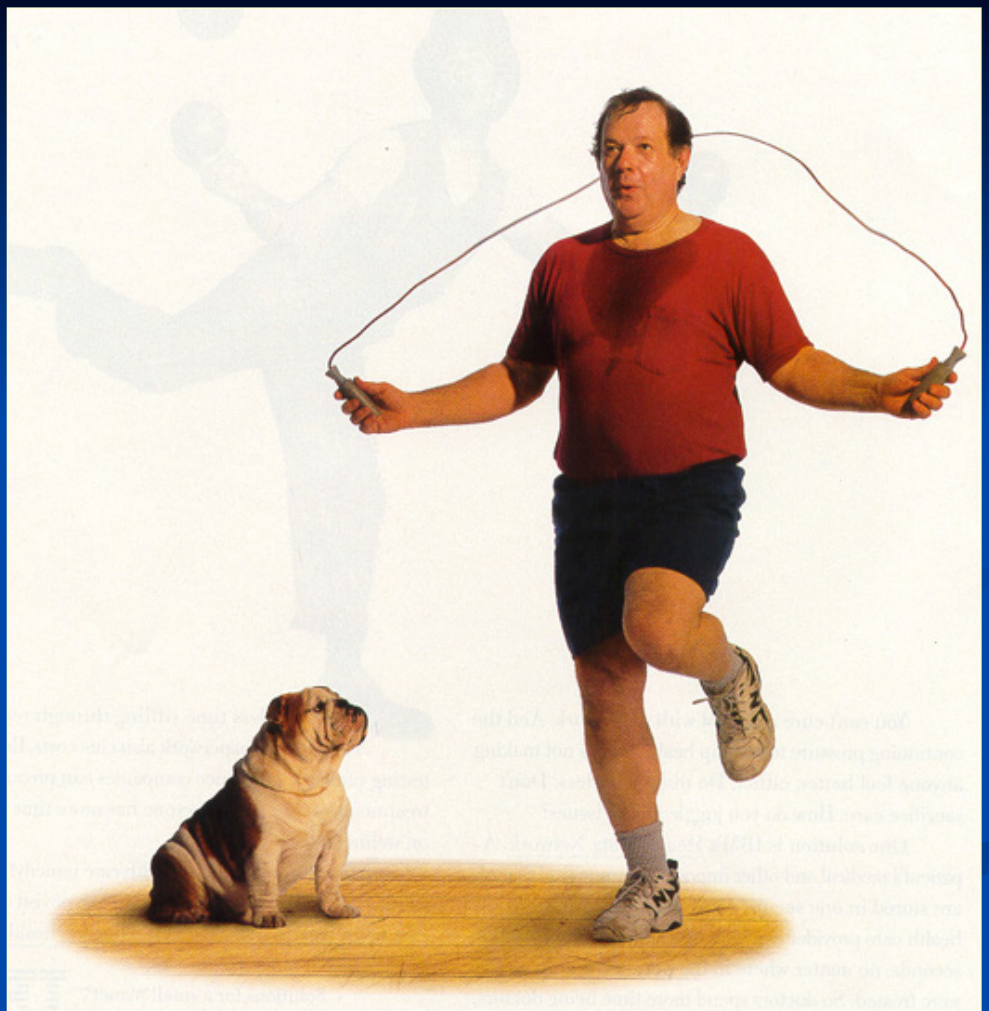
A. Lifestyle Modifications

(2) Nutrition

- timing of meals
- nutritional content of meals
- body weight

(2) Exercise

- increases utilization of glucose
- improves insulin utilization
- improves lipid profile



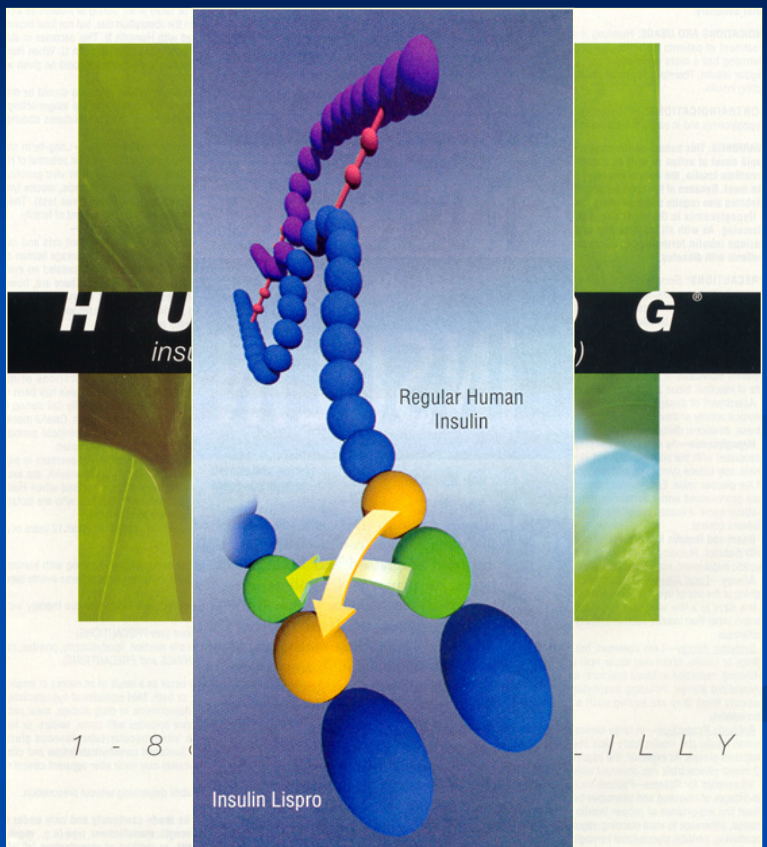
III. Pharmacologic Management of IDDM

A. Insulin Products

(1) Rapid-Acting Insulin

(a) Humalog (Lispro)

- onset: 10 - 15 min
- peak: 45 min - 1 hr
- duration: 2 - 4 hrs



(1) Short-Acting Insulin

Regular Insulin (Humulin R)

- onset: 30 - 60 min --> peak: 2 - 4 hrs
- duration: 5 - 7 hrs

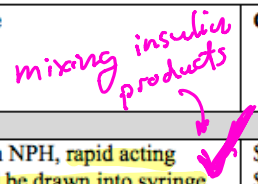
(2) Intermediate-Acting Insulin

NPH (Isophane)

- onset: 1 - 2 hrs --> peak: 6 - 14 hrs
- duration: 24+ hrs

Insulin Comparison Chart

Insulin Name	When does it start working? (onset)	When will the effect be the greatest? (peak)	How long will it lower blood glucose? (duration)	Notes for Use	Cost estimate
Rapid Acting					
Lispro (Humalog™)	<15 minutes	0.5-3 hours*	3-5 hours	If mixing with NPH, rapid acting insulin should be drawn into syringe first. Mixture should be given immediately to avoid effects on peak action.	$96 (10 ml vial) $183 (5x3 ml pen cartridges)
Aspart (Novolog™)	<15 minutes	0.5-3 hours*	3-5 hours		$102 (10 ml vial) $205 (5x3 ml pen cartridges)
Glulisine (Apidra™)	<15 minutes	0.5-3 hour*	3-5 hours		$96 (10 ml vial) $184 (5x3 ml pen cartridges
Short Acting					
Regular (Novolin R™ or Humulin R™)	0.5-1 hour	2-4 hours	4-8 hours	May be mixed with NPH in same syringe. Mixing order should be the clear regular drawn up first, then the cloudy NPH (ie "clear to cloudy").	$53 (10 ml vial Humulin or Novolin) $121 (5x3 ml Novolin pen cartridges) $89 (5x3 ml Innolet cartridges)
Intermediate Acting					
NPH (Novolin N™ or Humulin N™)	2-4 hours	4-10 hours	10-18 hours	Available as pen or in vial to be used with syringe.	$52 (10 ml vial Humulin or Novolin) $121 (5x3 ml pen cartridges) $91 (5x3 ml Innolet cartridges)
Long Acting					
Glargine (Lantus™)	4-6 hours	Same action throughout the day	24 hours	Do not mix with other insulins. Available as pen or in vial. Duration (clinical trial data): 6 hrs (0.1 U/kg), 12 hrs (0.2 U/kg),20 hrs (0.4 U/kg), 23 hrs (0.8 U/kg and 1.6 U/kg)	$97 (10 ml vial) $177 (5x3 ml Solostar pen cartridges)
Detemir (Levemir™)	2-3 hours	6-8 hours	Dose-dependent 5.7-23.2 hours		$95 (10 ml vial) $182 (5x3 ml pen cartridges)
Combinations					
Humulin or Novolin 70/30	0.5-1 hour	2-10 hours	10-18 hours	70% NPH +30% regular insulin. Insulin action includes 2 peaks (1 from each formulation).	$54 (10 ml vial) $135 (5x3 ml pen cartridges) $94 (5x3 ml Innolet cartridges)
Novolog Mix 70/30 Humalog Mix 75/25 or 50/50	<15 minutes	1-2 hours	10-18 hours	Novolog Mix: aspart protamine 70% + aspart 30% Humalog mix: 75/25=75% lispro protamine + 25% lispro 50/50=50% lispro protamine + 50% lispro Insulin action includes 2 peaks (1 from each formulation).	Humalog Mix 75/25: $102 (10 ml vial), $174 (5x3 ml pen cartridges)



C. Biochemical Indices of Metabolic Control

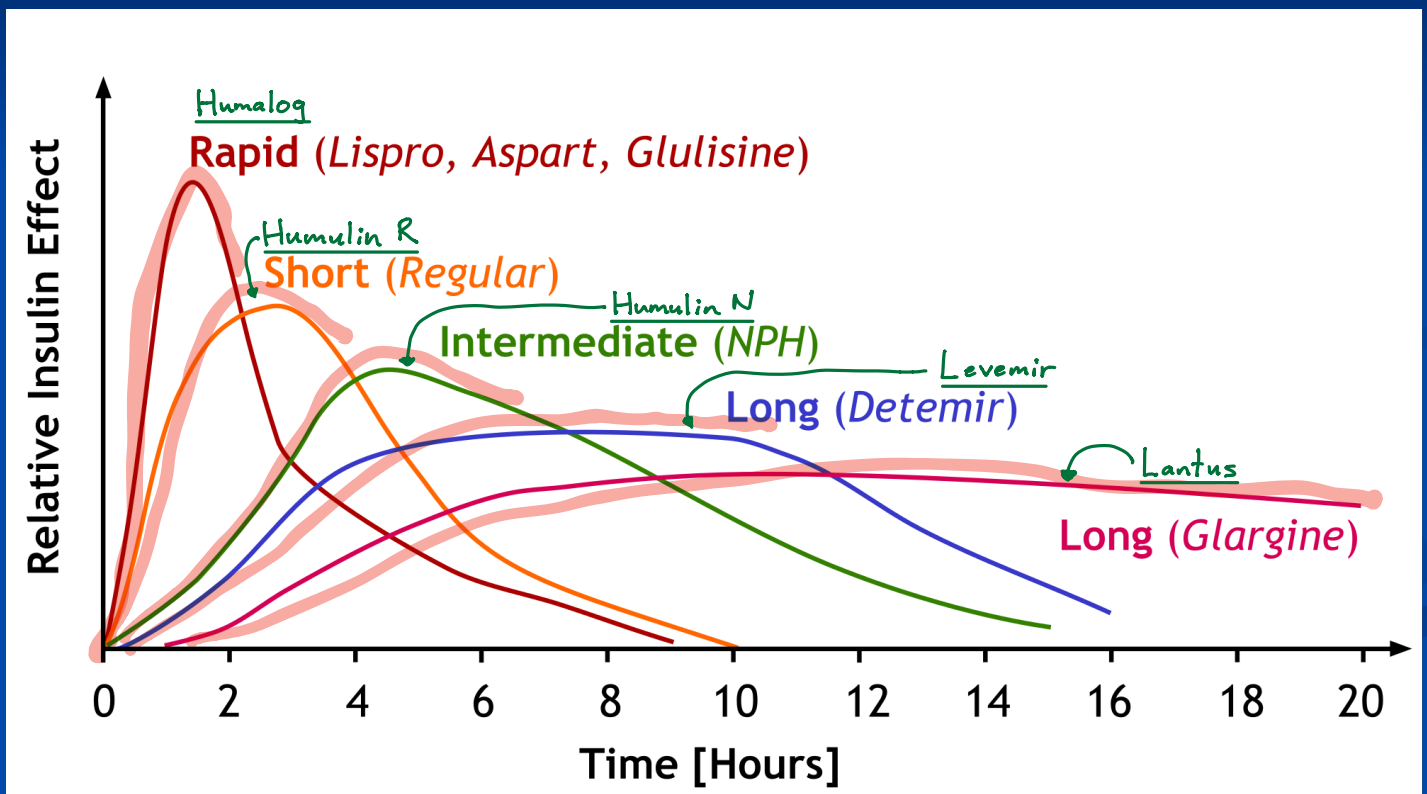
Indice	Normal	Intensive	Acceptable	Poor
Fasting	< 115	70-120	<140	>200
2 hrs pp	< 140	< 180	< 200	> 235
HgbA1c	4 - 6 %	6 - 7 %	8 - 9 %	> 10%
Urine Gluc	neg	rare	intermit	constant
Urine Keto	neg	rare	rare	intermit

D. Insulin Regimens

- daily insulin requirements:
    - 0.5 - 1.0 units insulin / kg bd wt / day
- general rule:
    - 1 - 2 units insulin --> ↓ 30-50 mg/dl BG

E. Time Profile Curves of Current Insulin Products

- Lispro (Humalog), Aspart (Novolog), Glulisine (Apidra), Regular (Humulin R), NPH (Humulin N), Detemir (Levemir), and Glargine (Lantus)

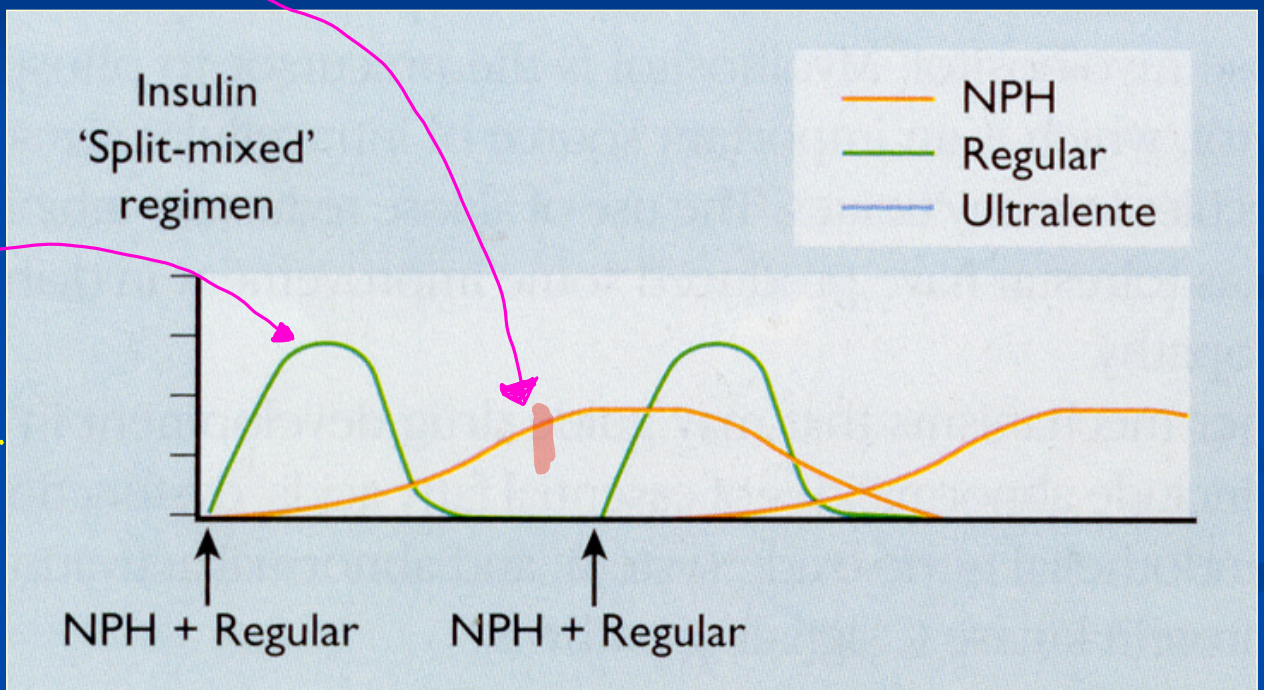


(1) Method 1: 7AM --> NPH:Reg (2/3 of daily dose)

6 PM --> NPH:Reg (1/3 of daily dose)

NPH at breakfast covers lunch

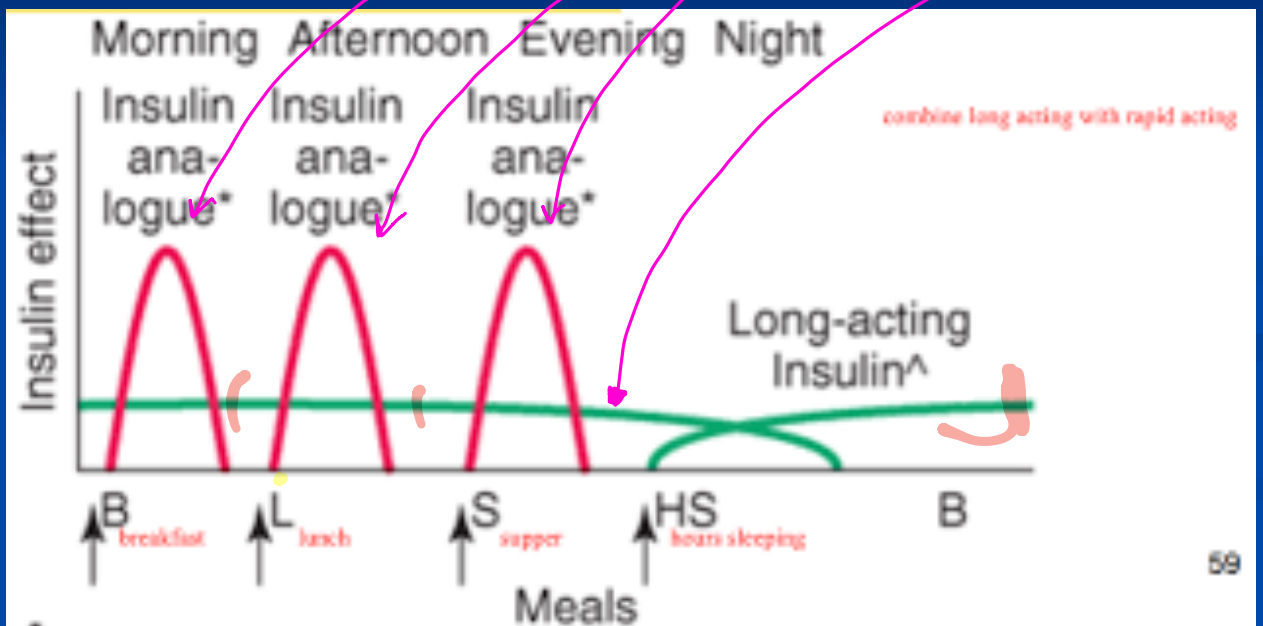
Reg Insulin at breakfast covers breakfast



(2) Method 2: Lispro (Humalog) + Glargine (Lantus)

covers each meal

basal insulin

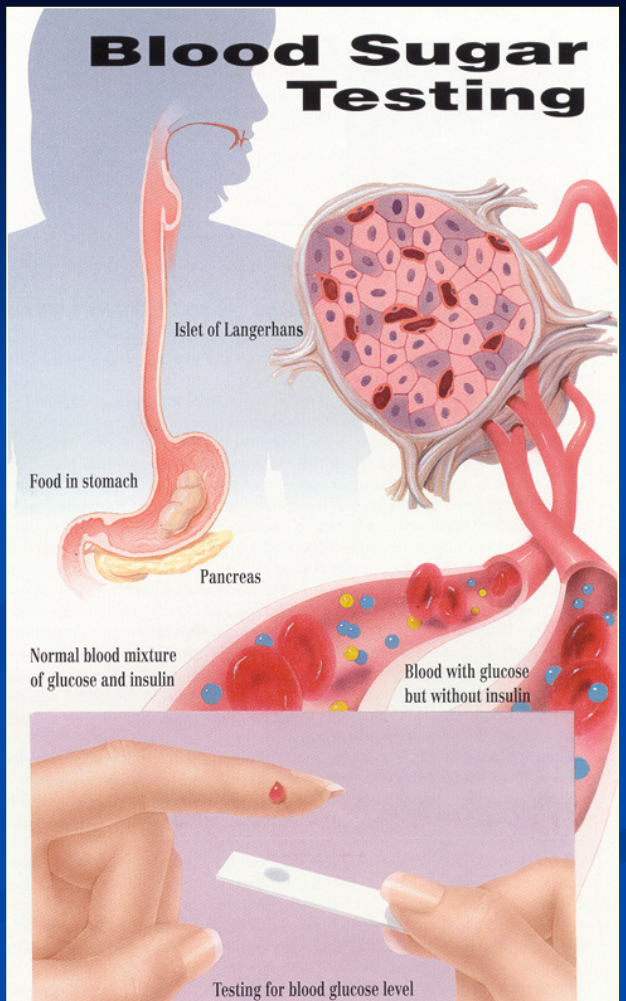


E. Monitoring Patients on Insulin Therapy

(a) ac & hs

(b) occasionally at 0300 during periods of insulin dose adjustments

(c) whenever hypoglycemia is suspected



F. Hypoglycemia

(1) Signs & Symptoms

- palpitations, tachycardia, blurred vision, sweaty palms, generalized sweating, tremors, hunger, confusion, anxiety, irritability, headache, tingling and numbness, and seizures
- nocturnal hypoglycemia --> nightmares, restless sleep, profuse sweating, and morning "hangover"

F. Hypoglycemia (cont.)

(2) Treatment --> 10-20 gm rapidly absorbed carbohydrate (MR x 1 in 15-20 min if BG<60 or still symptomatic)

- examples: OJ (1/2 cup), apply juice (1/3 cup), grape juice (1/4 cup), sugar (2 tsp or 2 cubes), Lifesavers (5-6 pieces), B/D glucose tabs (2 tabs)
- if patient is unconscious

  ---> glucagon 1 mg SQ, IM, or IV or

  ---> glucose 25 gm IV (Dextrose 50% 50 ml)

(3) Drugs Associated with Hypoglycemia

Drug	Effect	Mechanism
ethanol	+++	(-) glycogenolysis
		(-) gluconeogenesis
beta-blockers	++	(-) glycogenolysis
		masks sx's hypoglycemia
salicylates	++	↑ insulin secretion/sensitivity
		↑ serum sulfonylurea levels

G. Hyperglycemia

(1) Signs & Symptoms

- polydipsia, polyuria, polyphagia, fatigue, etc...

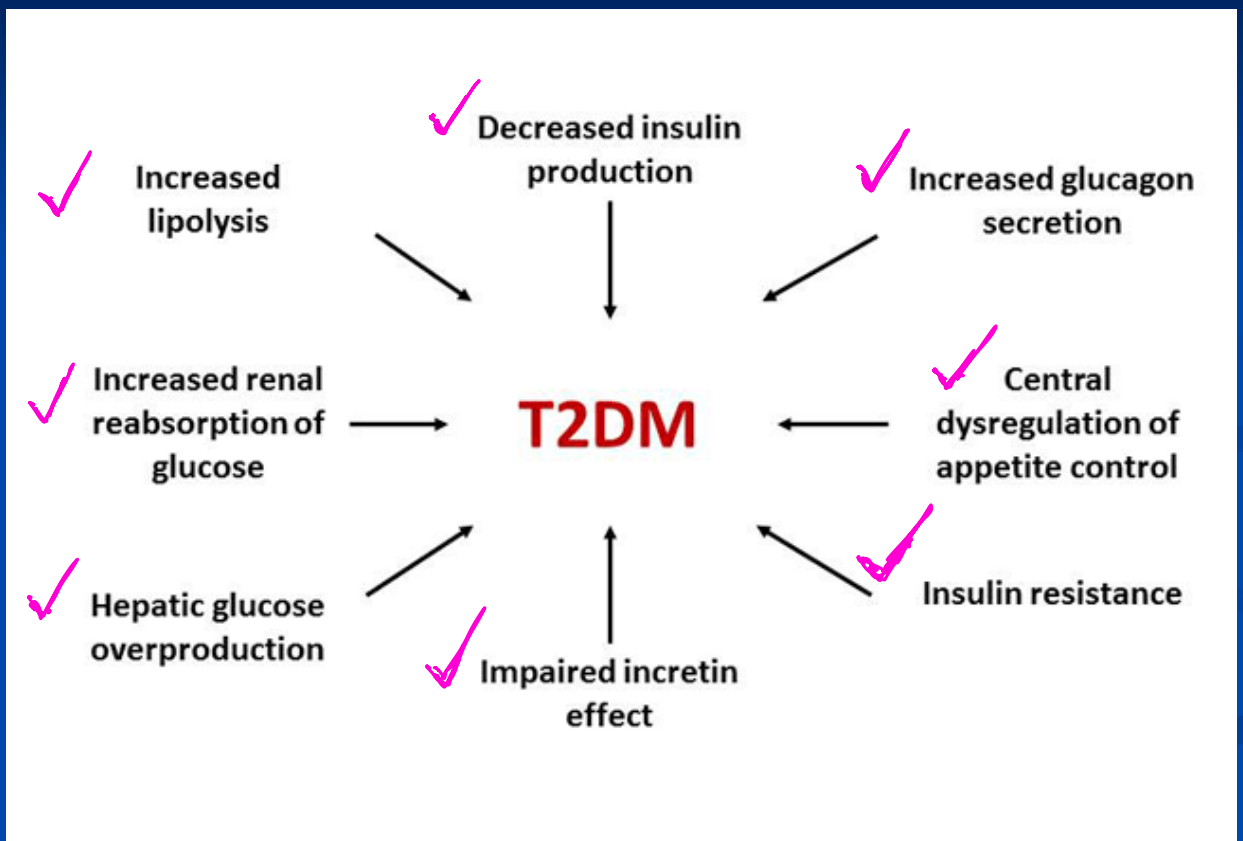
(2) Somogyi Effect --> "post-hypoglycemic hyperglycemia" or "rebound hyperglycemia"

- tx: → reduction of evening regular insulin dose

  → increase calories at evening meal

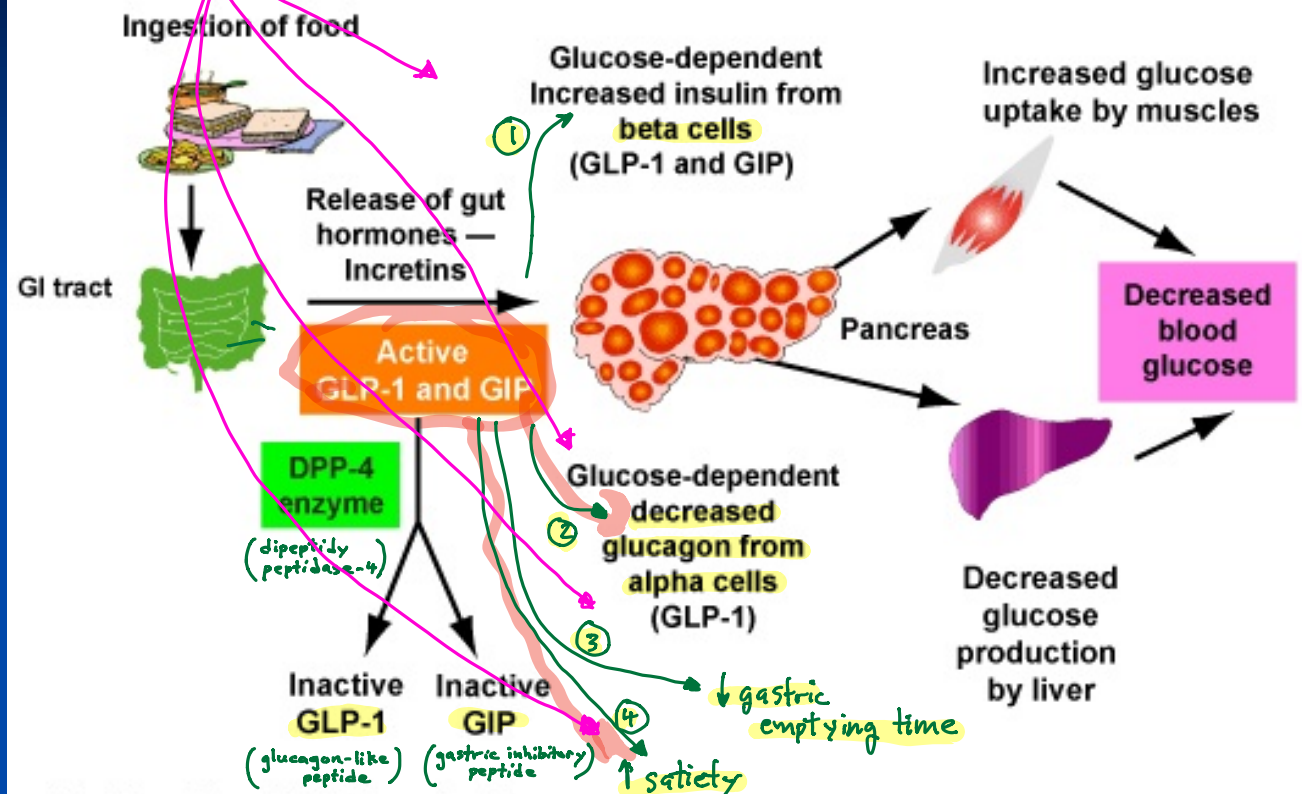
  → increase evening NPH dose

IV. Pharmacologic Management of NIDDM



Mechanisms of Action of Incretins (GLP-1 & GIP)

Role of Incretins in Glucose Homeostasis



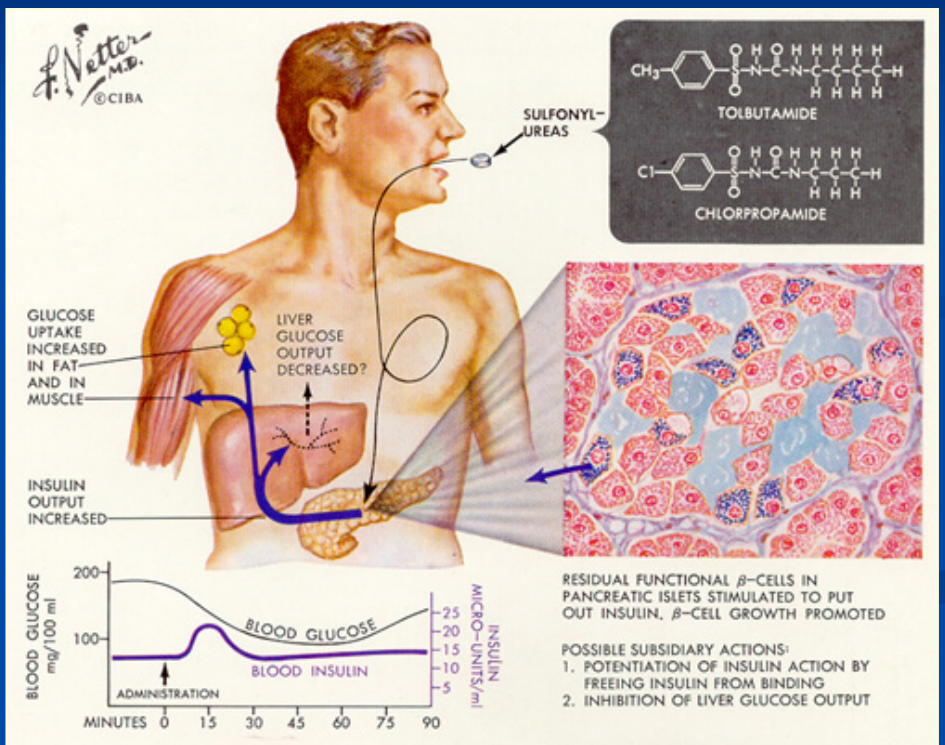
Abbreviation: GIP, gastric inhibitory polypeptide.

Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876-913. Ahrén B. *Curr Diab Rep*. 2003;2:365-372. Drucker DJ. *Diabetes Care*. 2003;26:2929-2940. Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430-441.

A. Sulfonylurea Drugs (cont.)

(1) Mechanism of Action

→ increase production and release of insulin by the pancreas ✓



A. Sulfonylurea Drugs (Mechanism of Action)

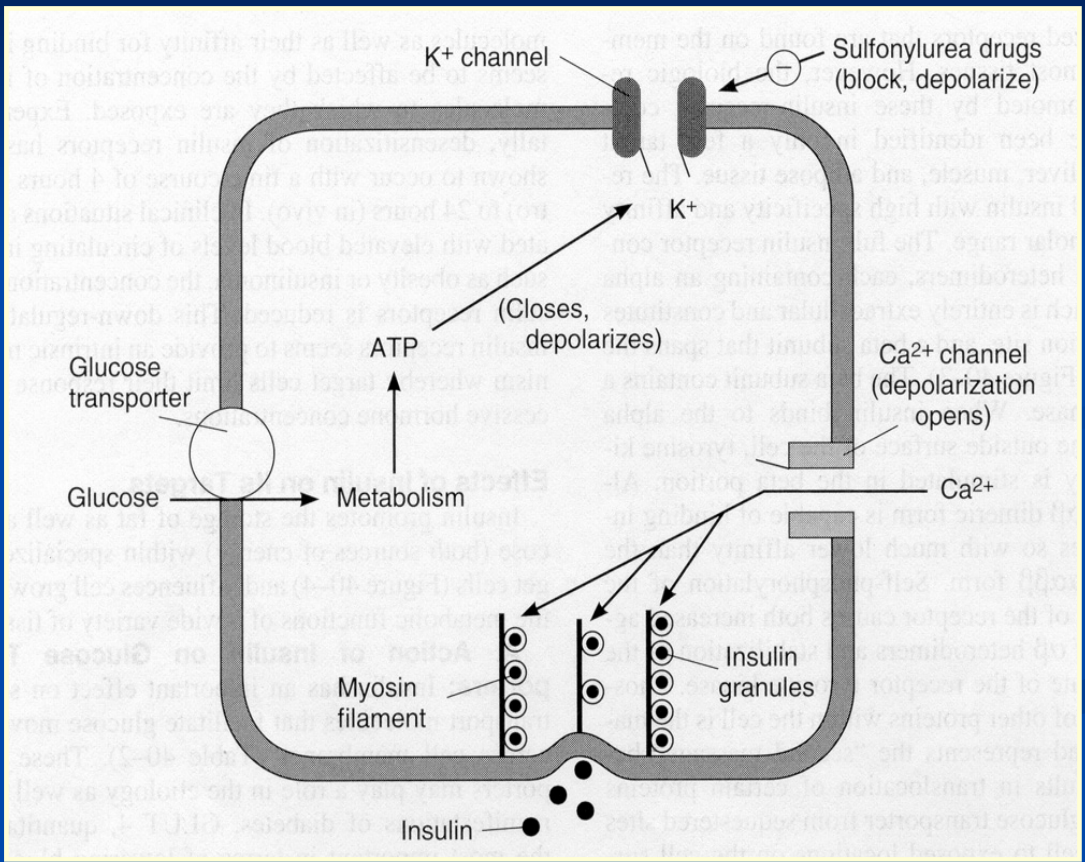
block K channels

↓

depolarizes beta cells

↓

insulin release



A. Sulfonylurea Drugs (cont.)

(1) Mechanisms of Action (cont.)

(b) reduction of serum glucagon levels

(c) increased affinity of insulin for receptor sites

A. Sulfonylurea Drugs (cont.)

First Generation Sulfonylureas

(1) Tolbutamide (Orinase)

(2) Tolazamide (Tolinase)

(3) Chlorpropamide (Diabinese)

A. Sulfonylurea Drugs (cont.)

Second Generation Sulfonylureas

- (1) Glyburide (Diabeta, Micronase)
- (2) Glipizide (Glucotrol)
- (3) Glimepiride (Amaryl)
  - longest duration of action (once daily) → greatest risk of hypoglycemia

- Side Effect: Potential of hypoglycemia

B. Metformin (Glucophage)

✓ first line agent for Type II DM

Mechanisms of Action

✓ → decreases hepatic glucose production

→ decreases intestinal absorption of glucose

→ improves insulin sensitivity (increases glucose uptake and utilization)

Metformin (cont.)

(b) side effects (most common): diarrhea, nausea, vomiting, bloating, flatulance

(c) dose: 500 mg to 2500 mg / day in divided doses with meals (BID)

✓(d) GFR < 30 ml/min → contraindicated

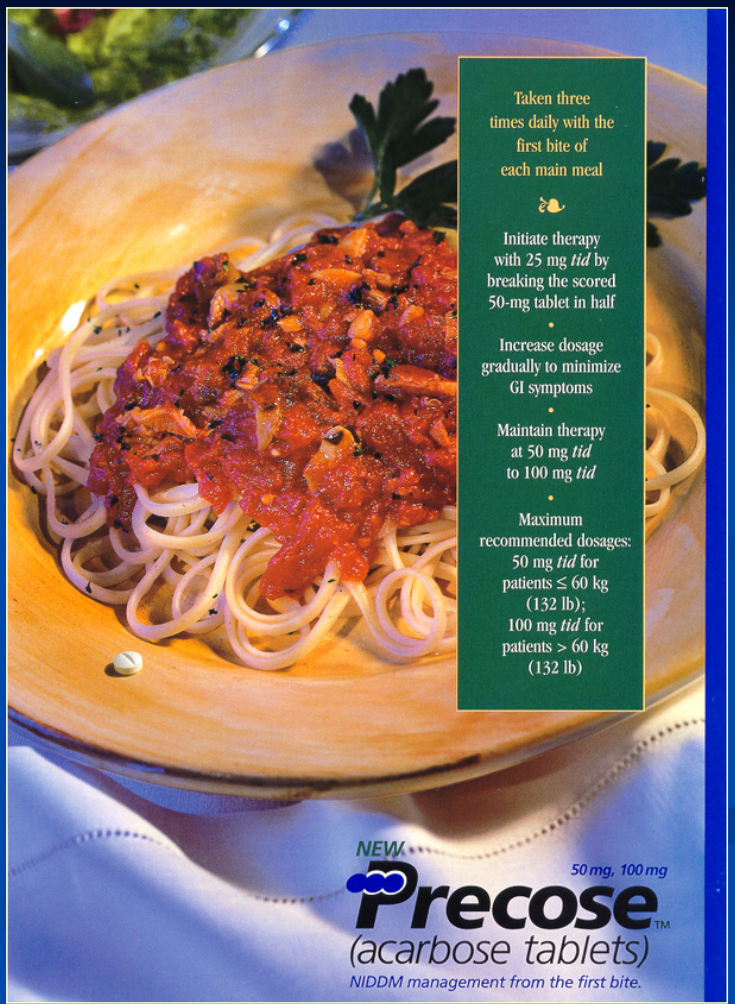
GFR < 45 ml/min → caution: risk vs benefit

high metformin levels → lactic acidosis

C. Acarbose (Precose)

Mechanism of Action

→ inhibits breakdown of carbohydrates by inhibiting alpha-glucosidase (secreted by small intestine)

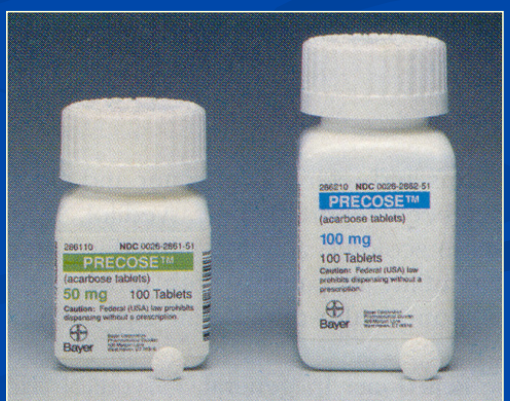


Acarbose (Precose)

(b) side effects (most common)

- abdominal pain, diarrhea, and flatulance (d/t undigested carbohydrates in lower GI tract)

(c) dose --> 50-100 mg TID with first bite of each meal



D. Thiazolidinediones: (TZD's = Glitazones) Rosiglitazone (Avandia) & Pioglitazone (Actos) ✓

Mechanism of Action of TZD's:

→ decrease hepatic glucose production

✓ → increase insulin sensitivity and improve glucose transport

(i.e., improving insulin sensitivity in muscle and adipose tissue and inhibiting hepatic gluconeogenesis)

TZD's (cont.): Rosiglitazone (Avandia) & Pioglitazone (Actos)

Side Effects: Weight gain, fluid retention, osteopenia, increase in CHF in those at risk

E. DPP-4 ("Gliptins") Inhibitors

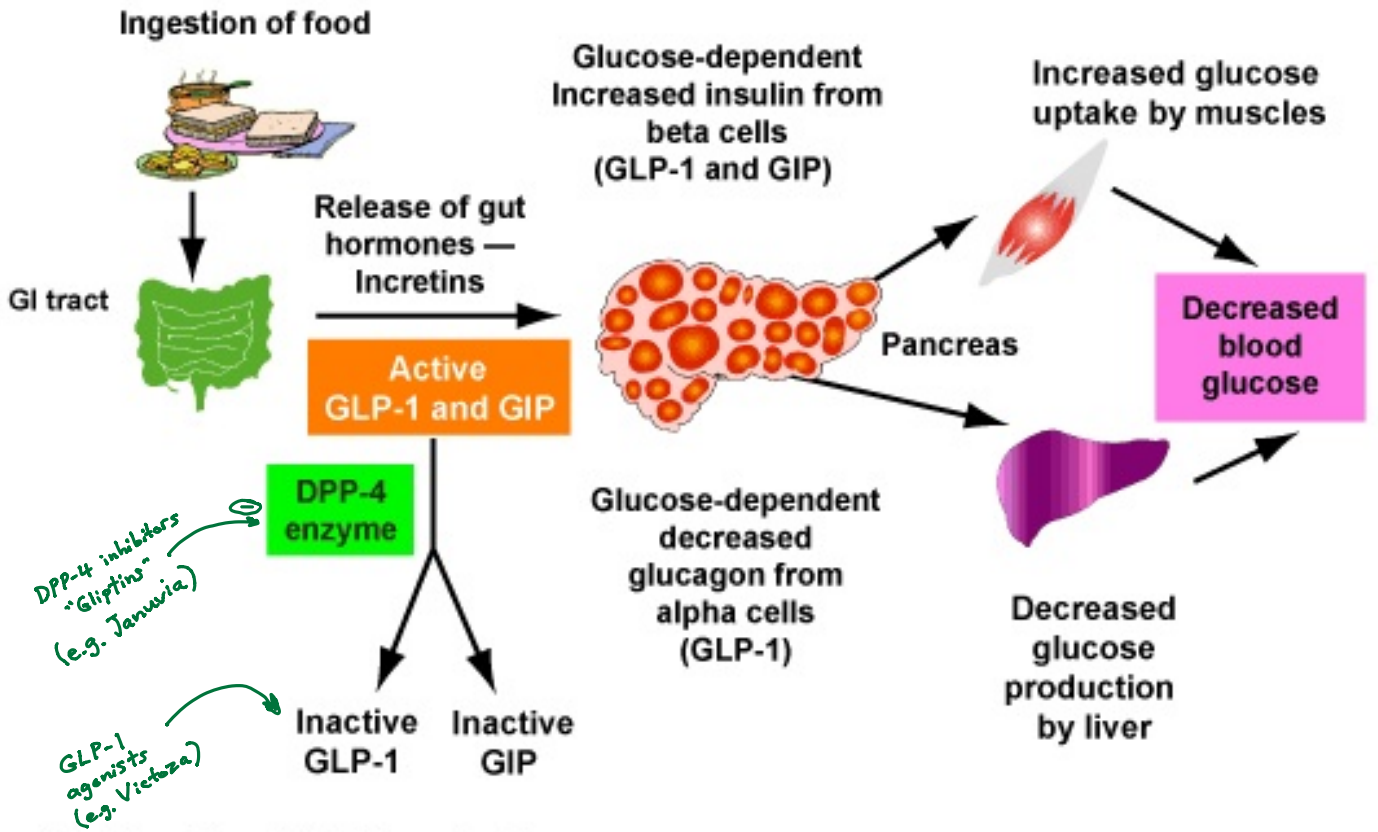
- Sitagliptin (Januvia)
  Linagliptin (Tradjenta)

MOA: slows the inactivation of incretin

incretin (GLP-1)
- → increase insulin secretion
- → decrease glucagon secretion
- → decrease gastric emptying time
- → increase satiety (neuronal signals)

Side Effects: URI, Stuffy nose, sore throat, diarrhea and stomach discomfort

Role of Incretins in Glucose Homeostasis



Abbreviation: GIP, gastric inhibitory polypeptide.

Kieffer TJ, Habener JF. *Endocr Rev*. 1999;20:876-913. Ahrén B. *Curr Diab Rep*. 2003;2:365-372. Drucker DJ. *Diabetes Care*. 2003;26:2929-2940. Holst JJ. *Diabetes Metab Res Rev*. 2002;18:430-441.

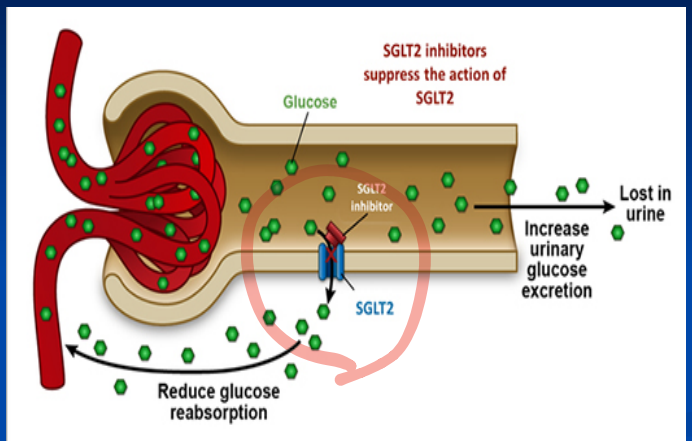
F. GLP-1 Receptor Agonists (Injectable)

- Exenatide (Byetta)
- Liraglutide (Victoza)

Mechanism of Action:
Increase incretin hormones → enhanced insulin secretion and reduced glucagon secretion

Side Effects: Nausea, anorexia, vomiting

G. SGLT2 (Sodium-Glucose Co-Transporter 2) Inhibitors



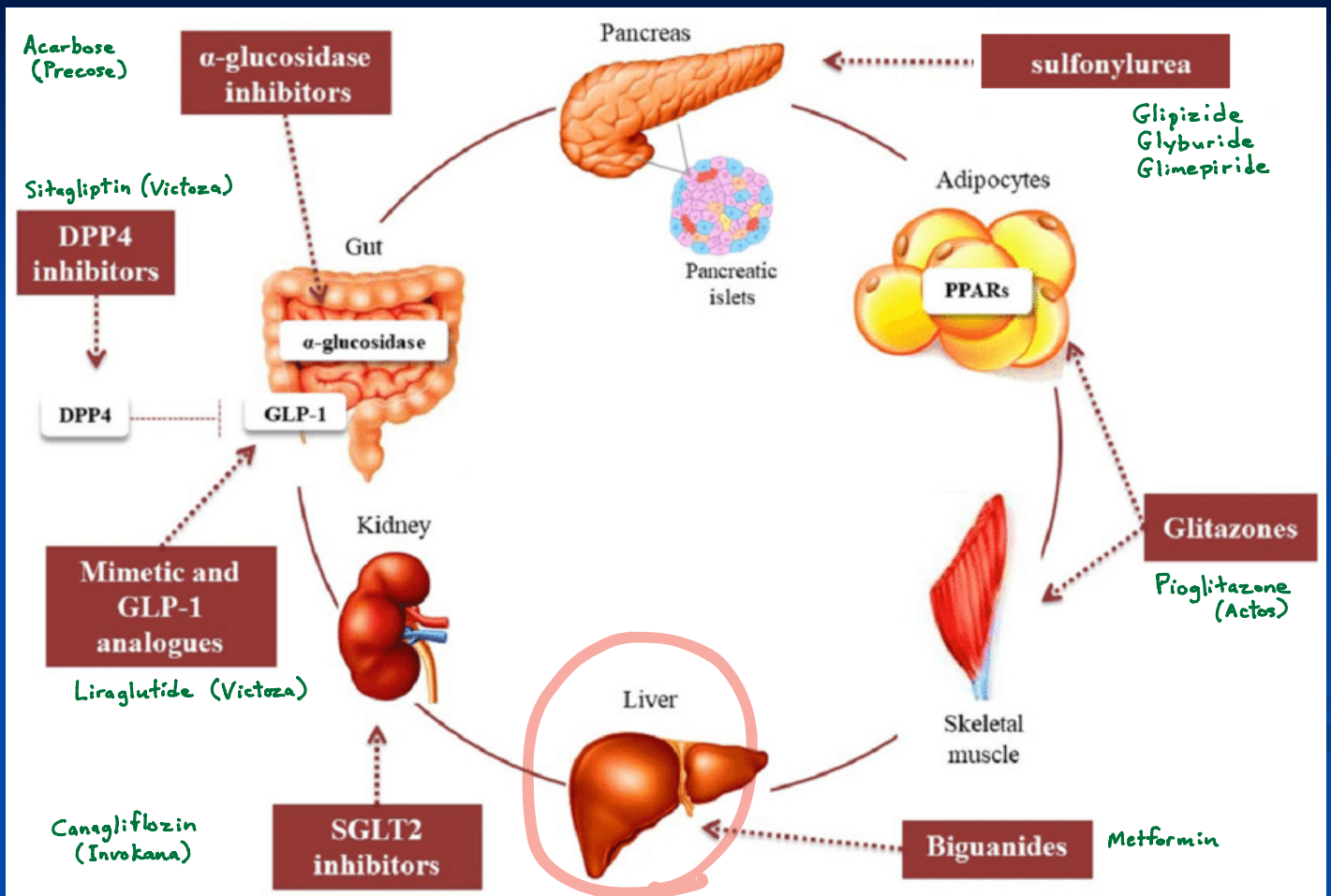
Dapagliflozin (Farxiga)

✓ Canagliflozin (Invokana)

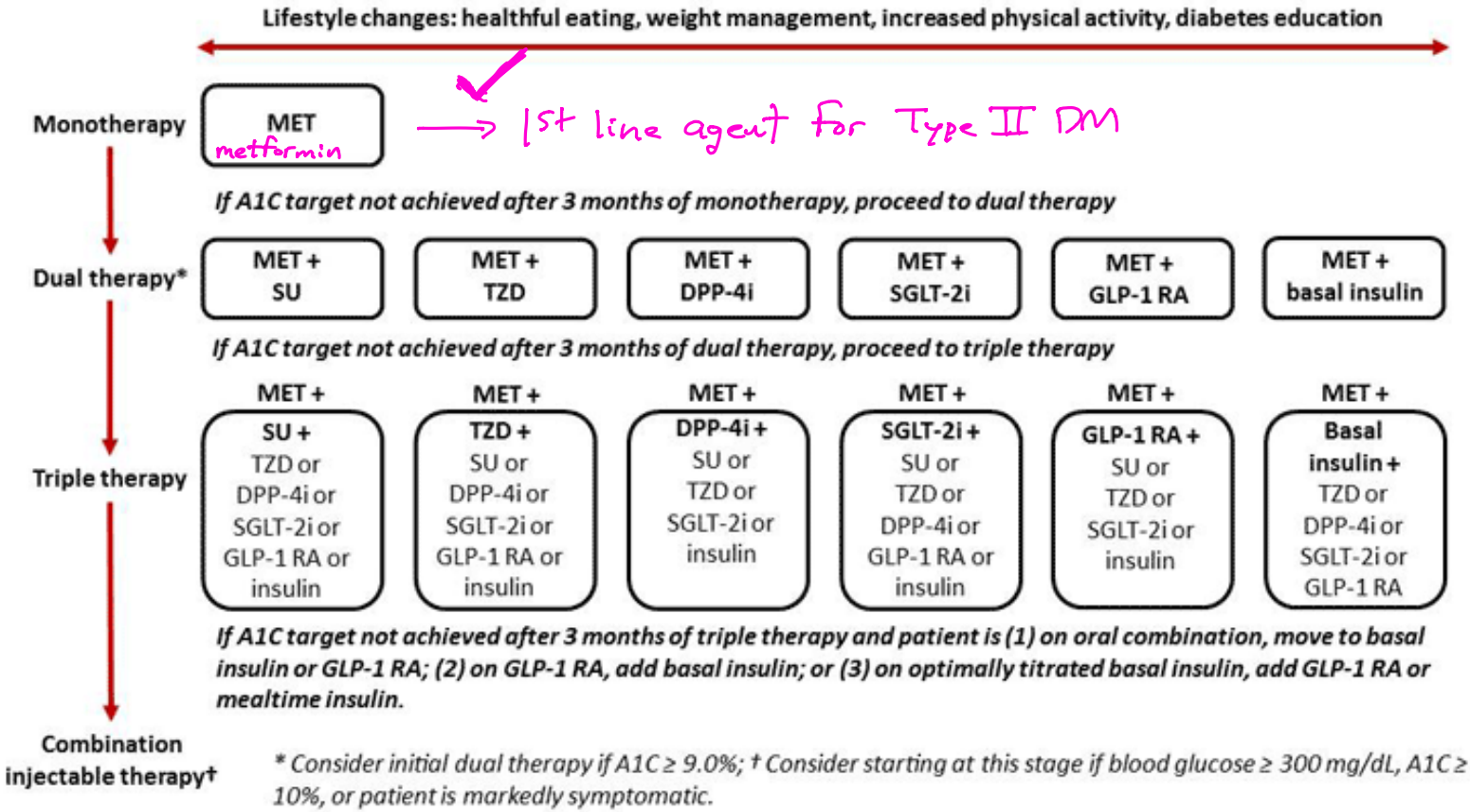
✓ Mechanism of Action: Lowers blood glucose by increasing kidney excretion of glucose into the urine

Side Effects: Dehydration, yeast infections, UTI's, and changes in urination

OVERVIEW: Pharmacologic Agents in the Treatment of Type II DM



V. Antihyperglycemia Tx in Adults w/ Type II DM




PHARMACY
CLOSED