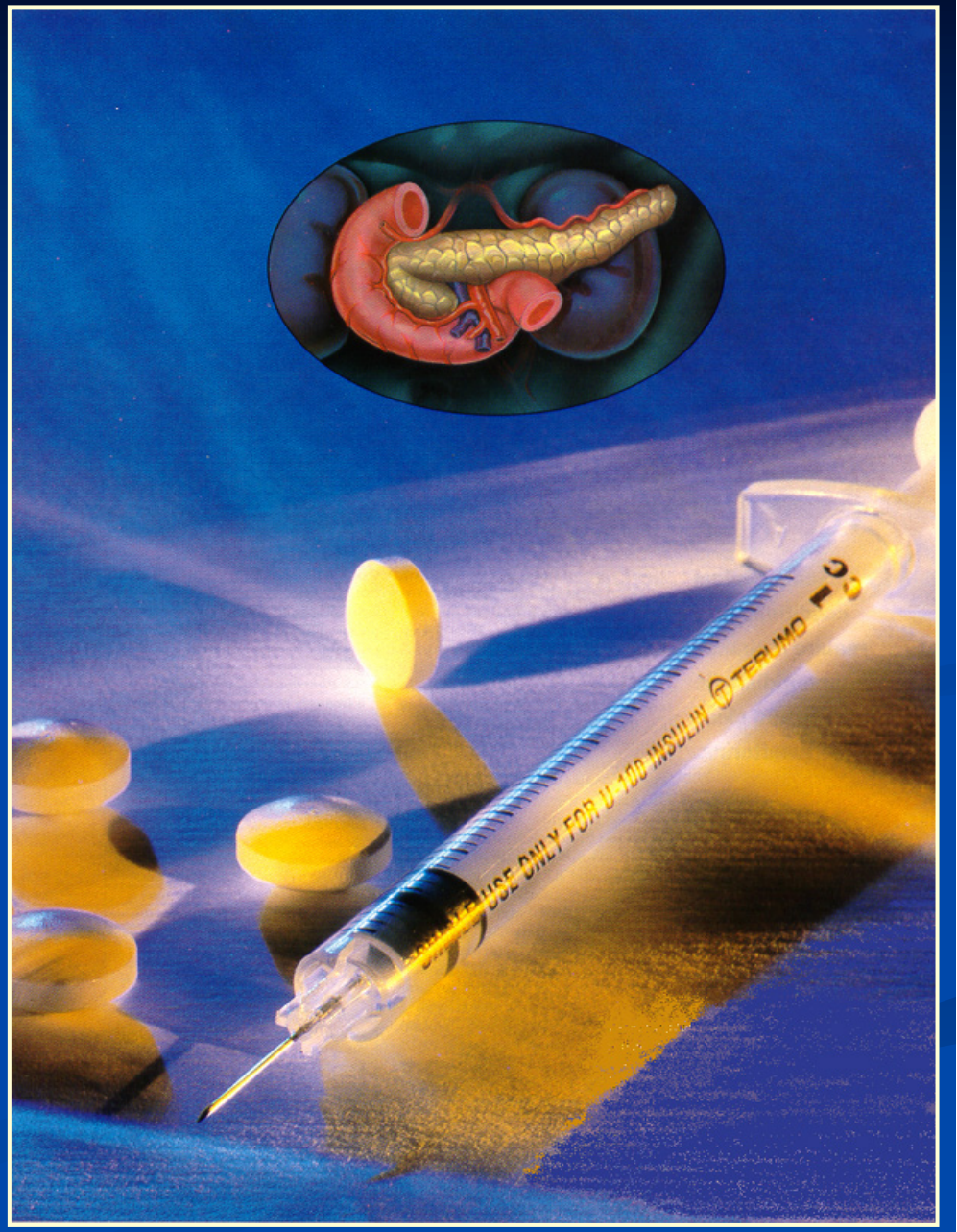
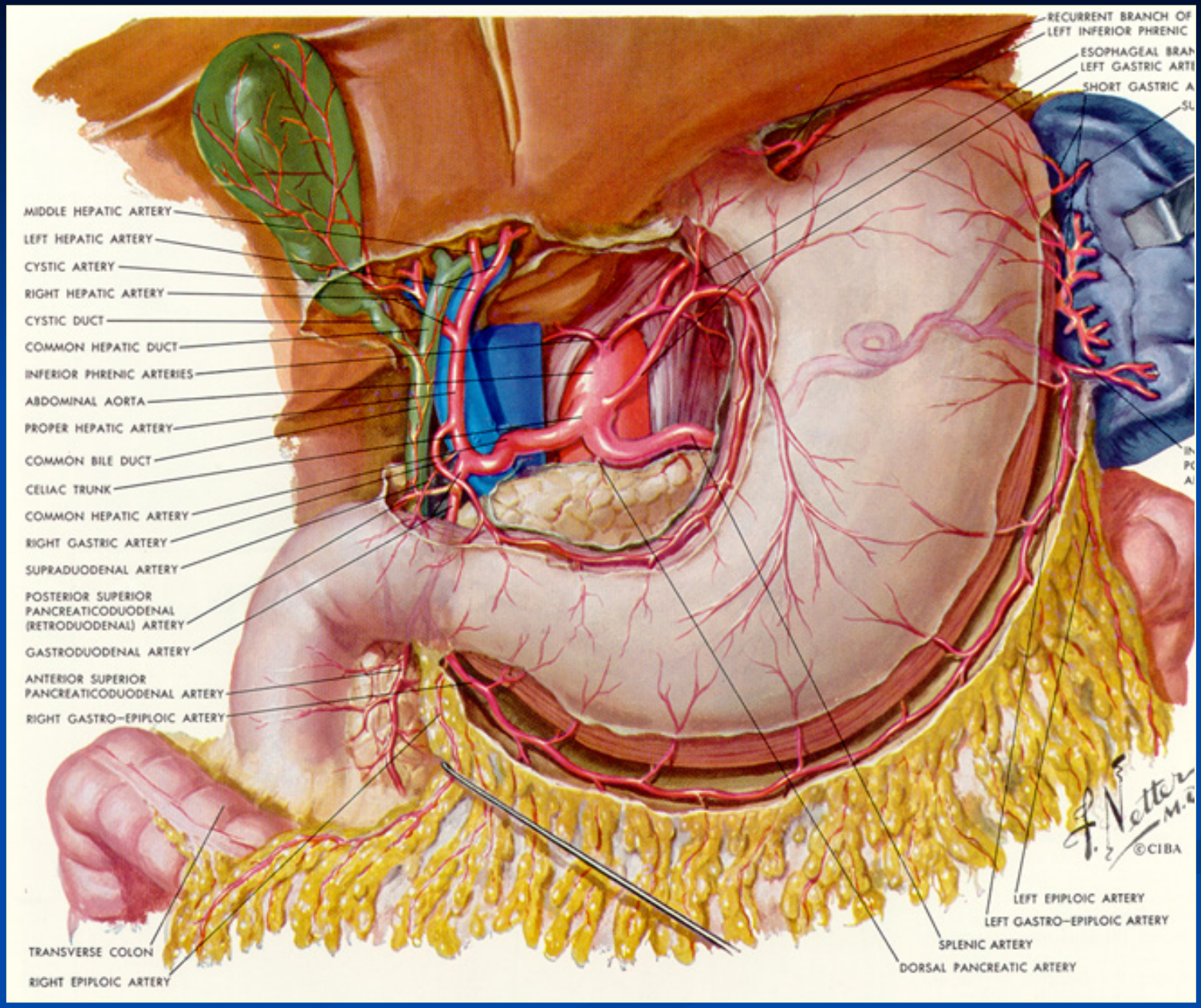
Management & Treatment of Diabetes Mellitus

Southern California University
of Health Sciences



ANATOMY


RECURRENT BRANCH OF
LEFT INFERIOR PHRENIC
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LEFT GASTRIC ART
SHORT GASTRIC A
MIDDLE HEPATIC ARTERY
LEFT HEPATIC ARTERY
CYSTIC ARTERY
RIGHT HEPATIC ARTERY
CYSTIC DUCT
COMMON HEPATIC DUCT
INFERIOR PHRENIC ARTERIES
ABDOMINAL AORTA
PROPER HEPATIC ARTERY
COMMON BILE DUCT
CELIAC TRUNK
COMMON HEPATIC ARTERY
RIGHT GASTRIC ARTERY
SUPRADUODENAL ARTERY
POSTERIOR SUPERIOR
PANCREATICODUODENAL
(RETRODUODENAL) ARTERY
GASTRODUODENAL ARTERY
ANTERIOR SUPERIOR
PANCREATICODUODENAL ARTERY
RIGHT GASTRO–EPIPLOIC ARTERY
TRANSVERSE COLON
RIGHT EPIPLOIC ARTERY
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LEFT GASTRO–EPIPLOIC ARTERY
SPLENIC ARTERY
DORSAL PANCREATIC ARTERY
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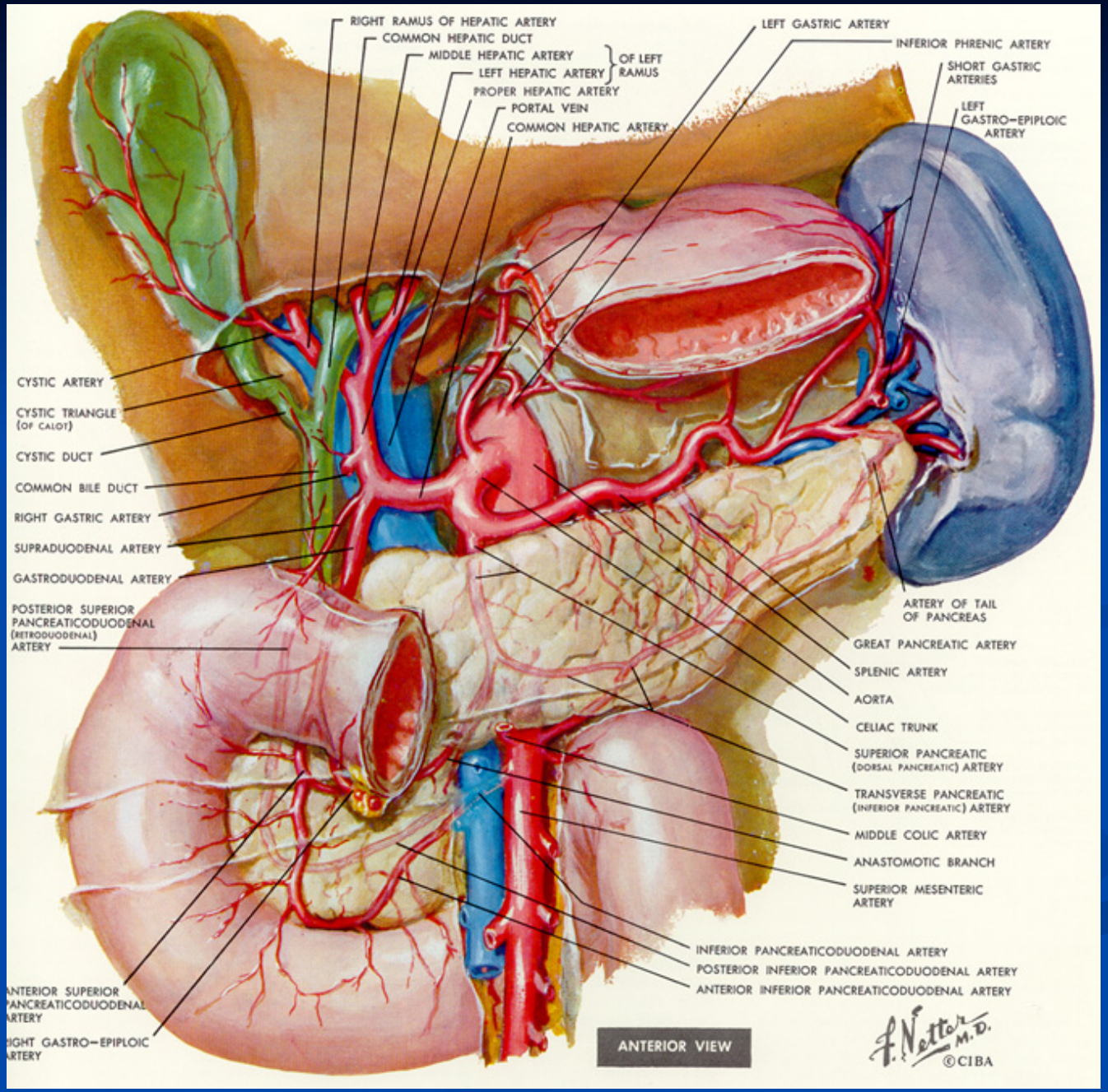
ANATOMY


RIGHT RAMUS OF HEPATIC ARTERY
COMMON HEPATIC DUCT
MIDDLE HEPATIC ARTERY
LEFT HEPATIC ARTERY
OF LEFT RAMUS
PROPER HEPATIC ARTERY
PORTAL VEIN
COMMON HEPATIC ARTERY
LEFT GASTRIC ARTERY
INFERIOR PHRENIC ARTERY
SHORT GASTRIC ARTERIES
LEFT GASTRO-EPIPLOIC ARTERY
CYSTIC ARTERY
CYSTIC TRIANGLE (OF CALOT)
CYSTIC DUCT
COMMON BILE DUCT
RIGHT GASTRIC ARTERY
SUPRADUODENAL ARTERY
GASTRODUODENAL ARTERY
POSTERIOR SUPERIOR PANCREATICODUODENAL (RETRODUODENAL) ARTERY
ARTERY OF TAIL OF PANCREAS
GREAT PANCREATIC ARTERY
SPLENIC ARTERY
AORTA
CELIAC TRUNK
SUPERIOR PANCREATIC (DORSAL PANCREATIC) ARTERY
TRANSVERSE PANCREATIC (INFERIOR PANCREATIC) ARTERY
MIDDLE COLIC ARTERY
ANASTOMOTIC BRANCH
SUPERIOR MESENTERIC ARTERY
INFERIOR PANCREATICODUODENAL ARTERY
POSTERIOR INFERIOR PANCREATICODUODENAL ARTERY
ANTERIOR INFERIOR PANCREATICODUODENAL ARTERY
ANTERIOR SUPERIOR PANCREATICODUODENAL ARTERY
RIGHT GASTRO-EPIPLOIC ARTERY
ANTERIOR VIEW
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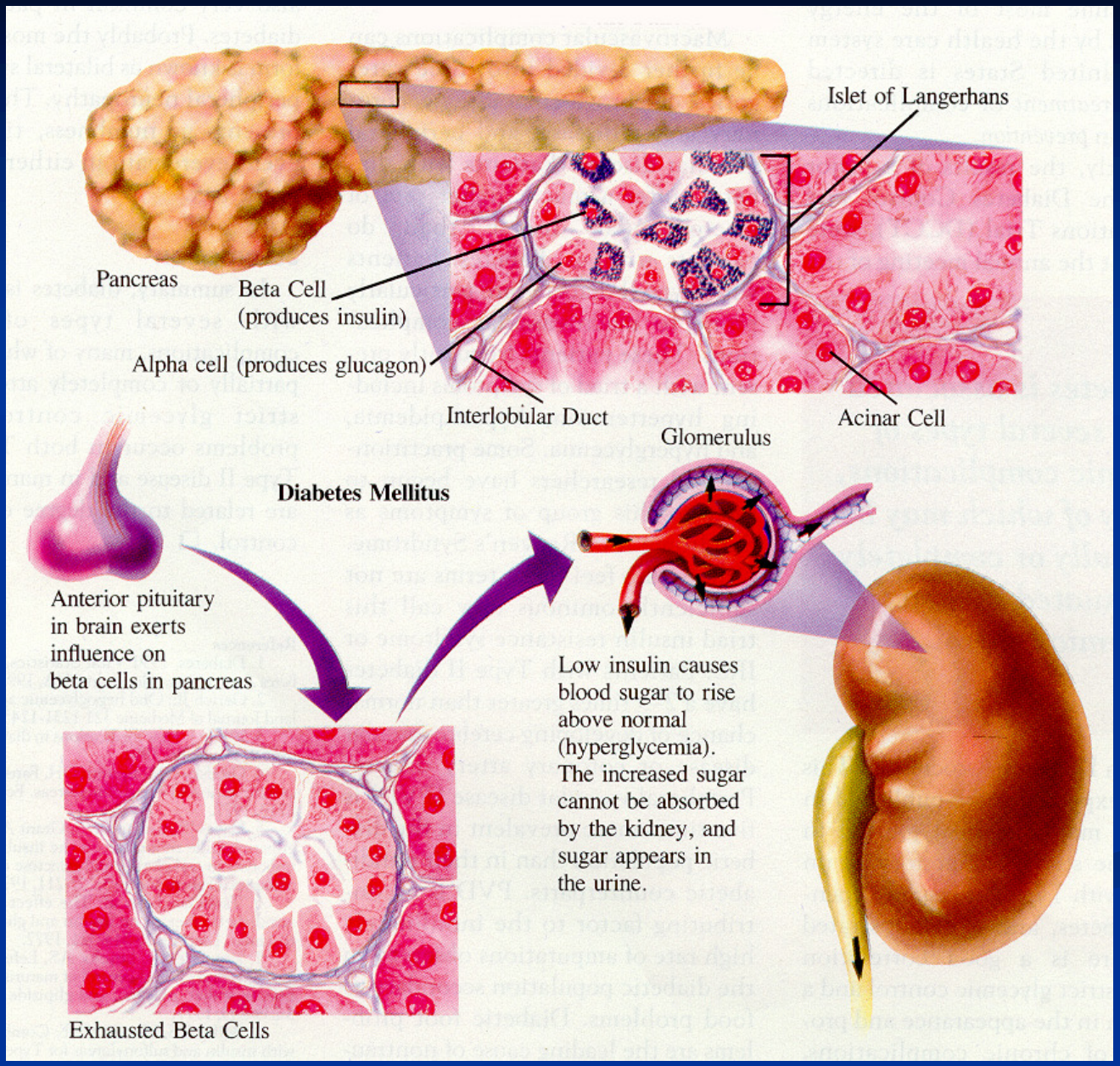
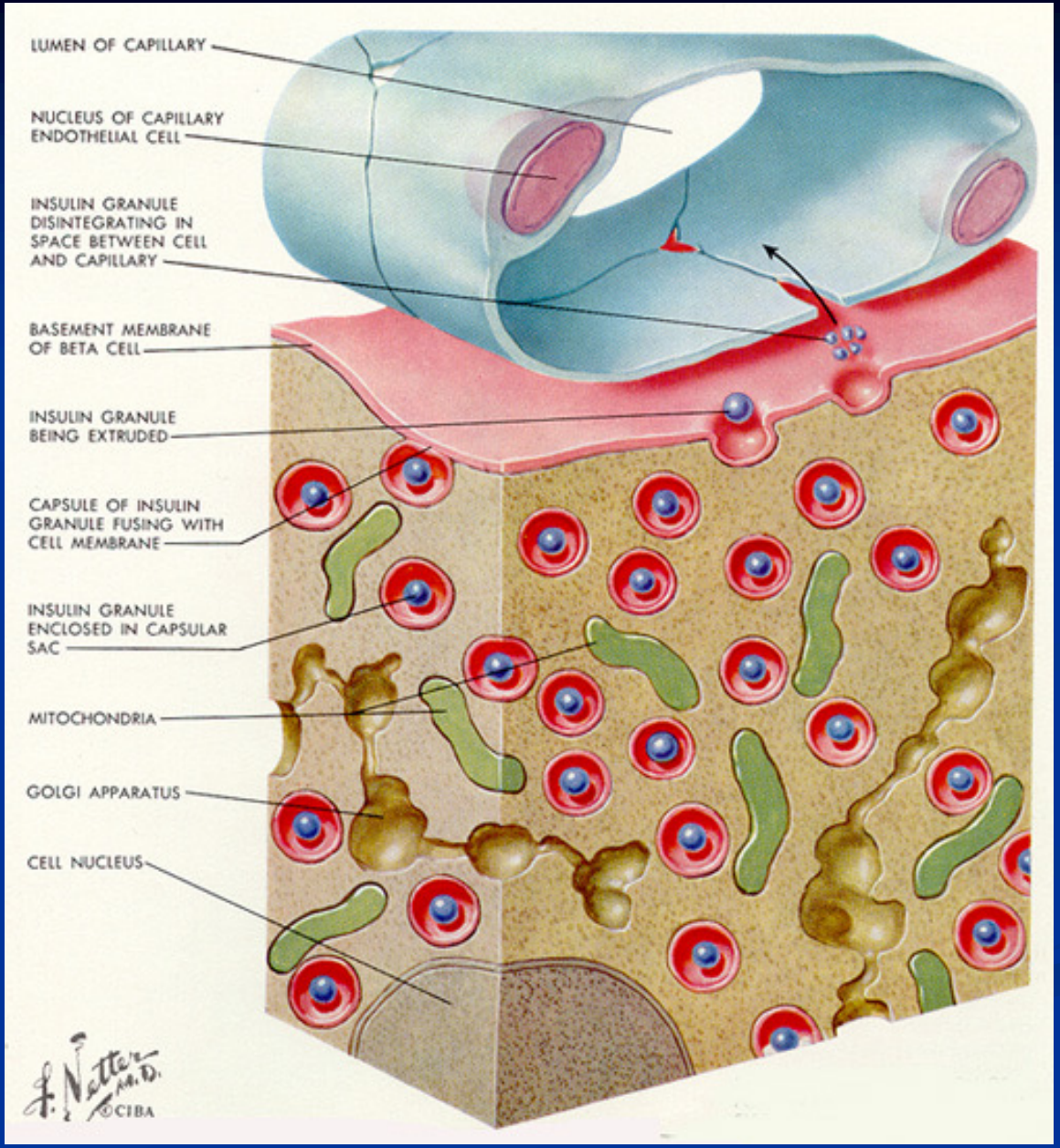
PHYSIOLOGY


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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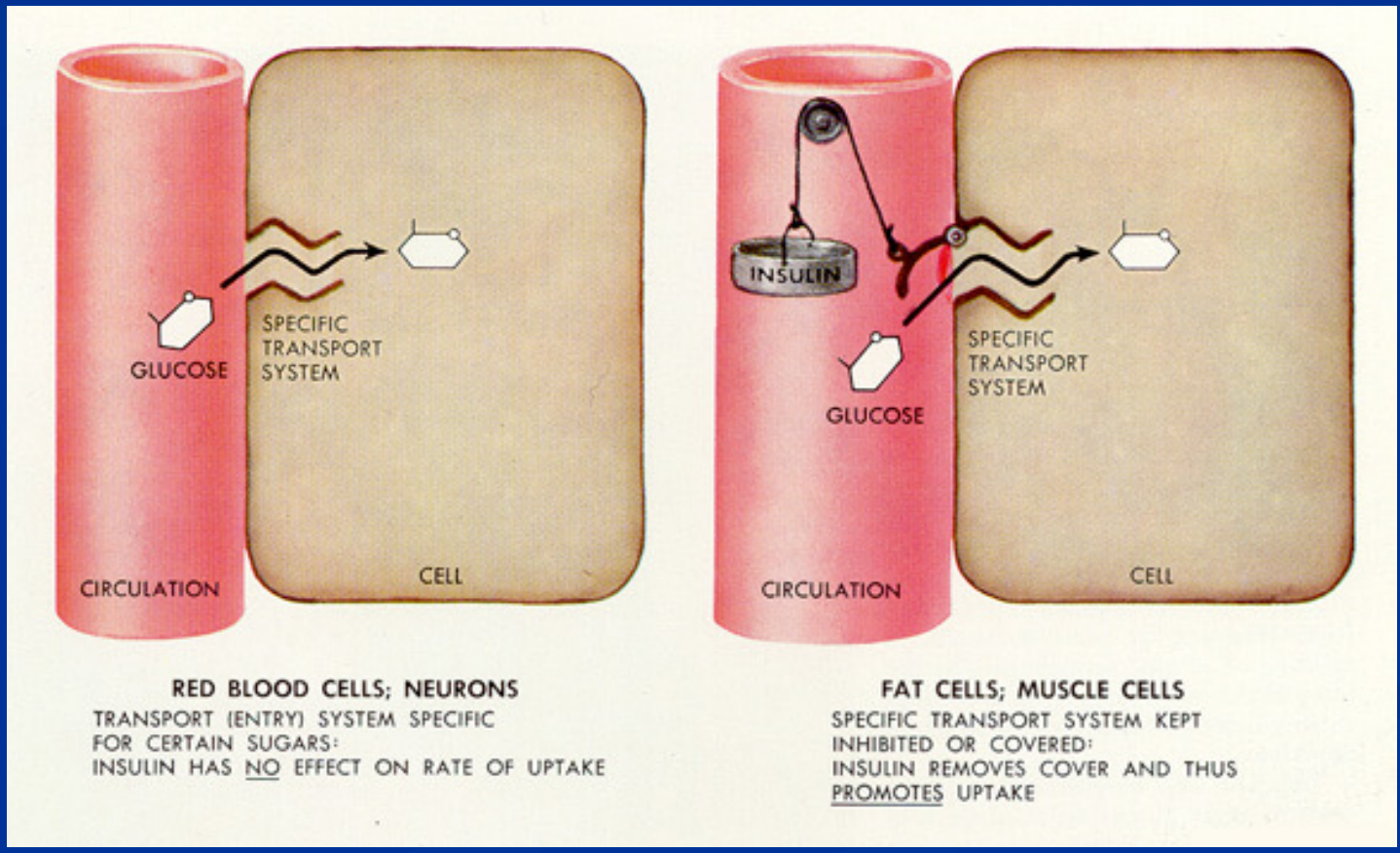
FUNCTION OF INSULIN



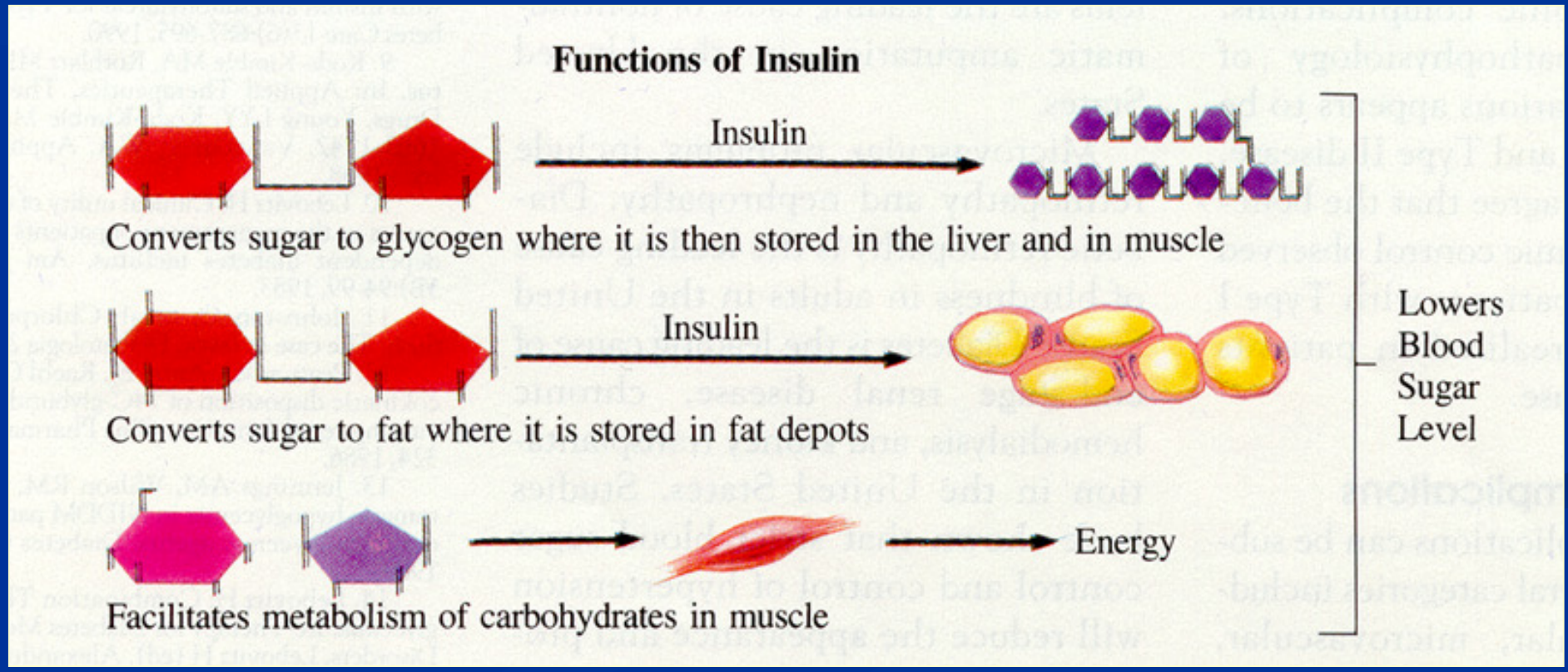
RED BLOOD CELLS; NEURONS

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

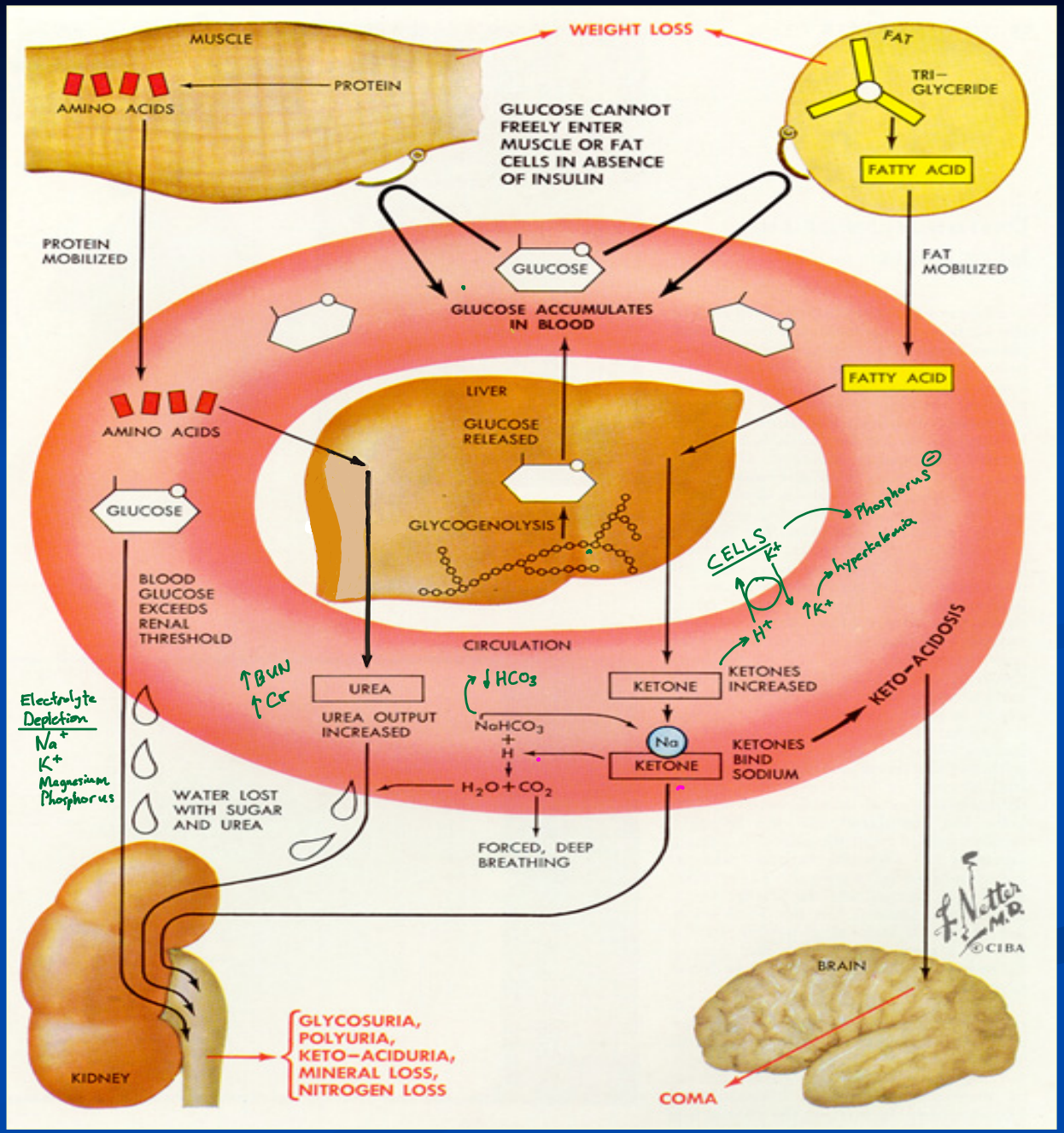
Diabetic Ketoacidosis (DKA)

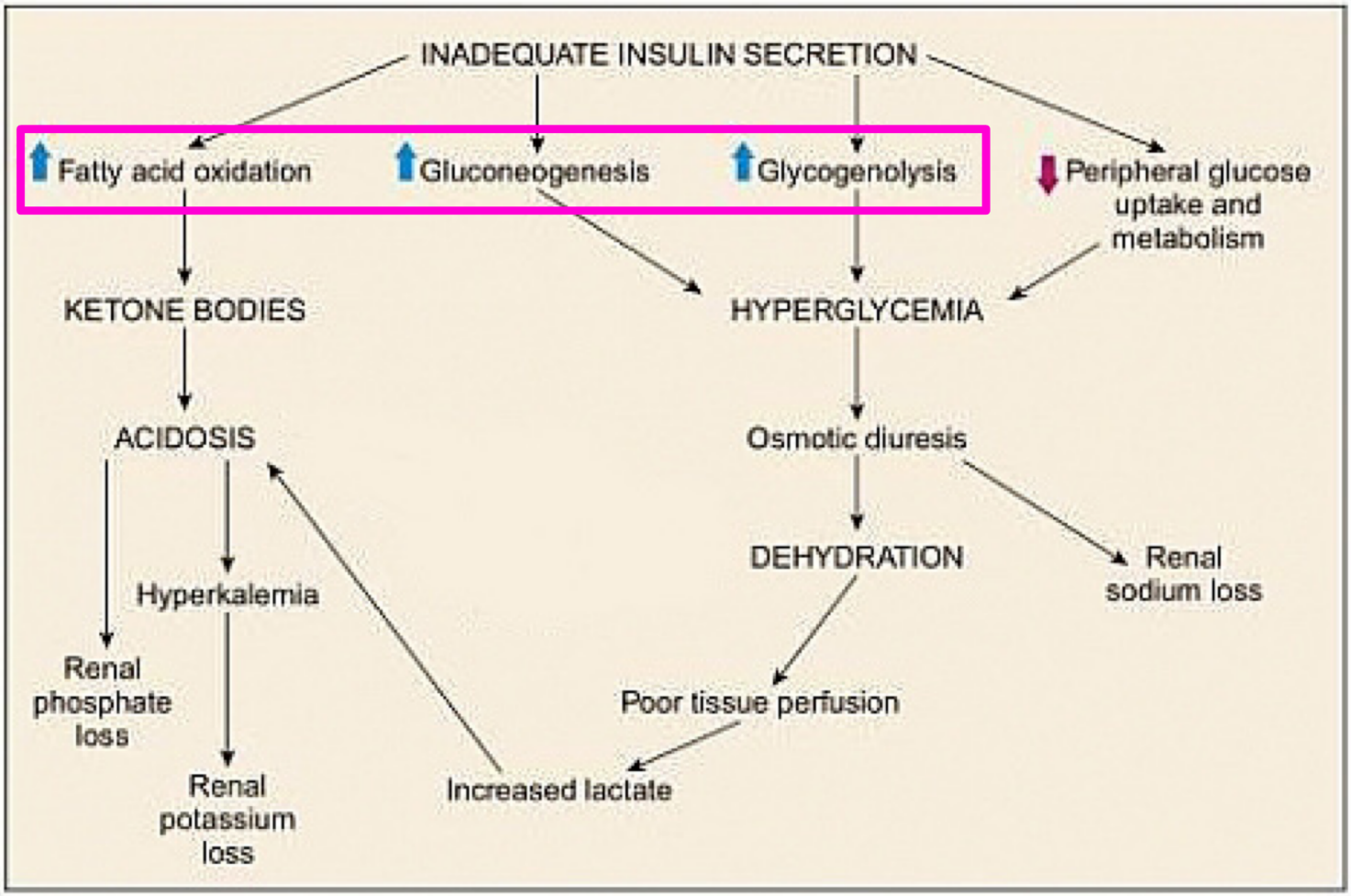
Diagnostic criteria for DKA

	DKA		
	Mild	Moderate	Severe
Plasma glucose(mg/dl)	More than 250	More than 250	More than 250
Arterial PH	7.25 – 7.30	7.00 – 7.24	Less than 7.00
Serum bicarbonate(mEq/L)	15 - 18	10 - 14	Less than 10
Urine ketones	+ve	+ve	+ve
Serum ketones	+ve	+ve	+ve
Effective serum osmolality(mOsm/kg)	Variable	Variable	Variable
Anion gap	More than 10	More than 12	More than 12
Alteration in sensoria	Alert	Alert / drowsy	Stupor / coma

Normal Values

BG: 90-110
pH: 7.35-7.45
HCO_3: 21-28



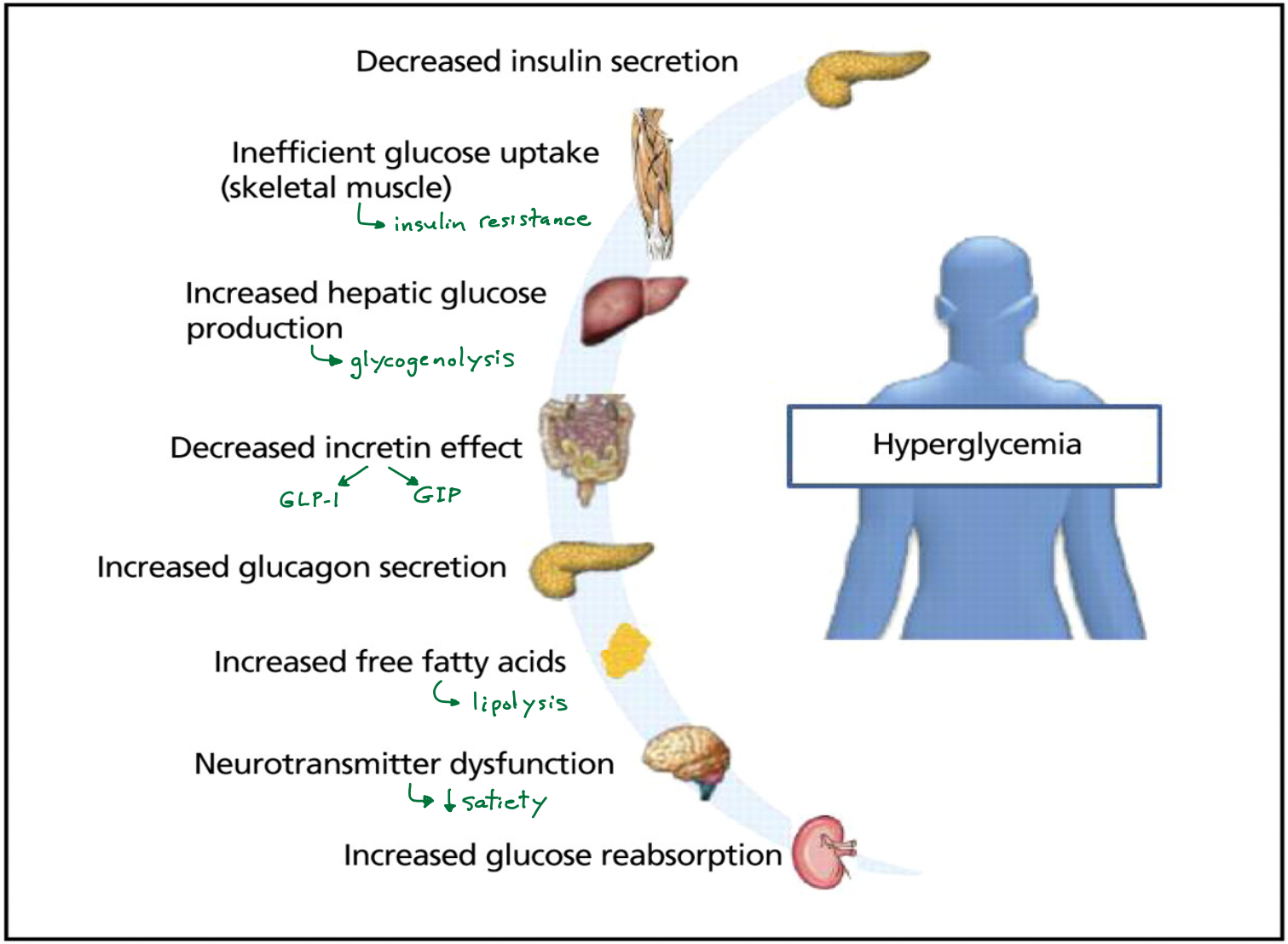

INADEQUATE INSULIN SECRETION
Fatty acid oxidation
Gluconeogenesis
Glycogenolysis
Peripheral glucose uptake and metabolism
KETONE BODIES
HYPERGLYCEMIA
ACIDOSIS
Osmotic diuresis
DEHYDRATION
Renal sodium loss
Hyperkalemia
Renal phosphate loss
Poor tissue perfusion
Renal potassium loss
Increased lactate

Glucose Level (mg/dL)	Low Dose Regimen	Medium Dose Regimen	High Dose Regimen
Humalog Sliding Scale	(0-6 UNITS) AC & HS	(0-12 UNITS) AC & HS	(0-18 UNITS) AC & HS
Serum FBS < 60	Dextrose 12.5 GM	Dextrose 12.5 GM	Dextrose 12.5 GM
60-150	0	0	0
150-200	1	2	3
201-250	2	4	6
251-300	3	6	9
301-350	4	8	12
351-400	5	10	15
> 400	6	12	18

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.)



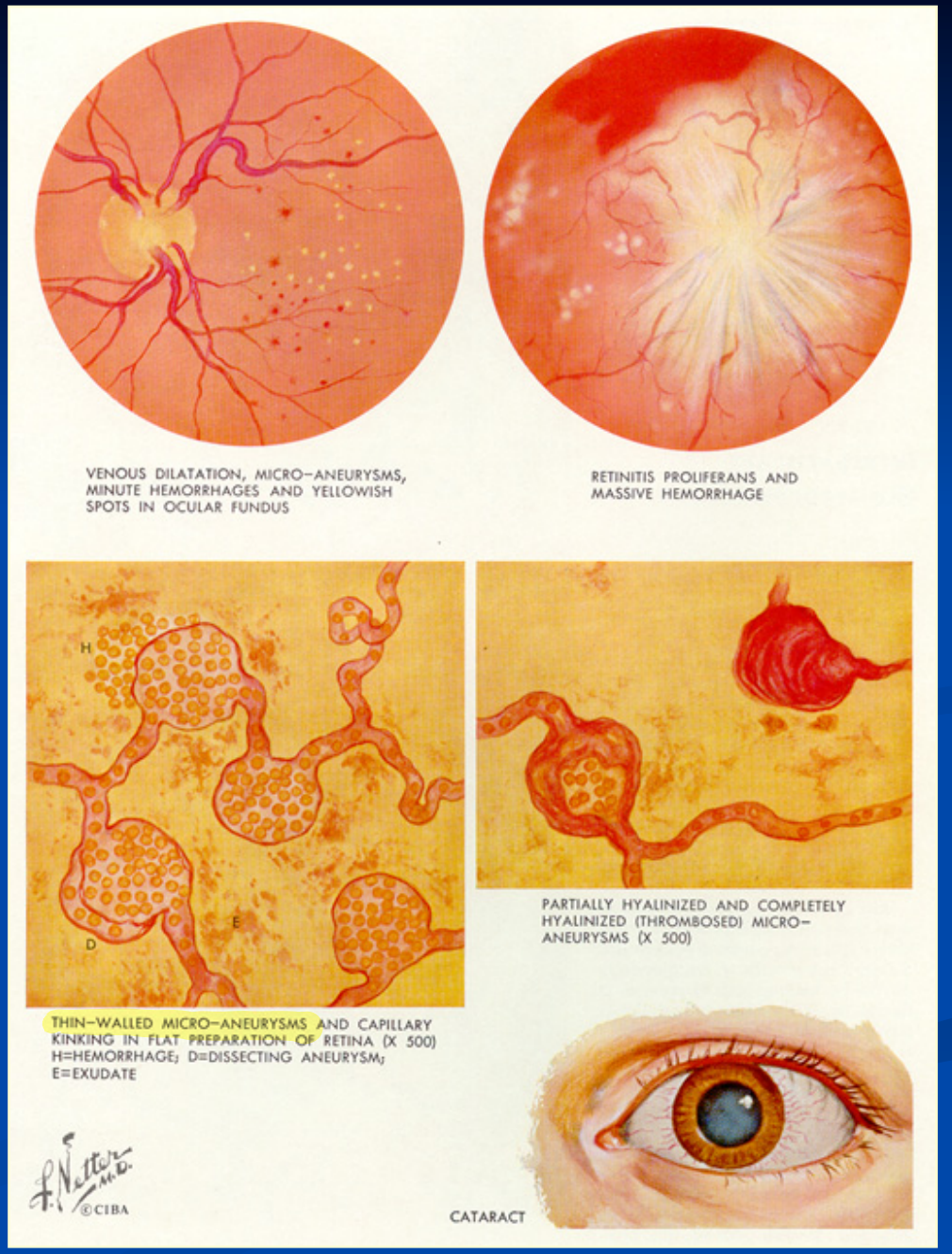
C. Complications of Diabetes

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

(2) Chronic Complications

(a) Microvascular

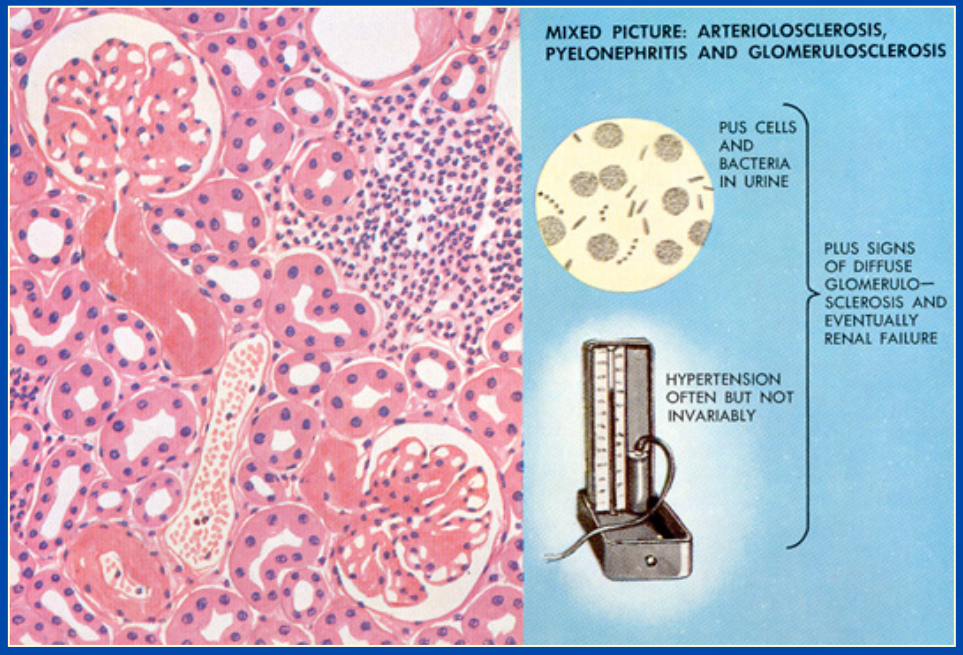
- diabetic retinopathy

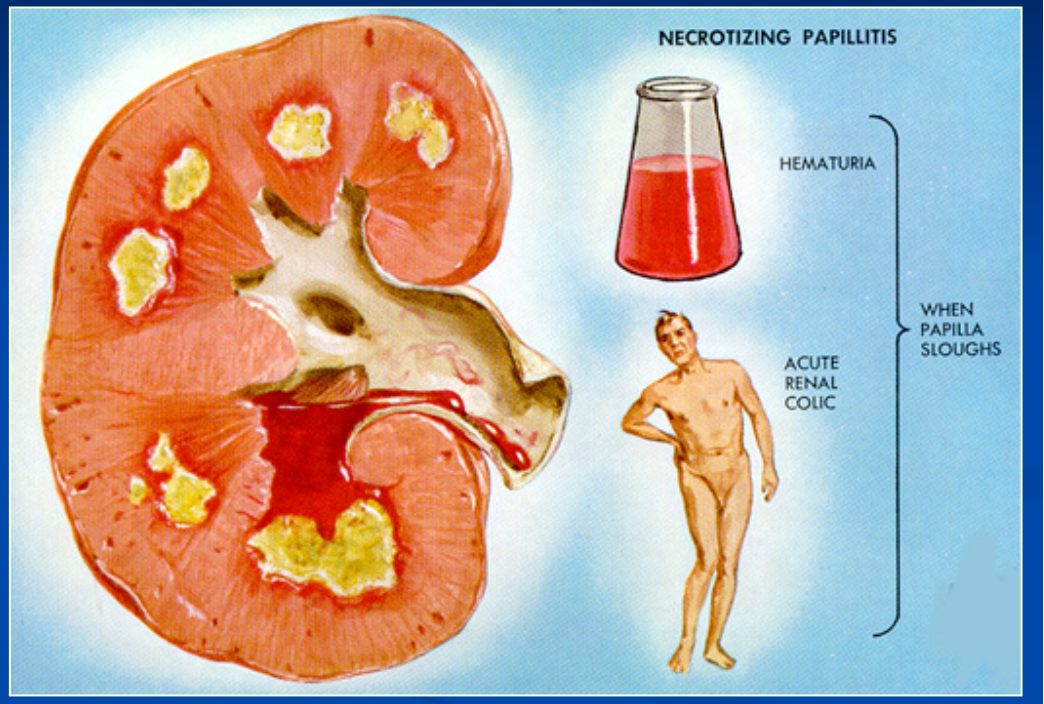


(2) Chronic Complications

b. kidney disease

- glomerulosclerosis
- pyelonephritis → CKD DKD

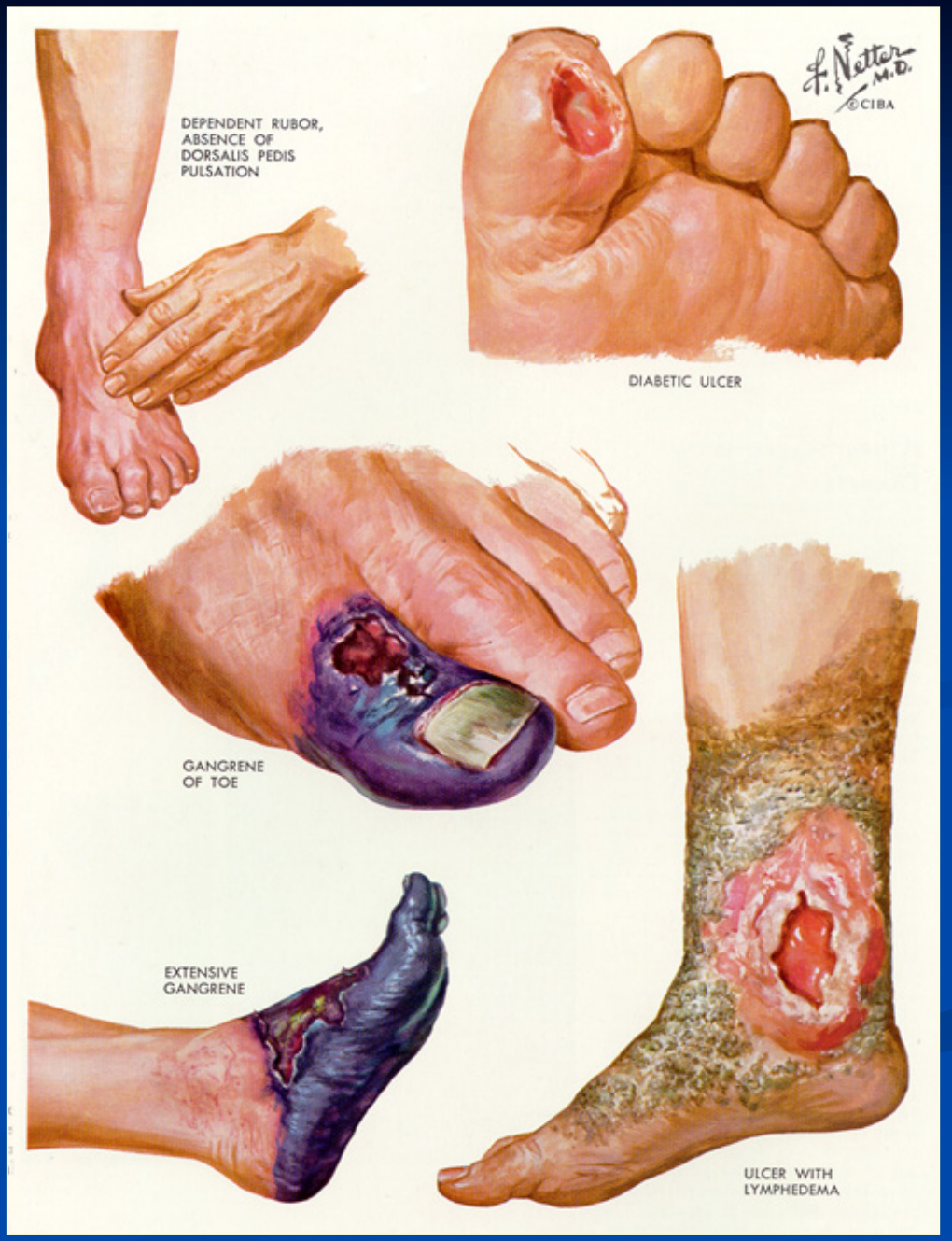




- necrotizing papillitus

(b) Macrovascular

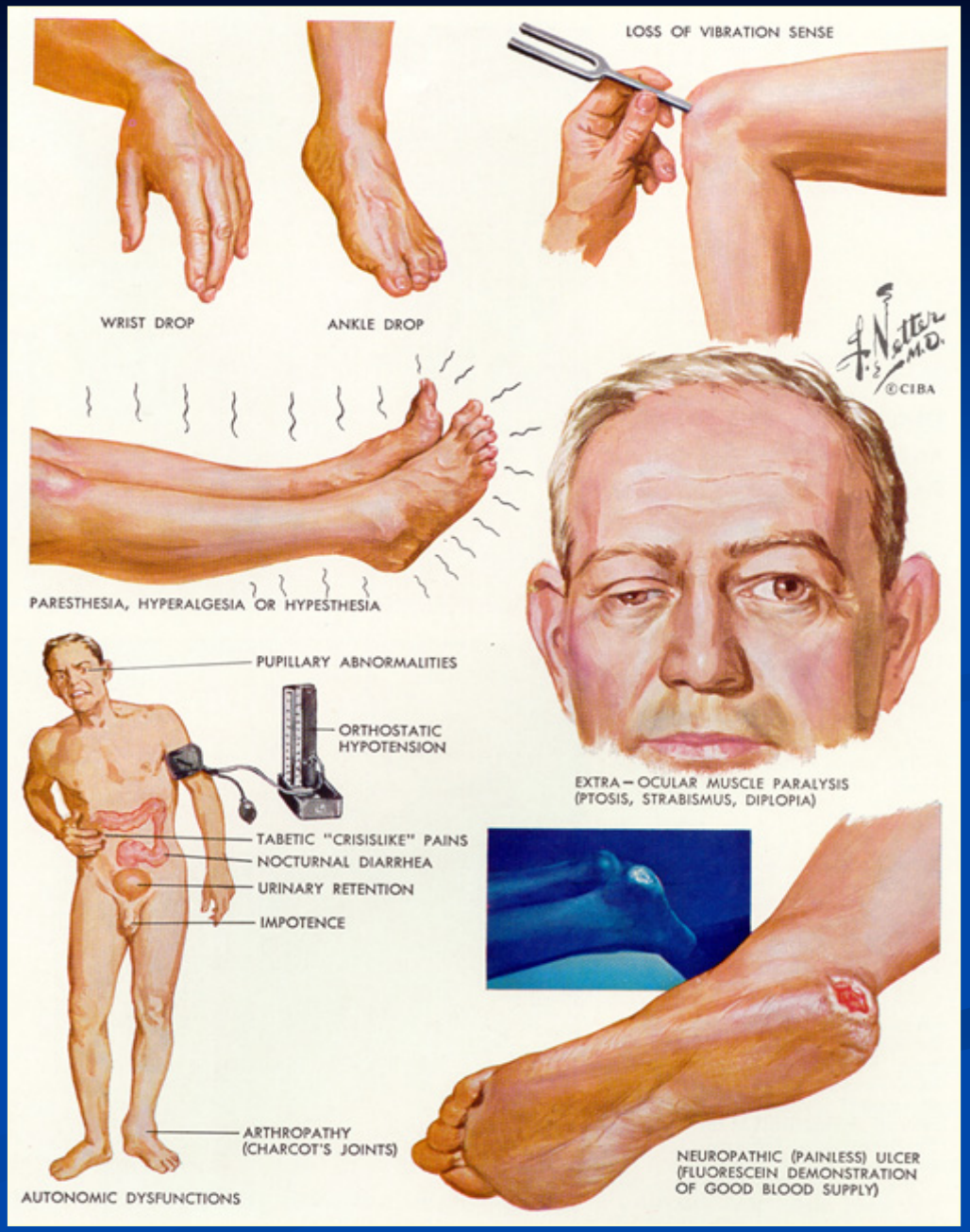
- cerebrovascular disease → ↑ stroke
- cardiovascular disease → ↑ MI
- peripheral vascular disease
  - ↳ diabetic foot infections



(c) Neuropathy

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

diabetic neuropathies



III. Criteria for diagnosis of PREDIABETES & DIABLETES

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

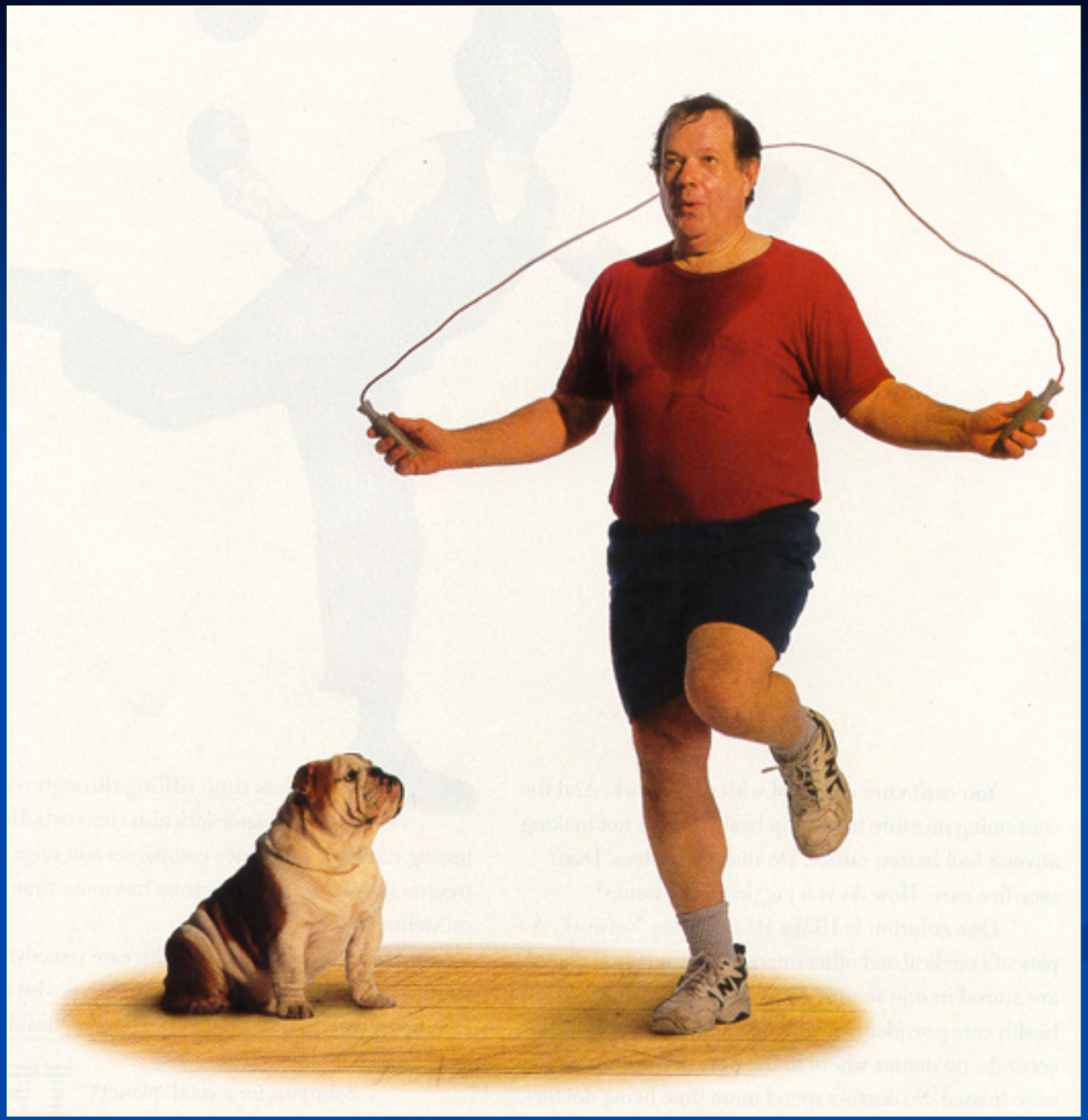
A. Lifestyle Modifications

(2) Nutrition

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

(2) Exercise

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



Sample Caloric Requirement (BEE) Calculation for Stressed Patients

Female: 655 + (9.6 x wt. in kg) + (1.85 x ht. in cm) – (4.7 x age)

Male: 66 + (13.7 x wt. in kg) + (5.00 x ht. in cm) – (6.8 x age)

Sample Calculation (based on patient-specific parameters: ht, wt, age, and disease state)

S.Y. is a 64 year-old female patient with major sepsis. Calculate her caloric requirement based on her pathologic condition. Her height is 5'4" and body weight is 140 pounds.

Conversion Factors:

- body weight from pounds to kg. : 140 lbs / 2.2 = 63.64 kg
- height from inches to cm. : 5'4" = 64 inches x 2.54 = 162.56 cm

BEE = 655 + (9.6 x **63.64**) + (1.85 x **162.56**) – (4.7 x **64**)

= (655 + 610.94 + 300.74) – (300.8)

= 1265.88 kcal / day

Multiply the BEE value by the appropriate "disease stress factor", which provides additional calories to account for the degree of physiologic stress (based on increased metabolic requirement during pathologic condition – i.e., major sepsis).

BEE for major sepsis = 1.5 x 1265.88

Answer → 1898.82 kcal / day

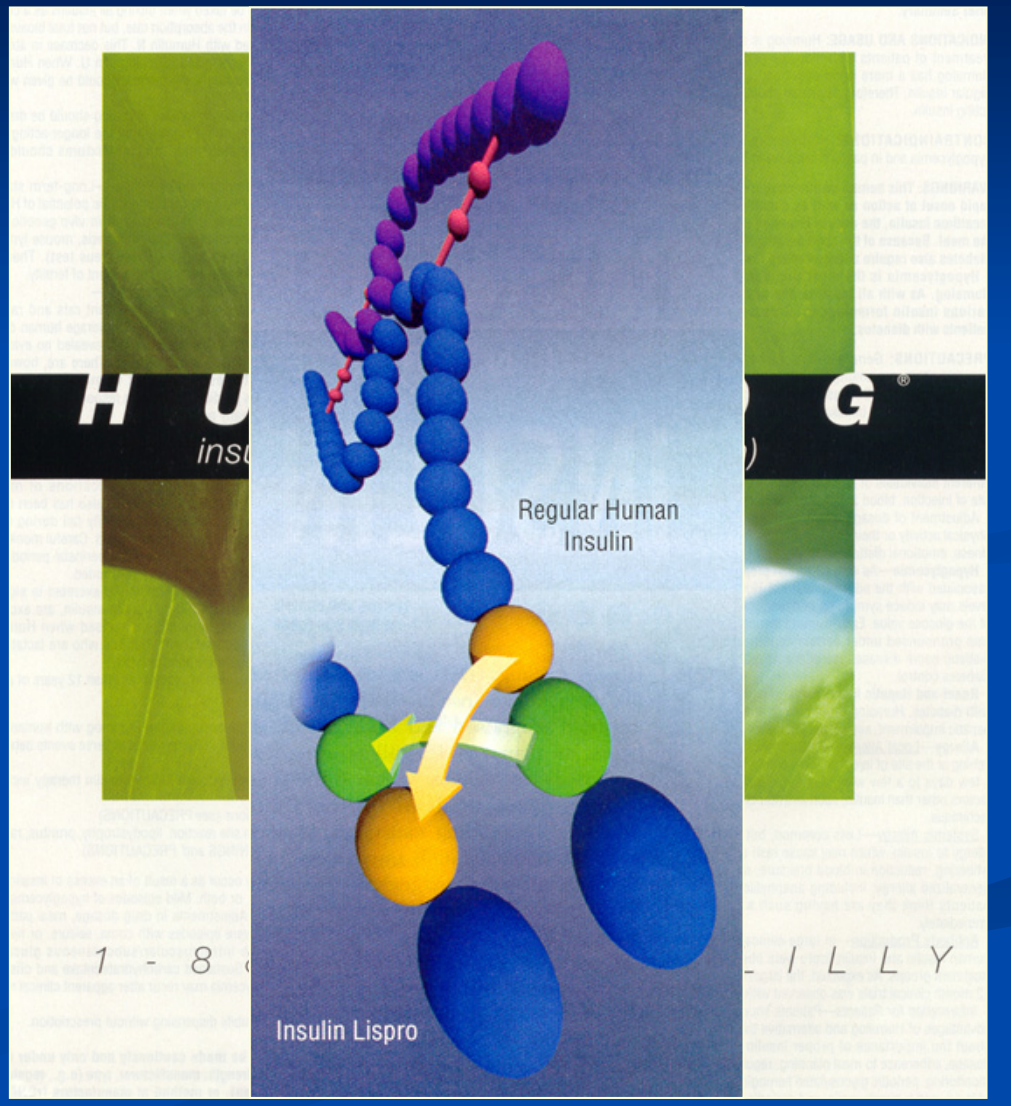
III. Pharmacologic Management of IDDM

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 AC & HS	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 AC & HS	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 Q12H	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 Q12H		$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

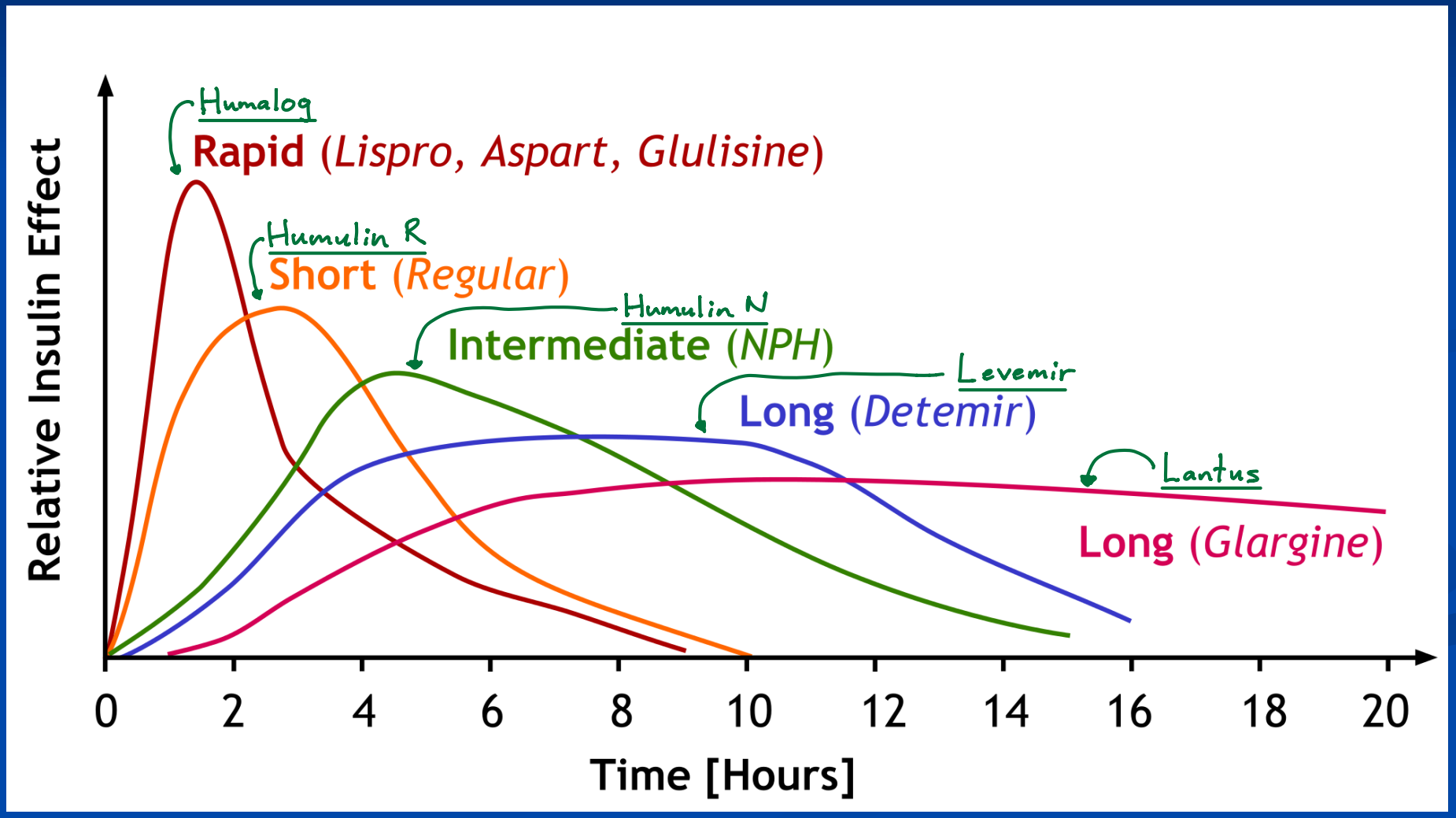
Indice	Normal	Intensive	Acceptable	Poor
Fasting	< 115	70-120	<140	>200
2 hrs pp	< 140	< 180	< 200	> 235
HgbA1c	4 - 6 %	6 - 7 %	7.5 - 8.0	> 9.0
Urine Gluc	neg	rare	intermit	constant
Urine Keto	neg	rare	rare	intermit

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

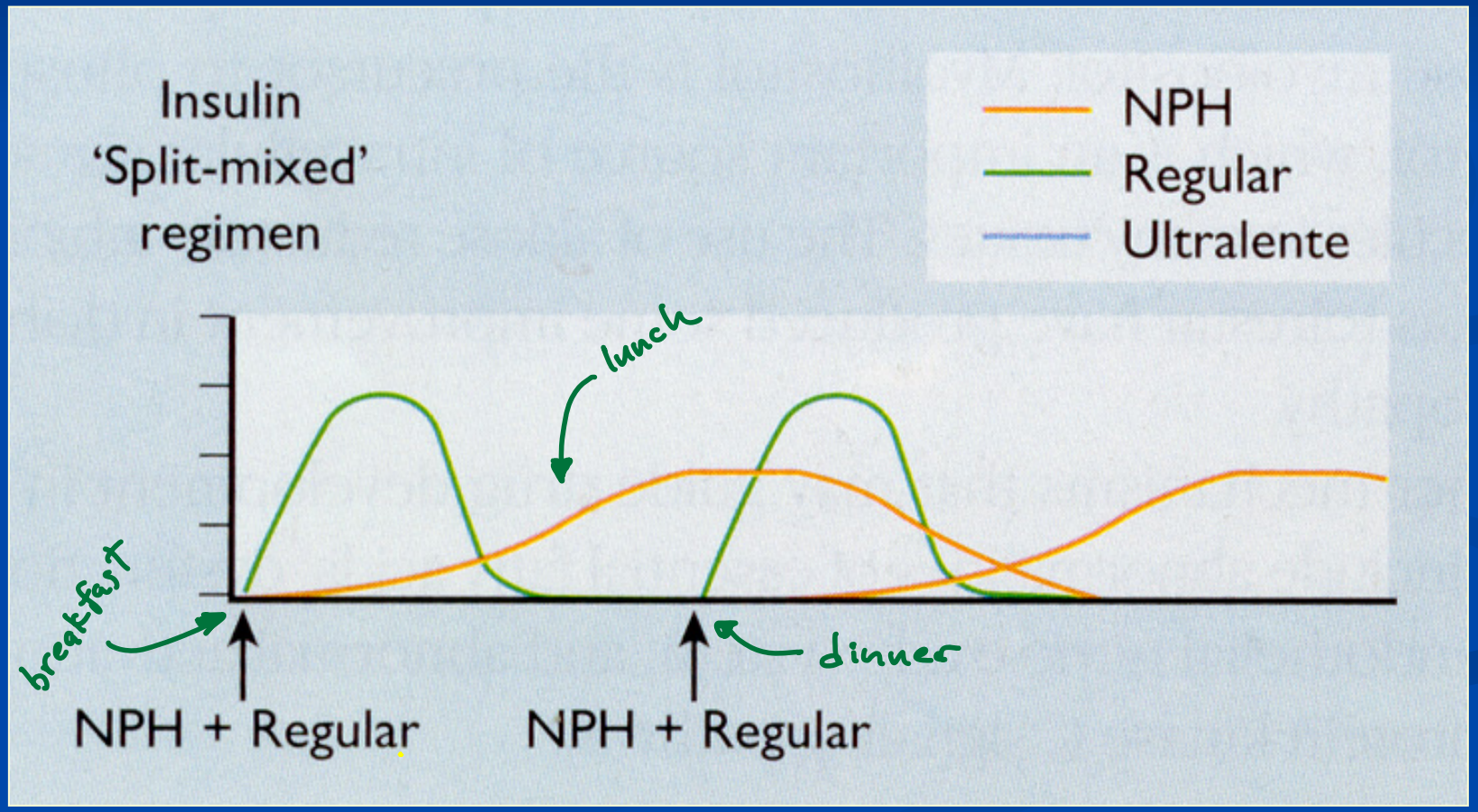
E. Time Profile Curves of Current Insulin Products

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

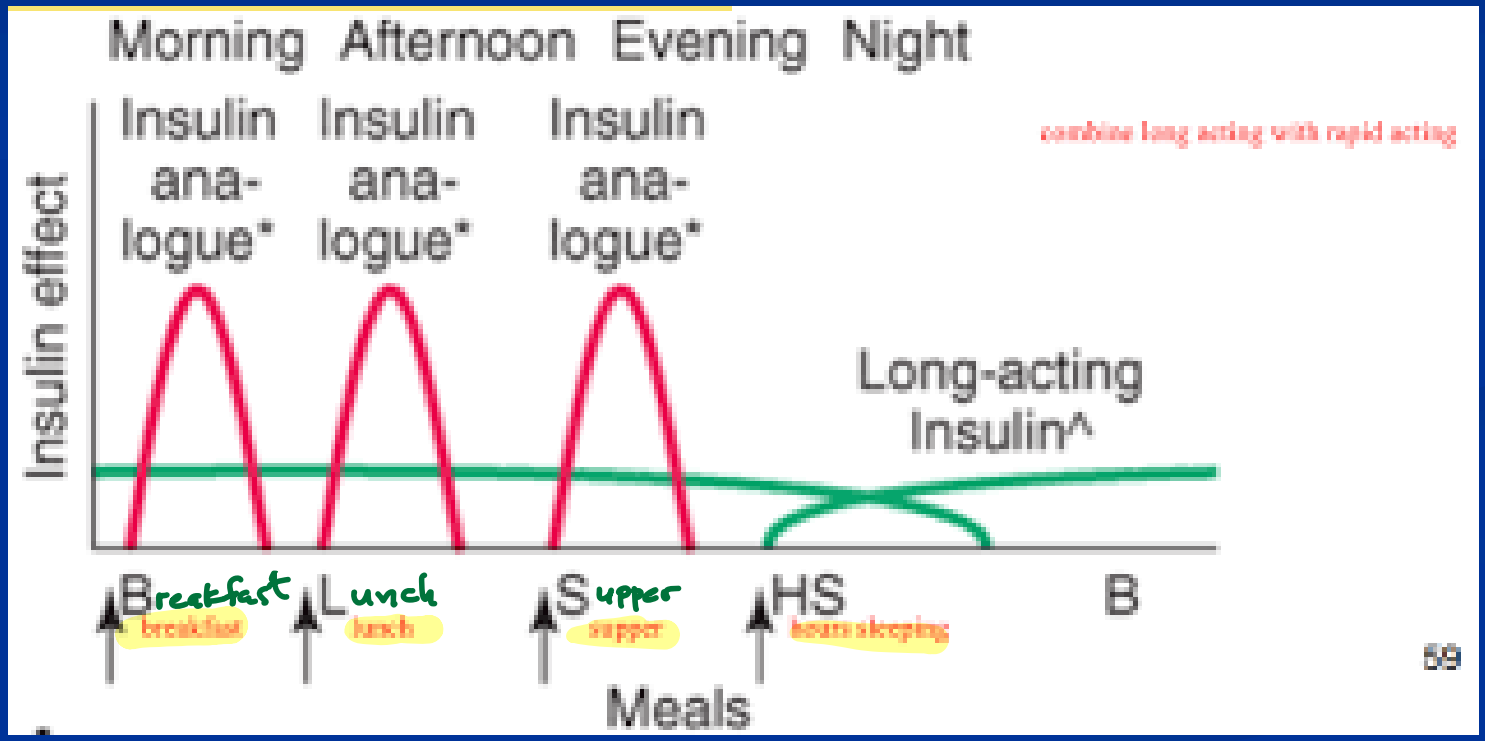


(1) Method 1: 7AM --> NPH:Reg (2/3 of daily dose)

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



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

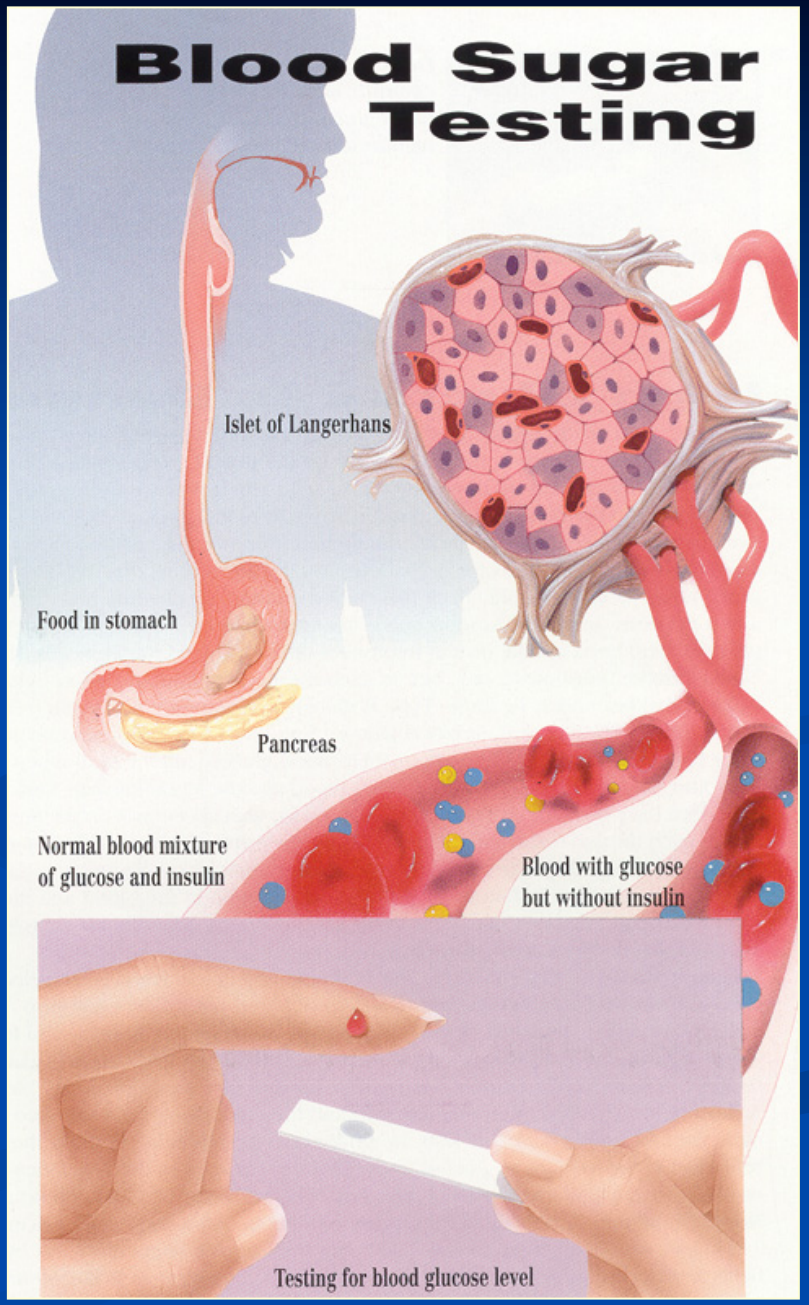


E. Monitoring Patients on Insulin Therapy

(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), apple 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 (β_2 blockade (liver))
		masks sx's hypoglycemia
salicylates (NSAIDs)	++	↑ insulin secretion/sensitivity
		↑ serum sulfonylurea levels (plasma protein binding displacement)

G. Hyperglycemia

(1) Signs & Symptoms

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

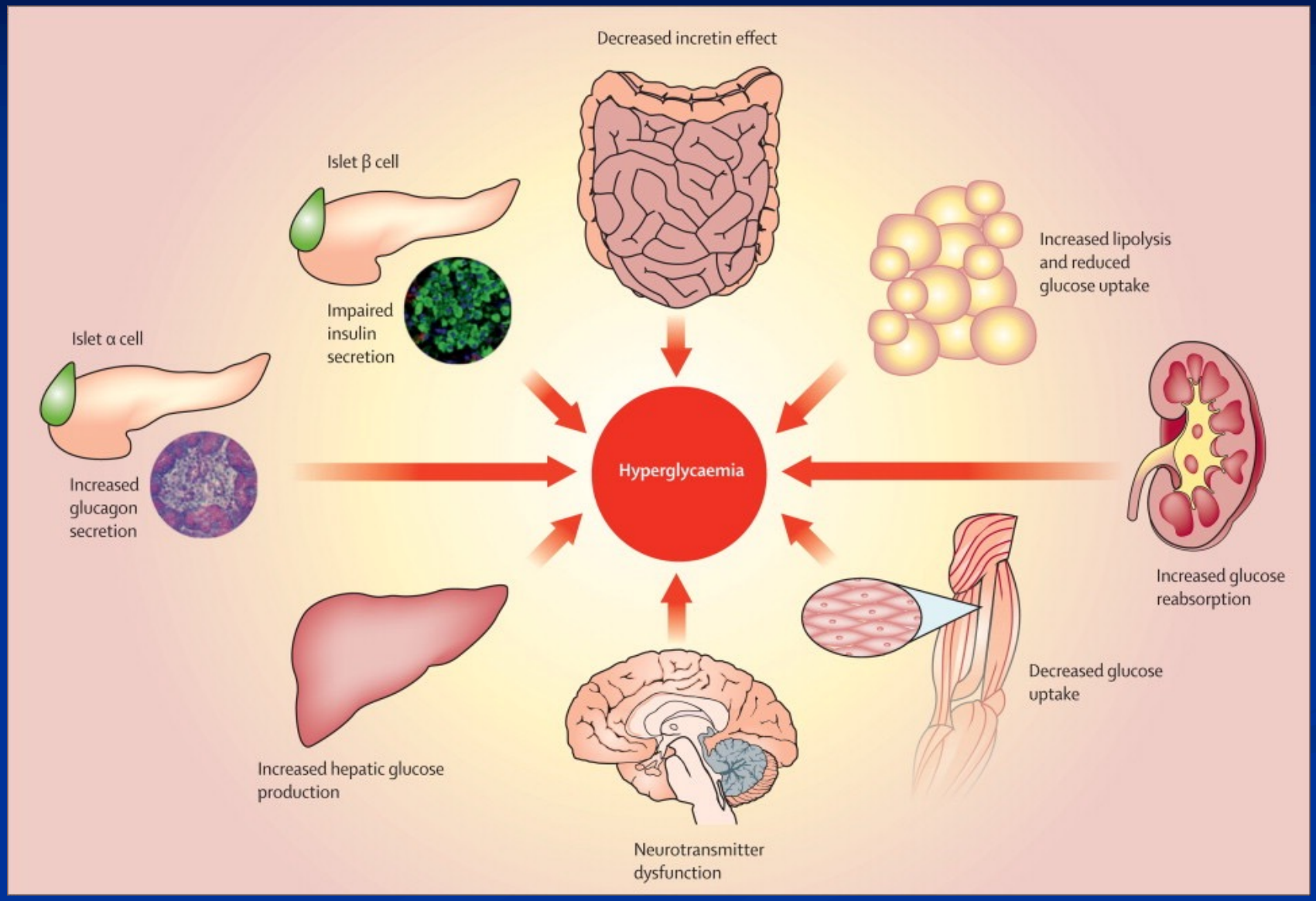
(2) Somogyi Effect --> "post-hypoglycemic hyperglycemia" or "rebound hyperglycemia"

- tx: → reduction of evening regular insulin dose

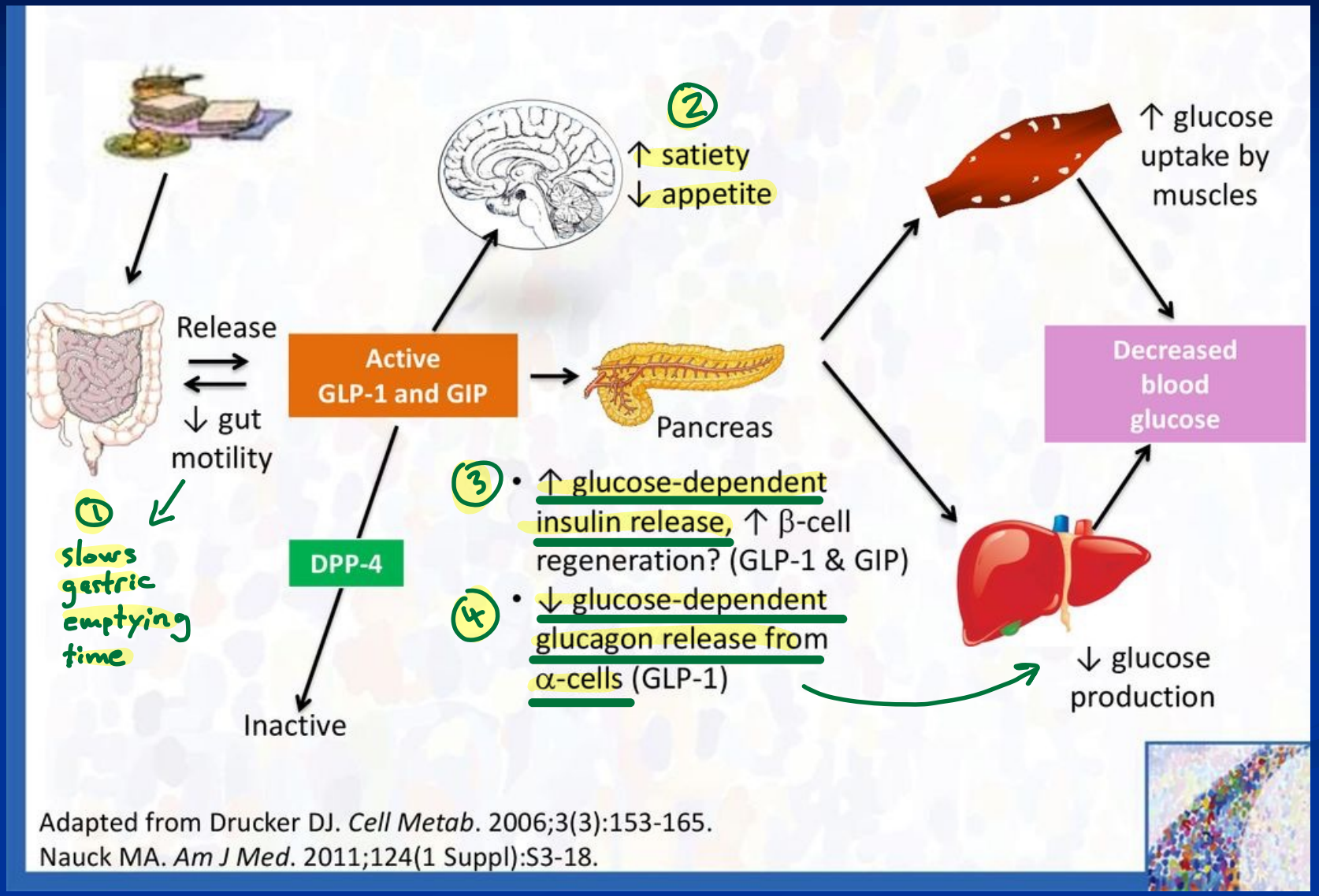
  → increase calories at evening meal

  → increase evening NPH dose

IV. Pharmacologic Management of Type II DM



Role of Incretins in Glucose Homeostasis

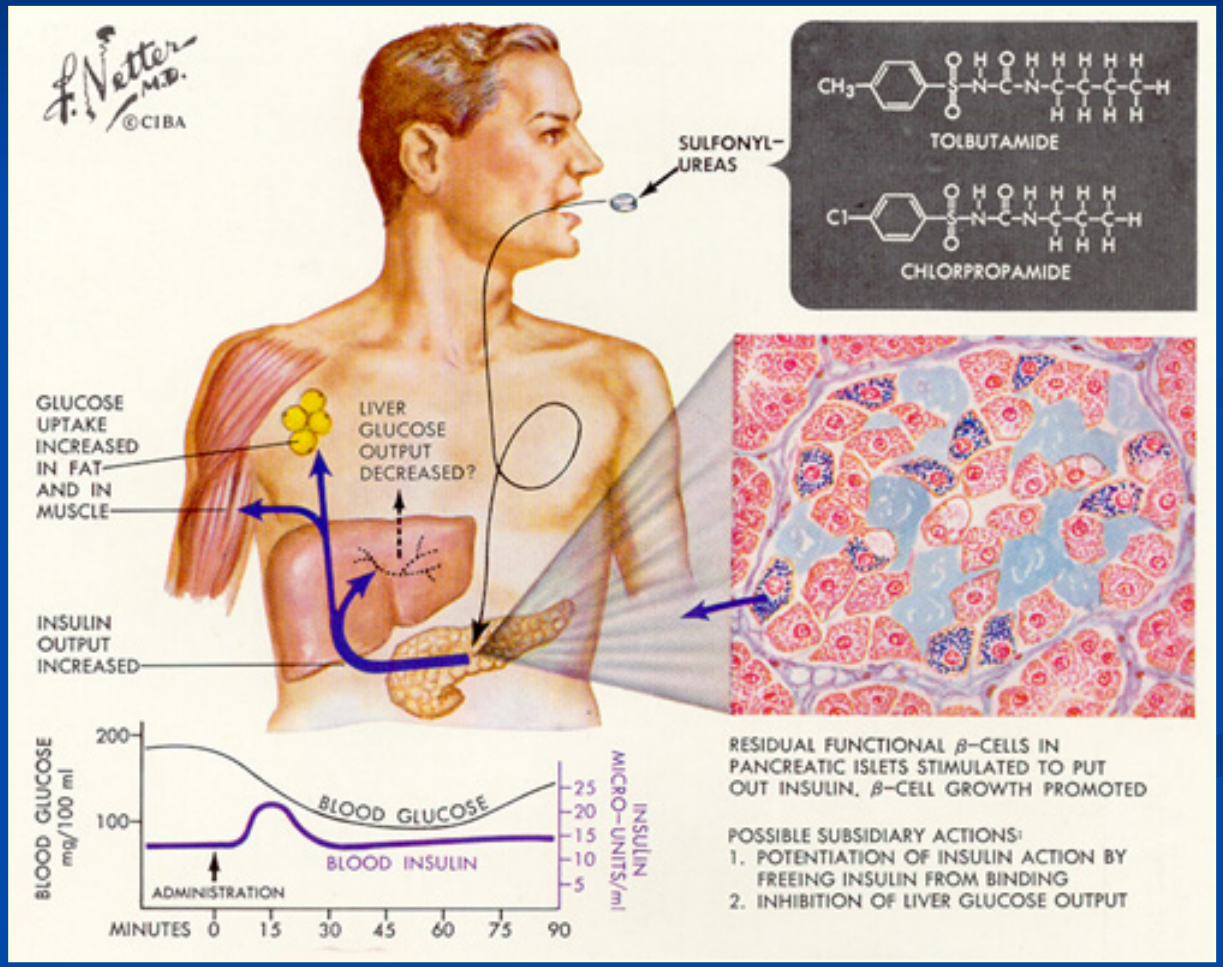


Adapted from Drucker DJ. *Cell Metab*. 2006;3(3):153-165.
Nauck MA. *Am J Med*. 2011;124(1 Suppl):S3-18.

A. Sulfonylurea Drugs (cont.)

(1) Mechanism of Action

→ increase production and release of insulin by the pancreas



A. Sulfonylurea Drugs (Mechanism of Action)

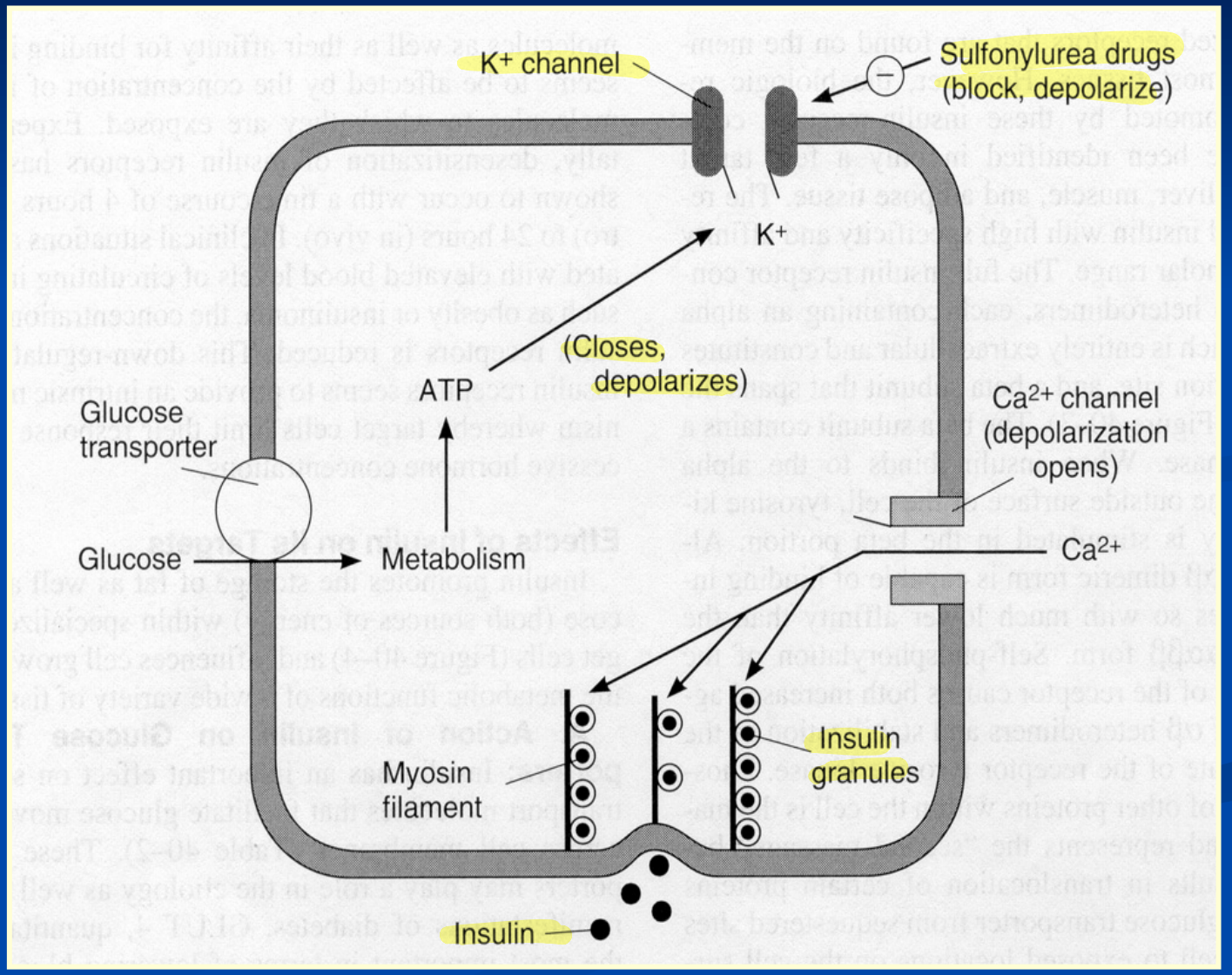
block K channels

↓

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 half-life → once daily dosing Q AM

Side Effect: Potential of hypoglycemia

B. Metformin (Glucophage)

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)

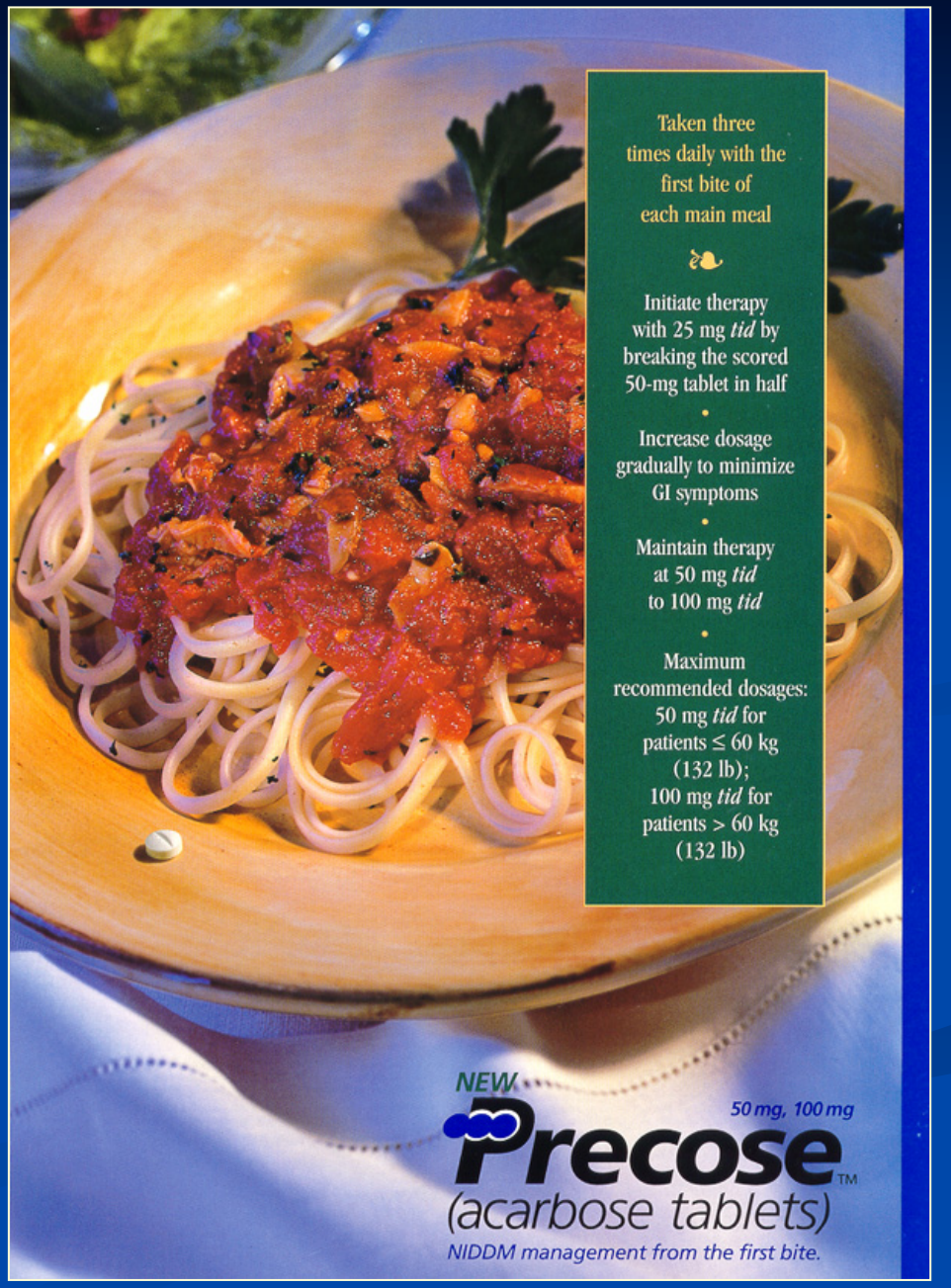
(d) GFR < 30 ml/min → contraindicated
GFR < 45 ml/min → caution: risk vs benefit

high metformin levels → lactic acidosis

C. Acarbose (Precose)

Mechanism of Action

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

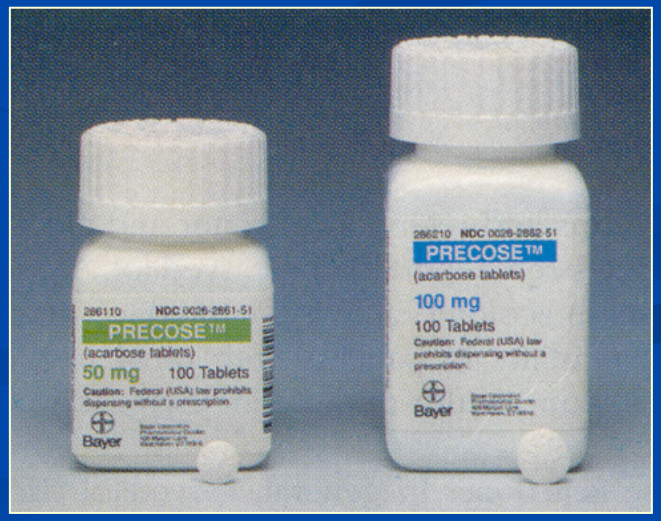


Acarbose (Precose)

(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: Rosiglitazone (Avandia) &
(TZD's = Glitazones) 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

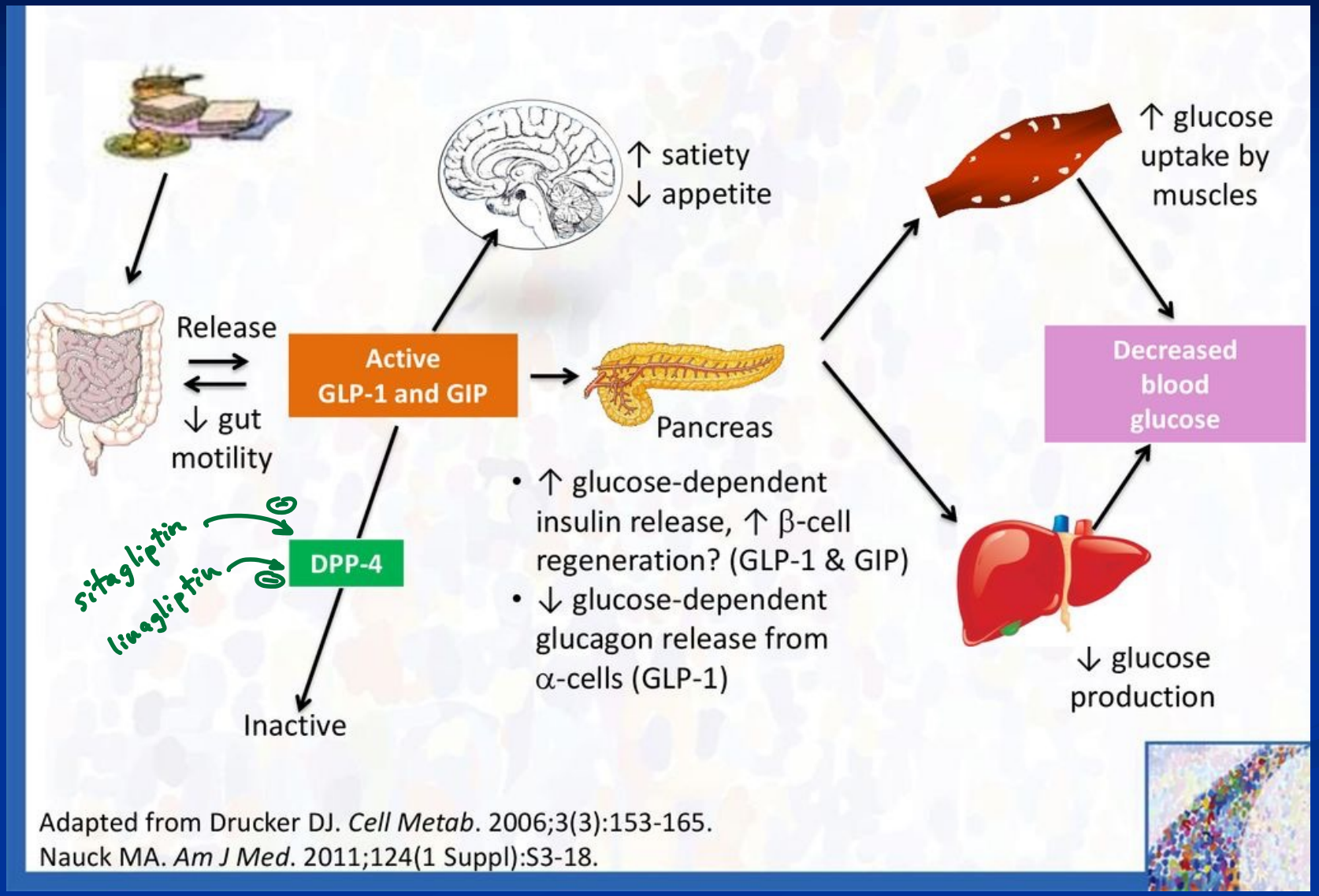
Sitagliptin (Januvia)
Linagliptin (Tradjenta)

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

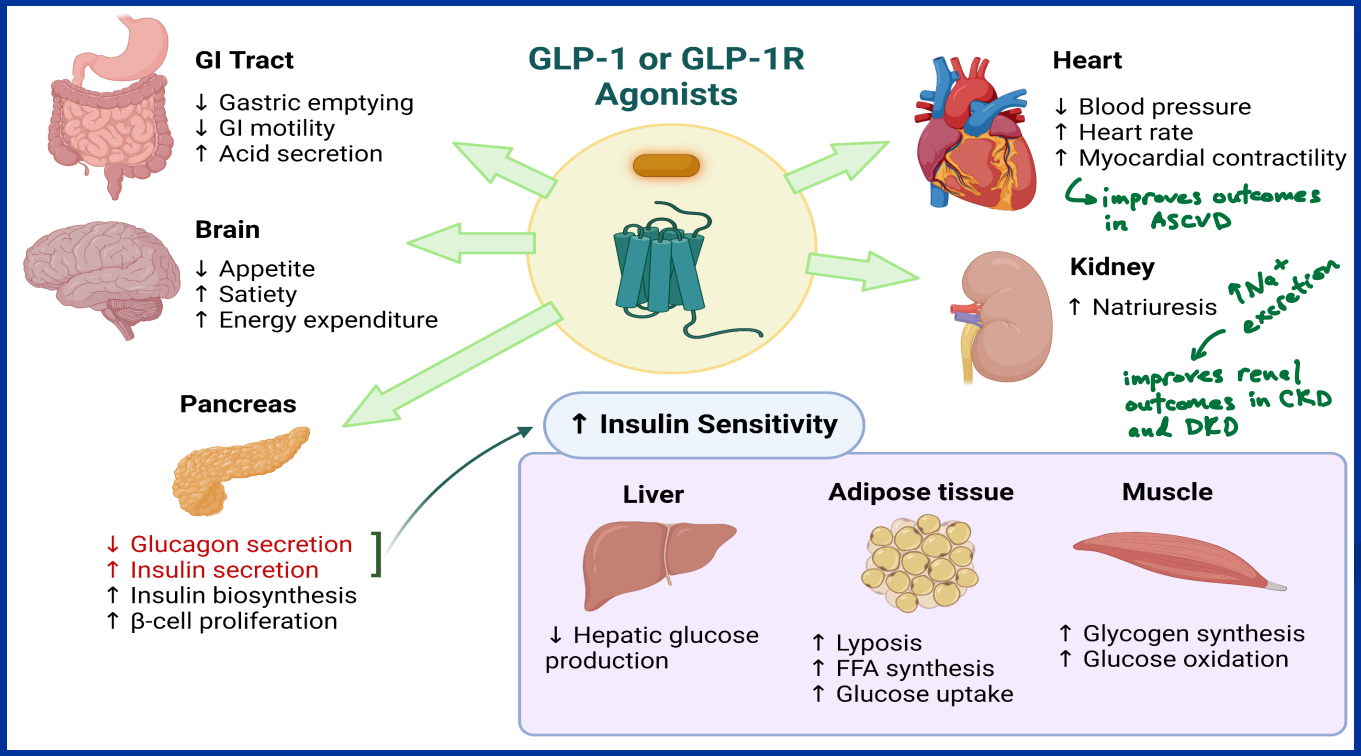


F. GLP-1 Receptor Agonists

- Semaglutide (Ozempic, Wegovy)
- Dulaglutide (Trulicity)
- Liraglutide (Victoza)
- Tirzepatide (Mounjaro)

injectable (SC) products

- ✓ Increase Insulin Release
  PLUS
- ✓ Decrease Glucagon Release
  PLUS
- ✓ Increases Satiety
  PLUS
- ✓ Slows Gastric Emptying Time



GLP-1 Receptor Agonists	Semaglutide (Ozempic, Wegovy) Dulaglutide (Trulicity) Liraglutide (Victoza) Tirzepatide (Mounjaro)

Adverse Effects (Gastrointestinal)

- Nausea (26-50%) and Vomiting; Diarrhea.
- Nausea: (1) reduced with gradual dose titrations and (2) wanes with continued use.

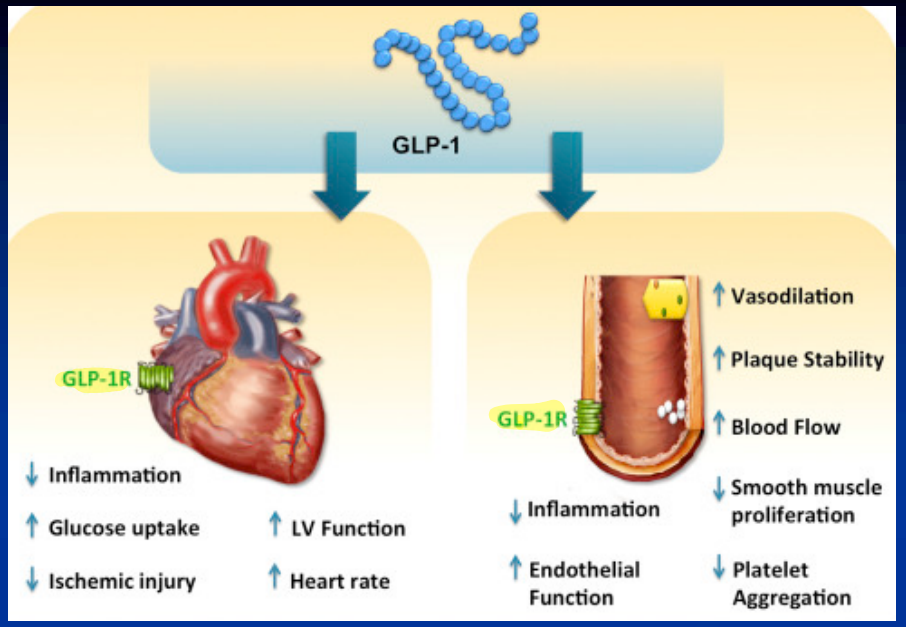
General Considerations

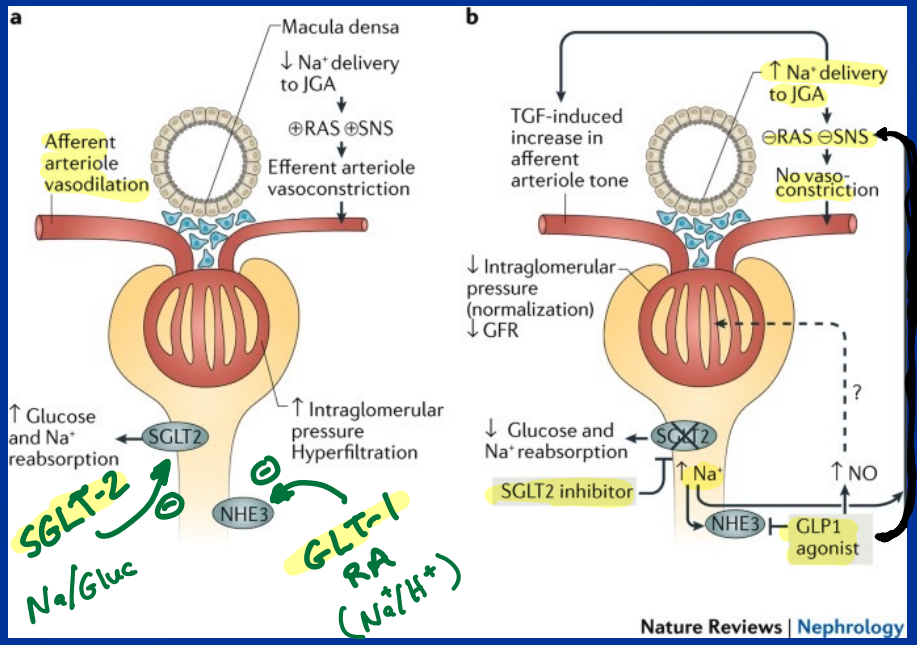
- GLP-1 receptor agonists are indicated for use in combination with metformin for patients with existing ASCVD when weight loss is a primary consideration and cost or injectables formulations of GLP-1 agonists are not limiting factors.
- GLP-1 receptor agonists may also be used in combination with basal insulin with or without metformin when HgbA1C levels remain persistently high.
- Tirzepatide (Monjaro) is a dual-acting GLP-1 and GIP receptor agonist for Type II diabetic patients without ASCVD who may benefit from weight loss, since there is insufficient evidence that tirzepatide provides protection against ASCVD.

GLP-1 Receptor Agonist Benefits in ASCVD (Atherosclerotic Cardio-vascular Disease) and CKD

CKD

- In CKD, GLP-1 RA induces natriuresis and diuresis by inhibiting the sodium–hydrogen exchanger 3 (NHE3) located in the renal proximal tubular → increases tubular sodium transport to the macula densa → reduces intraglomerular pressure and hyperfiltration → restores tubular glomerular feedback and improves kidney outcomes in CKD.
- In CKD, GLP-1 RA decreases circulating concentrations of angiotensin II → decreases BP and Na/H_2O retention.

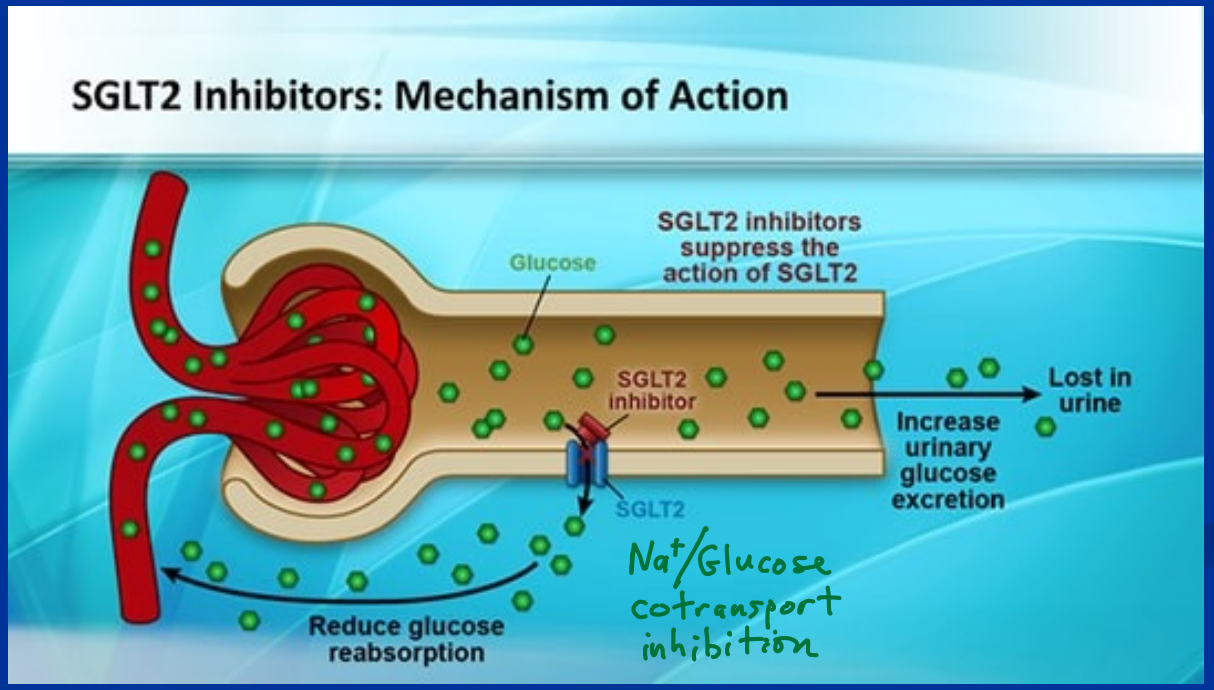




G. SGLT-2 Inhibitors (Sodium-Glucose Co-Transport Inhibitors)

Canaglifozin (Invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)

MOA: Lower blood glucose levels by increasing kidney excretion of glucose into the urine



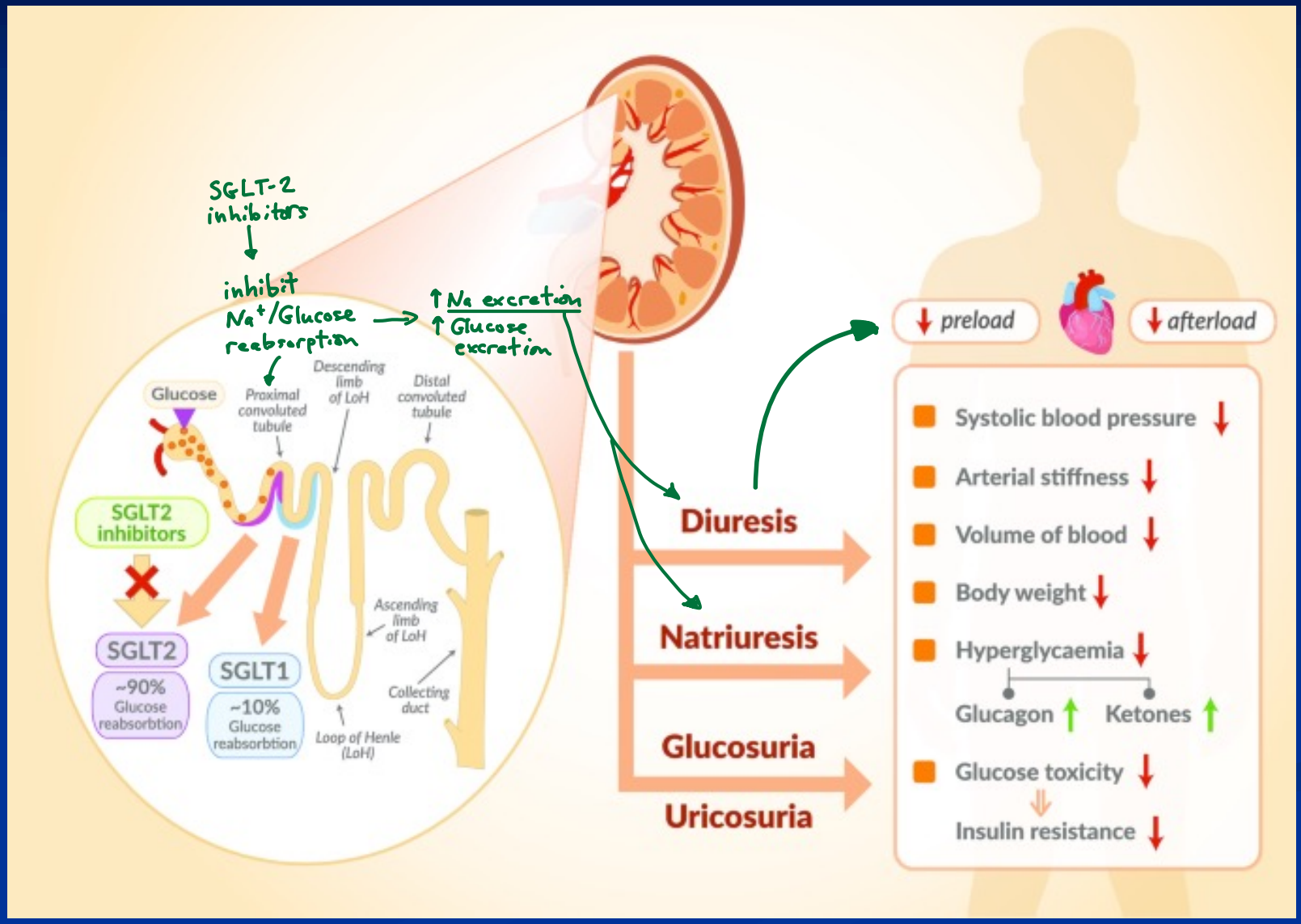
SGLT-2 Inhibitors
(Sodium-Glucose Co-Transport Inhibitors)

Canaglifozin (Invokana)
Dapagliflozin (Farxiga)
Empagliflozin (Jardiance)

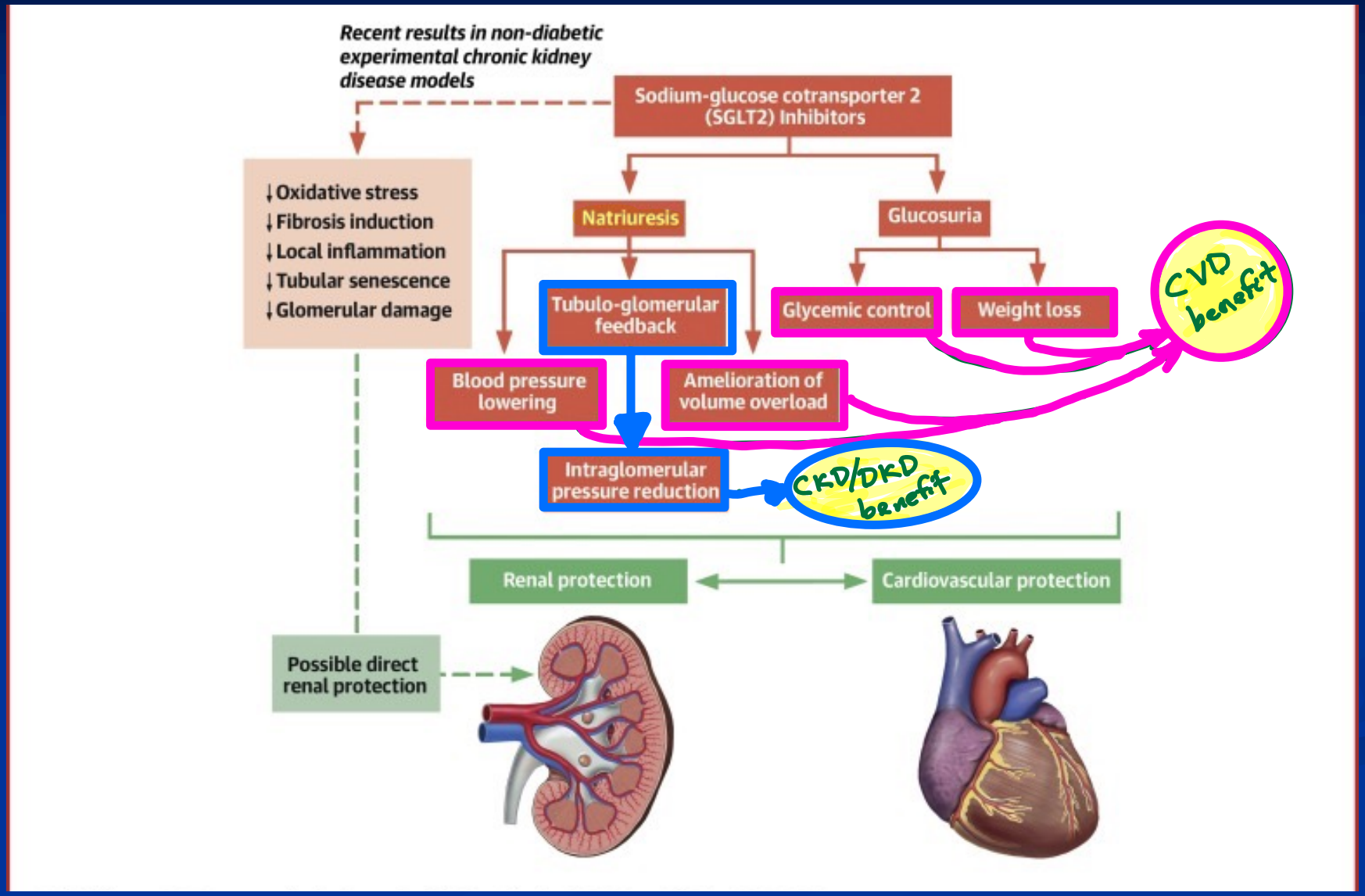
Adverse Effects: Yeast infections (vaginal candidal infections), UTIs, dehydration → hypotension, DKA, and bone fractures

Note: SGLT-2 Inhibitors are contraindicated in patients with CrCl ≤ 30 ml/min.

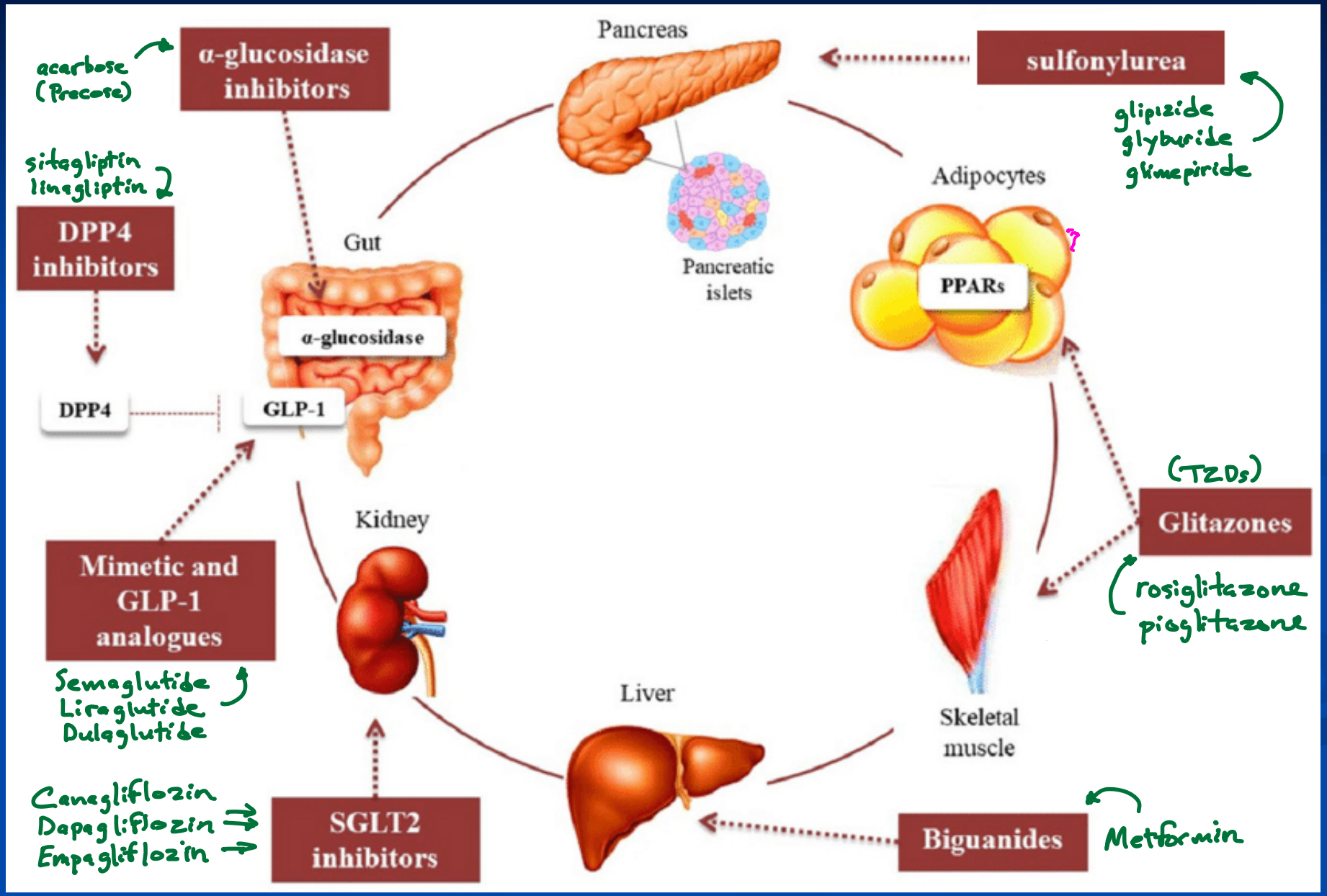
SGLT-2 Inhibitors: Cardiovascular Protection



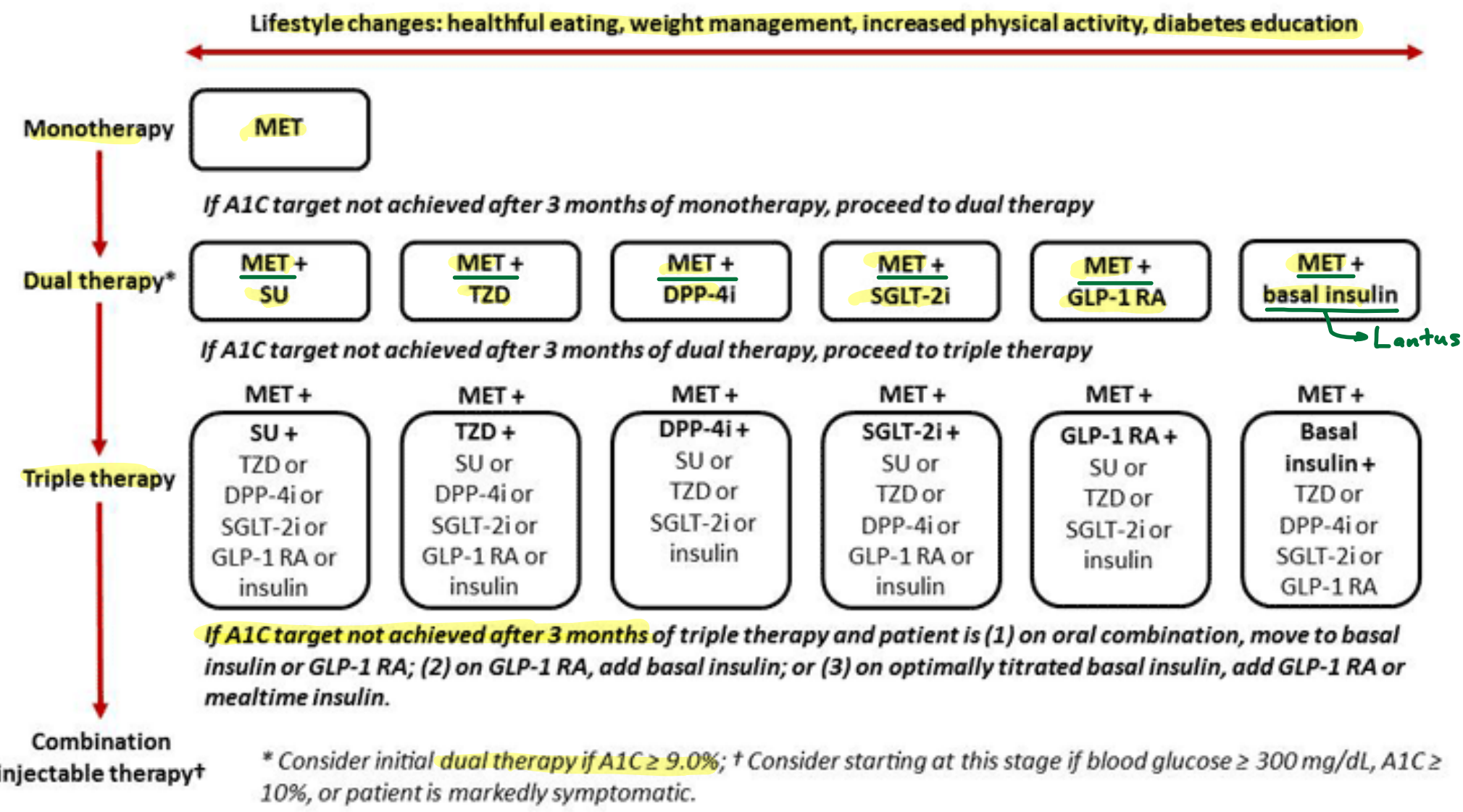
SGLT-2 Inhibitor Cardiorenal Protection Summary



OVERVIEW: Pharmacologic Agents in the Treatment of Type II DM



V. Antihyperglycemia Tx in Adults w/ Type II DM



Summary of Glucose-Lowering Pharmacologic Agents in Type II DM

Intervention	Expected decrease in A1C with monotherapy (%)	Advantages	Disadvantages
Initial therapy			
Lifestyle change to decrease weight and increase activity	1.0 to 2.0	Broad benefits	Insufficient for most within first year owing to inadequate weight loss and weight regain
Metformin	1.0 to 2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency (eGFR <30 mL/min/1.73 m^2)*
Additional therapy¶			
Insulin (usually with a single daily injection of intermediate- or long-acting insulin initially)	1.5 to 3.5	No dose limit, rapidly effective, improved lipid profile	1 to 4 injections daily, monitoring, weight gain, hypoglycemia, analogs are expensive
Sulfonylurea (shorter-acting agents preferred)	1.0 to 2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
GLP-1 receptor agonist (daily to weekly injections)	0.5 to 1.5	Weight loss, reduction in major adverse cardiovascular events (MACE) (liraglutide, semaglutide, dulaglutide) in patients with established CVD and potentially for those at high risk for CVD	Requires injection, frequent GI side effects, expensive
Thiazolidinedione	0.5 to 1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, HF, weight gain, bone fractures, potential increase in MI (rosiglitazone) and bladder cancer (pioglitazone)
SGLT2 inhibitor	0.5 to 0.7	Weight loss, reduction in systolic blood pressure, reduced cardiovascular mortality in patients with established CVD, improved renal outcomes in patients with nephropathy	Vulvovaginal candidiasis, urinary tract infections, bone fractures, lower limb amputations, DKA
DPP-4 inhibitor	0.5 to 0.8	Weight neutral	Possible increased risk of HF with saxagliptin, expensive
Alpha-glucosidase inhibitor	0.5 to 0.8	Weight neutral	Frequent GI side effects, 3 times/day dosing


PHARMACY
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