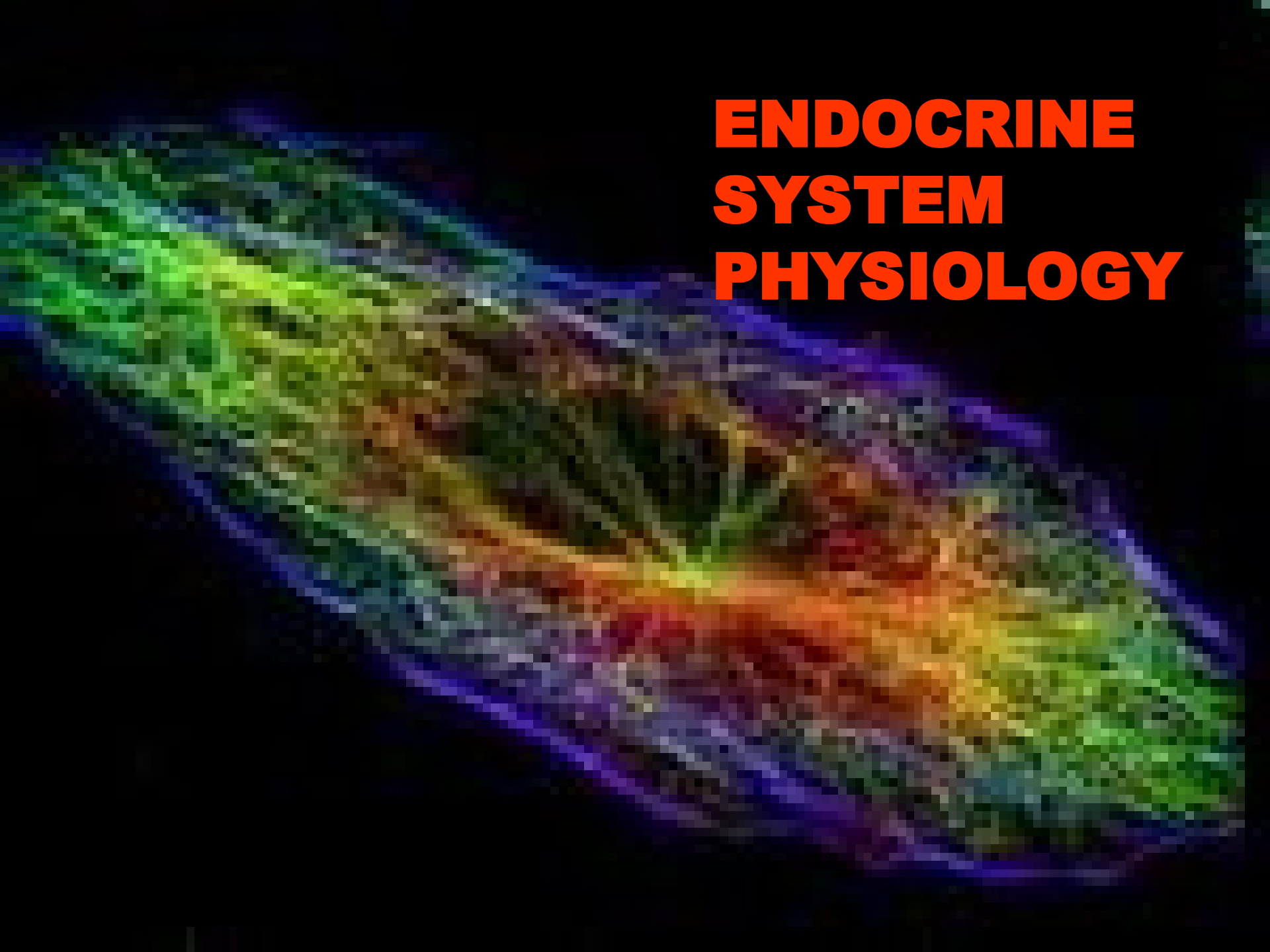
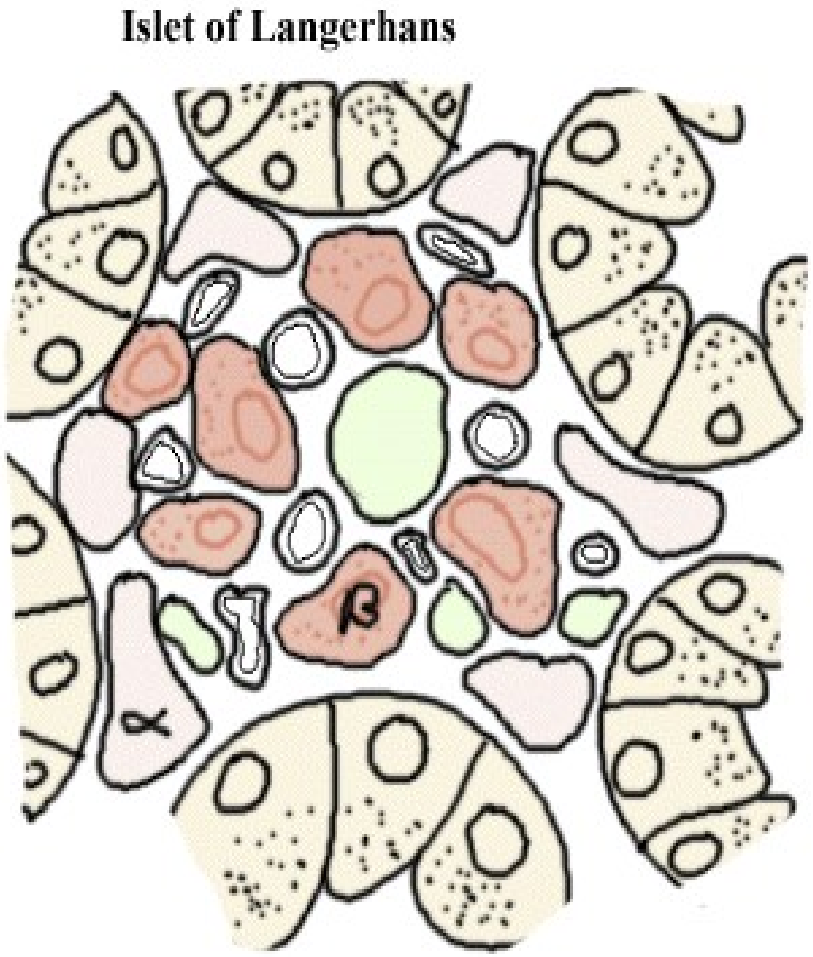

ENDOCRINE
SYSTEM
PHYSIOLOGY

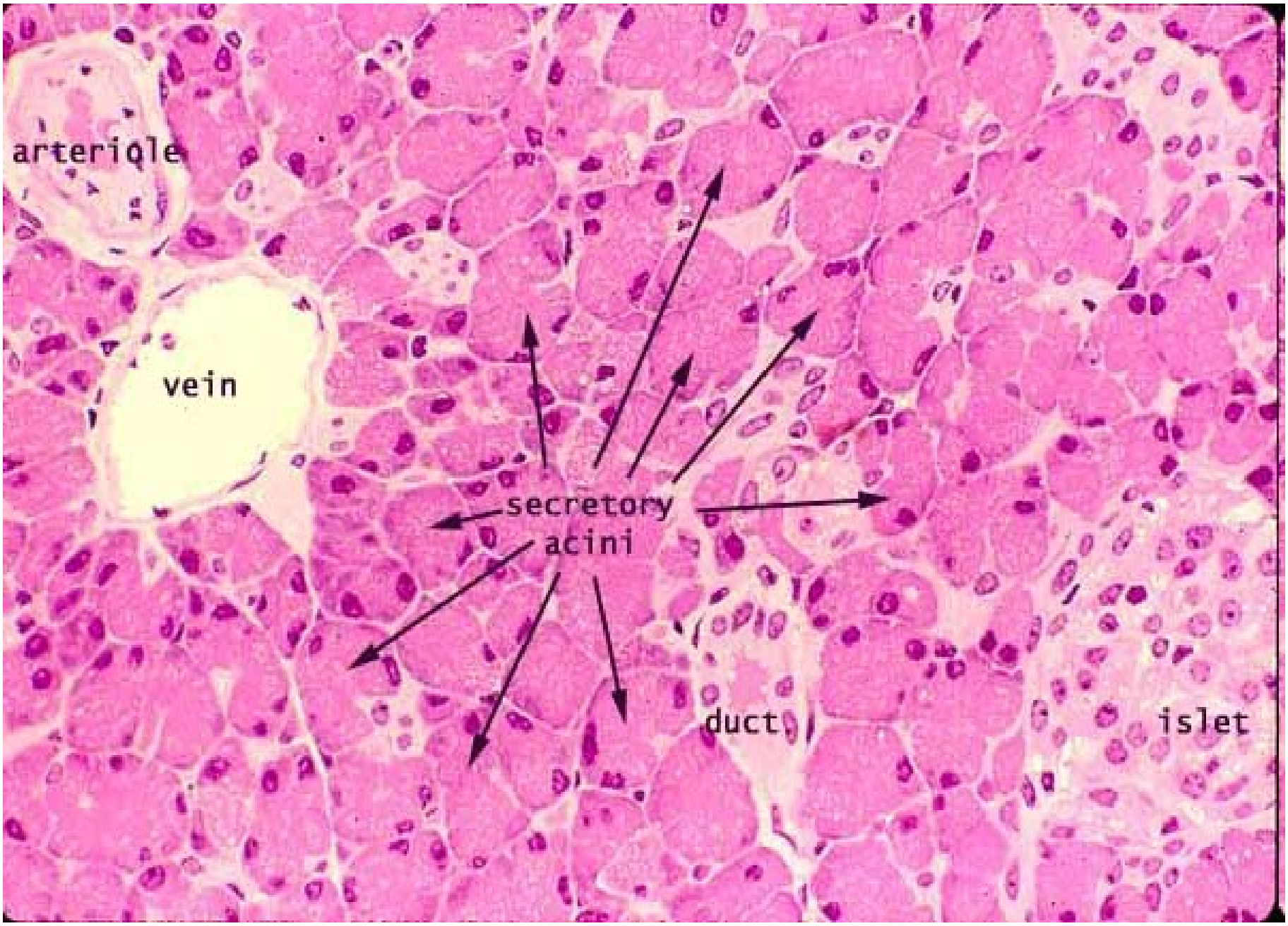
ENDOCRINE PANCREAS

- The endocrine pancreas consists of islets of Langerhans, which form 2% of the pancreatic tissue.
- Each islet consists of approximately 3000 cells.
- The human endocrine pancreas consists of approximately one million islets.



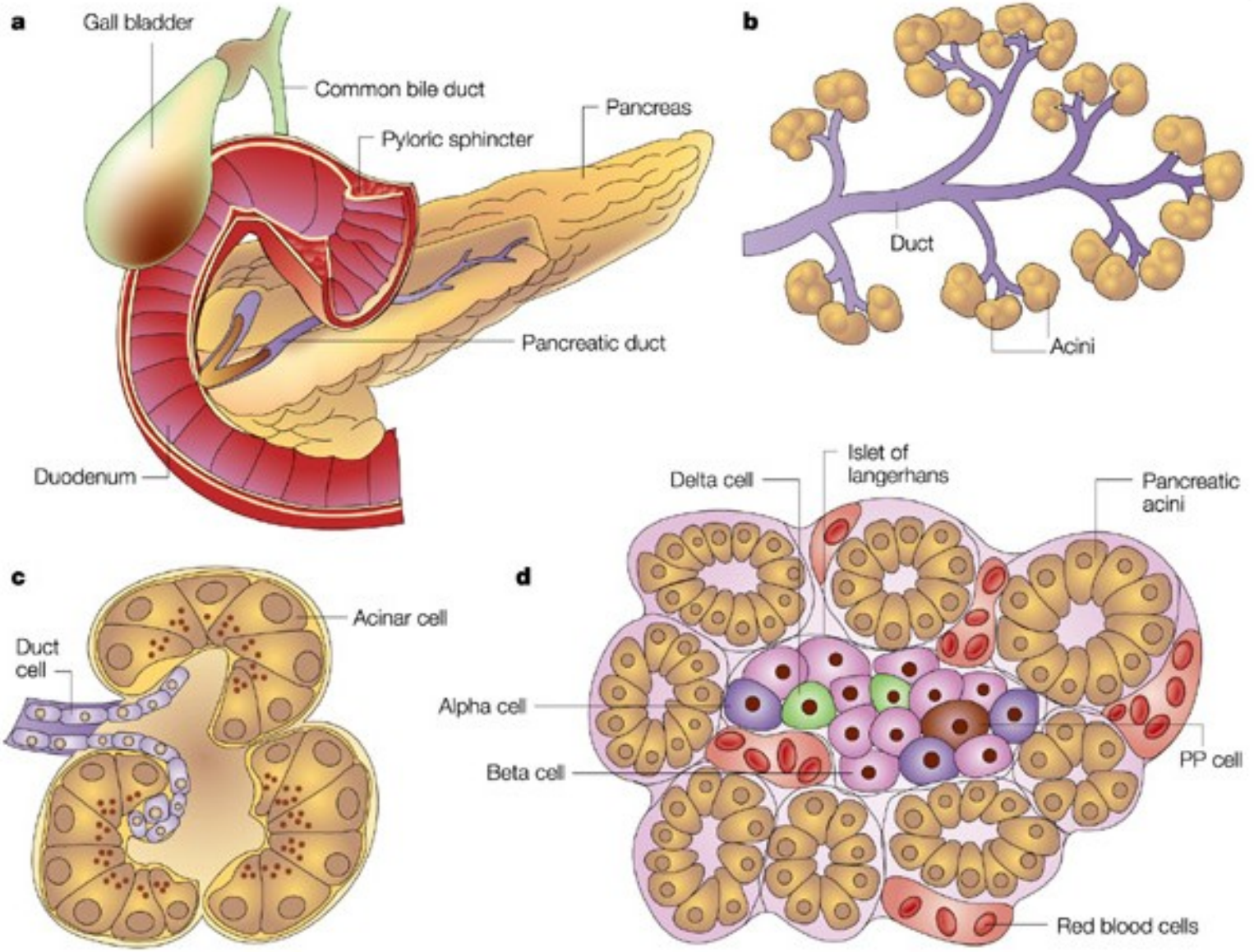
Endocrine Pancreas - Overview

- Islets of Langerhans (beta, alpha, delta cells)
  - Scattered in the head, body and tail of pancreas
  - Embedded in the enzyme secreting exocrine portion
  - Pink, granular cytoplasm with neuroendocrine granules
  - Each nest of islet cells has its own capillary network into which secretions are discharged
- Minor endocrine component
  - Scattered endocrine cells in the ducts leading from exocrine acini


arteriole
vein
secretory
acini
duct
islet

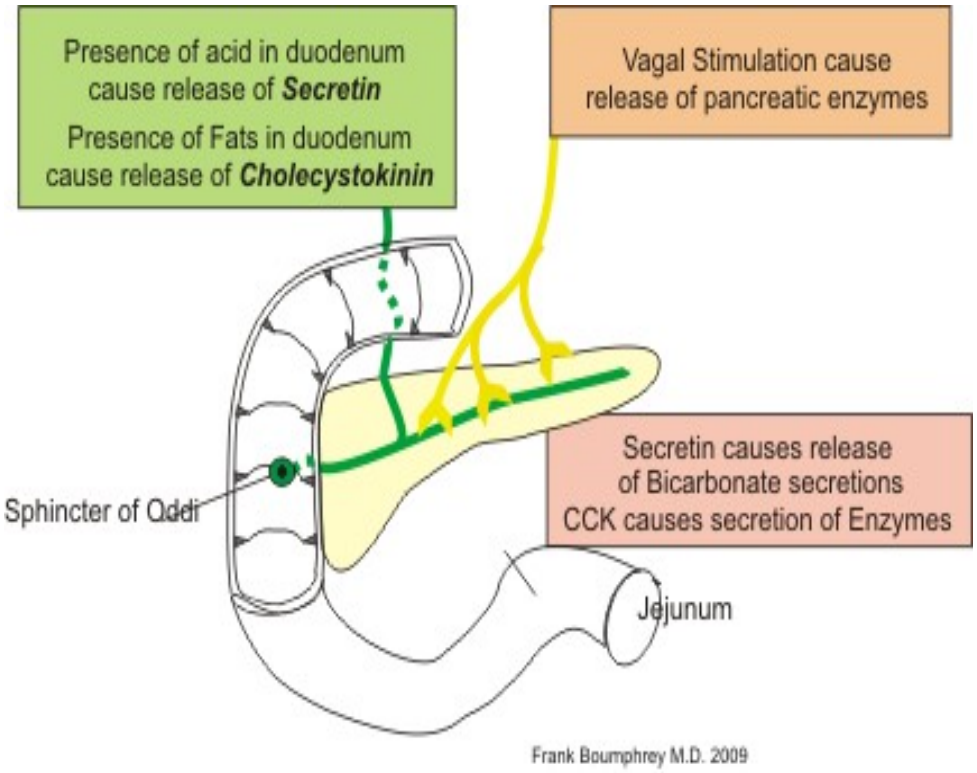
FOUR TYPES OF CELLS

- 1. Alpha cells make up about 25% of the islet cells and are the source of glucagon, which consists of 29 amino acid residues.
- 2. Beta cells constitute about 60% of the islet cells and are associated with insulin synthesis. This polypeptide consists of 51 amino acid residues.
- 3. Delta cells form about 10% of the islet cells and are the source of somatostatin, which is a tetradecapeptide.
- 4. Pancreatic polypeptide (PP or F) cells form approximately 5% of the islet cells and synthesize a polypeptide that contains 36 amino acid residues.


a
Gall bladder
Common bile duct
Pancreas
Pyloric sphincter
Pancreatic duct
Duodenum
b
Duct
Acini
c
Acinar cell
Duct cell
d
Islet of langerhans
Delta cell
Pancreatic acini
Alpha cell
Beta cell
PP cell
Red blood cells

NEUROTRANSMITTERS

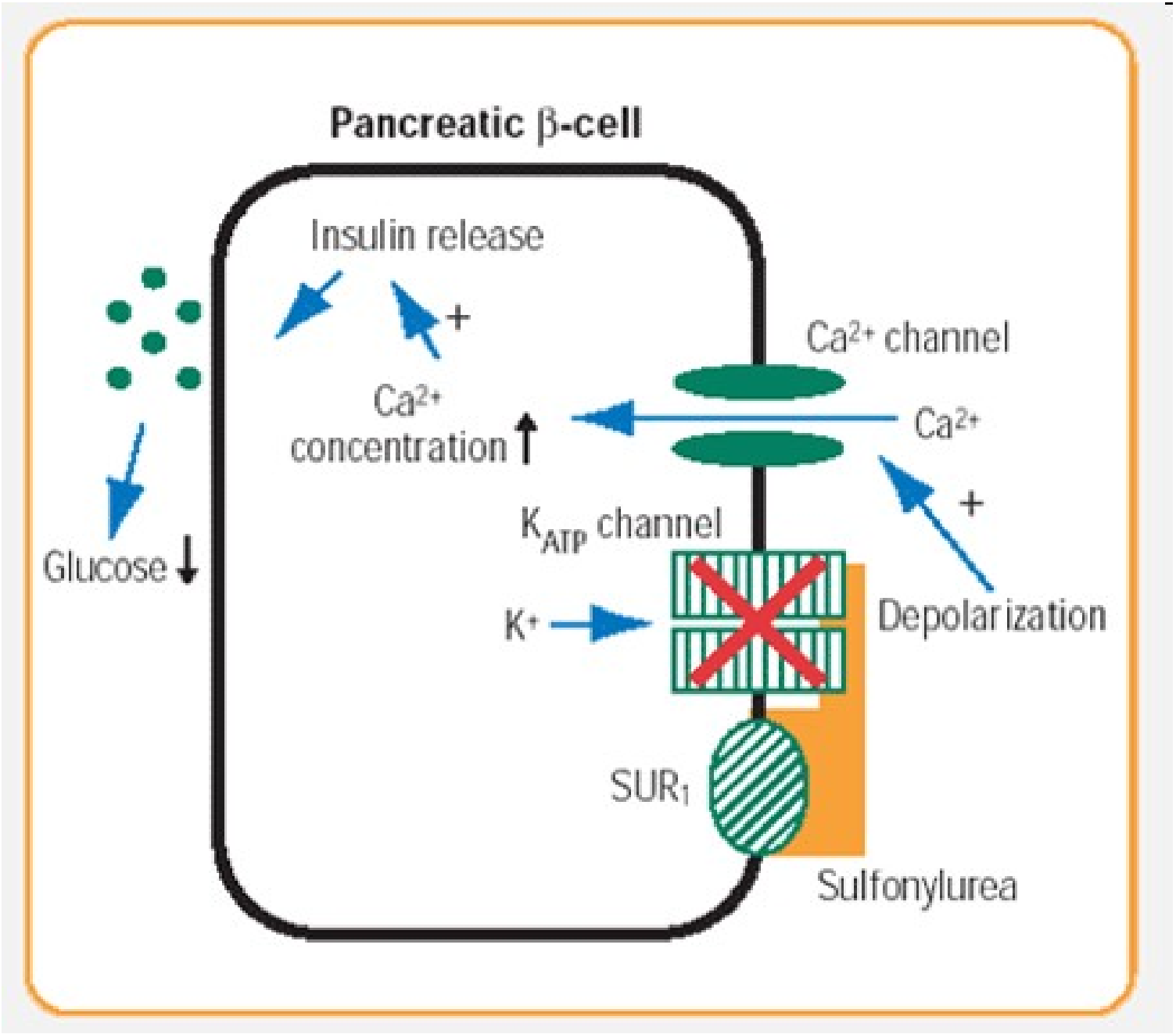
Unmyelinated postganglionic sympathetic and parasympathetic nerve fibers terminate close to the three cell types (alpha, beta, and delta cells) and modulate pancreatic endocrine function via the secretion of neurotransmitters.



Control of Pancreatic Secretions

NEUROTRANSMITTERS

- Acetylcholine secretion causes insulin release only when glucose levels are elevated. Acetylcholine appears to inhibit somatostatin release.
- Norepinephrine secretion from sympathetic stimulation via activation of the alpha-receptor leads to inhibition of insulin release. Norepinephrine stimulates somatostatin release.
- Epinephrine. Despite the dual alpha- and beta-adrenergic receptor system in beta cells, the alpha-adrenergic action of epinephrine predominates, so that insulin secretion is inhibited (insulin release is mediated by a beta-adrenergic receptor).


Pancreatic β-cell
Insulin release
+
Ca2+ channel
Ca2+
concentration
Ca2+
KATP channel
+
Glucose
K+
Depolarization
SUR1
Sulfonylurea

CONTROL OF SECRETIONS

The alpha-, beta-, and delta-cells constitute a functional syncytium, which forms a paracrine control system for the coordinated secretion of pancreatic polypeptides.

- **1. Insulin inhibits alpha cell secretion (glucagon), thereby increasing peripheral glucose uptake and opposing glucagon-mediated glucose production (gluconeogenesis).**
- **2. Glucagon stimulates beta cell secretion (insulin) and delta cell secretion (somatostatin) leading to hypoglycemia, which, in turn, increases hepatic glucose production and opposes hepatic glucose storage.**

CONTROL OF SECRETIONS

- 3. Somatostatin inhibits alpha cell (glucagon) and beta cell (insulin) secretion, producing hypoglycemia and inhibition of intestinal glucose absorption. The lowering of blood glucose levels by somatostatin in diabetic patients results from the inhibition of glucagon secretion and reduced intestinal absorption of glucose.
- 4. Pancreatic polypeptide (PP) inhibits insulin and somatostatin secretion via a direct pancreatic effect.

Transcriptional Regulators of the Pancreas Lineage

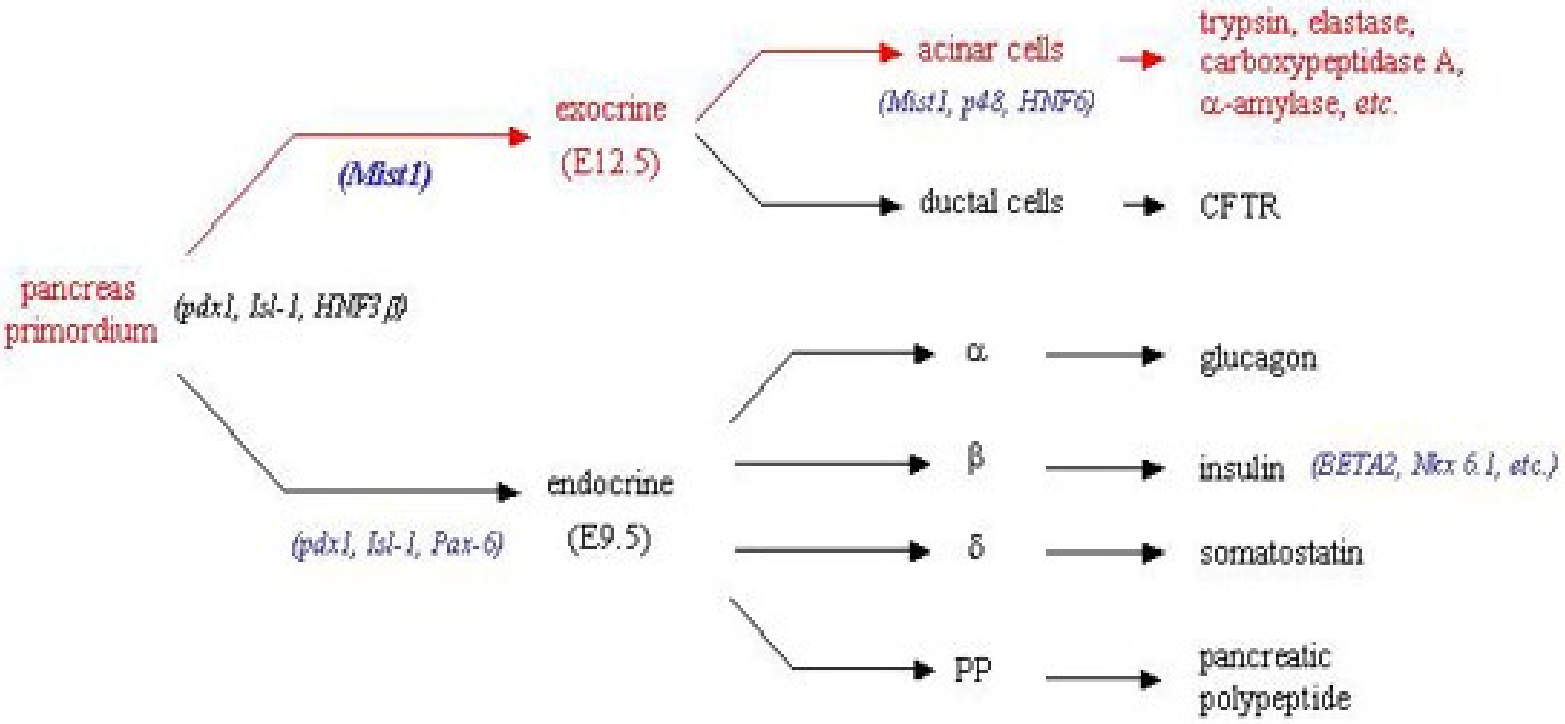


Figure 3: Schematic diagram highlighting the different cell lineages of pancreas development and several transcription factors involved in specifying the lineages.

CFTR - cystic fibrosis transmembrane conductance regulator

BIOSYNTHETIC ORGANIZATION OF THE BETA CELL

- **1. Human proinsulin is a single-chain polypeptide of 86 amino acid residues, with a molecular weight of approximately 9000 daltons.**

  A) Intracellular proteolytic cleavage of proinsulin forms insulin and C-peptide

  B) The conversion of proinsulin is not fully completed, and about 5% of the secretory product of the beta cell is proinsulin, which has about 5% of the biological activity of insulin

  C) C-peptide increases glucose uptake into skeletal muscle in both normal subjects and subjects with type 1 diabetes mellitus (DM).

  D) The plasma half-life of proinsulin is 15 minutes.

BIOSYNTHETIC ORGANIZATION OF THE BETA CELL

- 2. C-peptide is the connecting peptide remaining after cleavage of proinsulin to insulin. In humans, it consists of 31 amino acid residues.
- A) Beta cell secretory products consist of equimolar amounts of insulin and C-peptide; therefore, circulating C-peptide concentrations reflect beta cell activity.
- B) The normal fasting concentration of C-peptide in peripheral blood is approximately 1.0-3.5 ng/ml.
- C) C-peptide increases glucose uptake into skeletal muscle in both normal subjects and type 1 diabetes mellitus.
- D) The plasma half-life of C-peptide is 30 minutes.

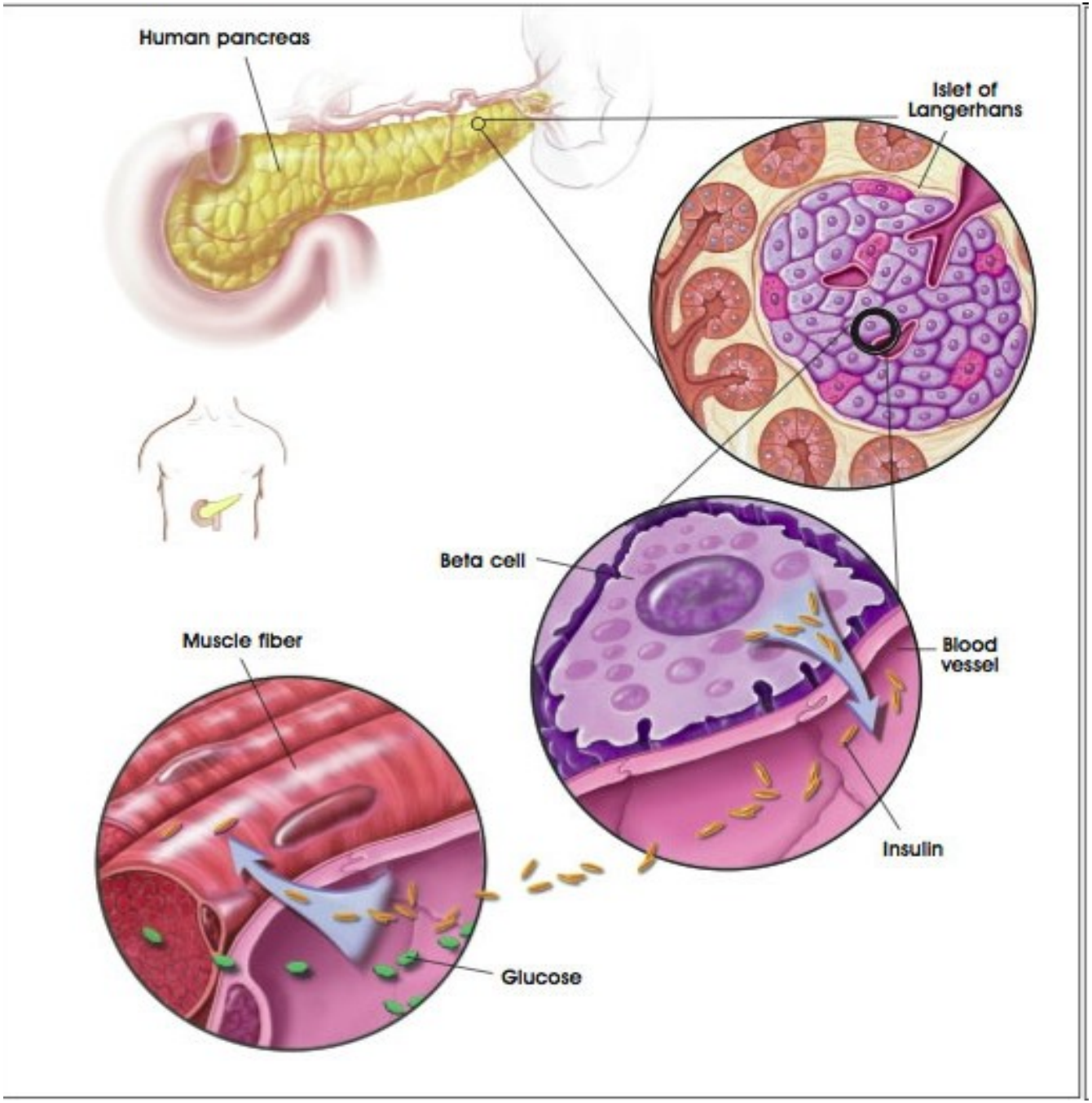
BIOSYNTHETIC ORGANIZATION OF THE BETA CELL

- **3. Insulin is stored in the beta cell granules as a crystalline hexamer complex with two atoms of zinc per hexamer. In plasma, insulin is transported as a monomer.**

  A) Insulin has a molecular weight of about 6000 daltons and contains 51 amino acid residues.

  B) Insulin secretion requires the presence of extracellular Ca. Inside the beta cell, Ca binds to a Ca-binding protein called calmodulin.

  C) The plasma half-life of insulin is 5 minutes.


Human pancreas
Islet of Langerhans
Beta cell
Blood vessel
Muscle fiber
Insulin
Glucose

CONTROL OF INSULIN SECRETION

1. Carbohydrates

- a. Monosaccharides that can be metabolized (e.g., hexose, triose) are more potent stimuli of insulin secretion than carbohydrates that cannot be metabolized (e.g., mannose).
- b. The principal stimulus for insulin release is glucose. As the blood glucose level rises above 4.5 mmol/L (80 mg/dl), it stimulates the release and synthesis of insulin.
- c. Substances that inhibit glucose metabolism (e.g., D-mannoheptulose) interfere with insulin secretion.
- d. The reduction of glucose to sorbitol may contribute to insulin secretion.
- e. Glucose also stimulates somatostatin release.

CONTROL OF INSULIN SECRETION

2. Gastrointestinal (GI) hormones

- **a. The plasma concentration of insulin is higher after oral administration of glucose than after it has been administered intravenously, even though the arterial blood glucose concentration remains lower. This augmented release of insulin following an oral glucose dose is a result of the secretion of GI hormones, including:**

  1) Gastric inhibitory peptide, which appears to be the principal GI potentiator of insulin release.

  2) Gastrin.

  3) Secretin.

  4) CCK – cholecystokinin.

- **b. GI hormones also augment somatostatin release.**

CONTROL OF INSULIN SECRETION

3. Amino acids

- a. Amino acids vary in their ability to stimulate beta cells. Among the essential amino acids, in decreasing order of effectiveness, are arginine, lysine, and phenylalanine.
- b. The stimulation of insulin secretion by oral administration of amino acids exceeds that of intravenously administered amino acids. Protein-stimulated secretion of CCK, gastrin, or both may mediate this effect.
- c. The analogues of leucine and arginine that cannot be metabolized also stimulate insulin secretion.

CONTROL OF INSULIN SECRETION

4. Fatty acids and ketone bodies are not known to have an important role in the regulation of insulin secretion in humans. The ingestion of medium-chain triglycerides causes a small increment in insulin levels.

5. Islet hormones. Glucagon stimulates insulin secretion and somatostatin inhibits insulin secretion. Somatostatin inhibits gastrin and secretin secretion, glucose absorption, and GI motility.

CONTROL OF INSULIN SECRETION

6. Other hormones

- **Growth hormone induces an elevation in basal insulin levels that precedes a change in blood glucose levels, suggesting a direct beta-cytotropic effect.**
- **Hyperinsulinemia also has been observed with exogenous and endogenous increments of corticosteroids, estrogens, progestogens, and parathyroid hormone. Since blood glucose concentrations are not reduced with these hormones, it is inferred that these hormones have an anti-insulin effect.**

CONTROL OF INSULIN SECRETION

7. Obesity.

Hyperinsulinemia is observed in obese patients. An increase in body weight in the absence of a disproportionate increase in body fat does not affect insulin levels.

8. Ions.

Both K and Ca are necessary for normal insulin and glucagon responses to glucose. Therefore, hypokalemia leads to glucose intolerance.

9. Cyclic nucleotides.

Cyclic AMP is a releaser of insulin.

ACTIONS OF INSULIN:

CARBOHYDRATE METABOLISM

Liver

- The liver takes up glucose when the circulating concentration is high and releases it when the blood glucose level is low.
- Glucose transport in hepatocytes depends on an insulin-insensitive isoform of the glucose transporter (GLUT-2), and net uptake or release of glucose depends on whether the concentration of free glucose is higher in the extracellular fluid or in the intracellular fluid.

ACTIONS OF INSULIN: CARBOHYDRATE METABOLISM

Liver

The two enzymes that catalyze phosphorylation of glucose to glucoses-phosphate are hexokinase and glucokinase.

- Hexokinase is saturated at normal plasma glucose concentrations and is not regulated by insulin.

- Hexokinase is found in most tissues, has a high affinity for glucose and other hexoses, and has a low maximum velocity.

ACTIONS OF INSULIN: CARBOHYDRATE METABOLISM

Liver

- Glucokinase is only half-saturated at blood glucose concentrations between 90 and 100 mg/dl (5.0-5.5 mmol/L). Thus, the activity of this enzyme is insulin- and glucose-dependent.

- Glucokinase is found only in liver, has a low affinity for glucose only, and has a high maximum velocity. It is active when glucose concentrations are relatively high.

****

- Insulin diminishes hepatic glucose output by activating glycogen synthetase and by inhibiting gluconeogenesis.

CARBOHYDRATE METABOLISM: MUSCLE

The insulin-dependent facilitated diffusion mechanism for glucose is found in skeletal and cardiac muscle.

- Muscle is the principal site of insulin-stimulated glucose disposal; less glucose is transported into adipose tissue.
- Glucose transport across muscle cell membranes requires insulin.
- Insulin activates glycogen synthetase, which causes glycogen synthesis, and phosphofructokinase, which causes glucose utilization.
- Glucose uptake in exercising muscle is not dependent on increased insulin secretion. In resting muscle, glucose is a relatively unimportant fuel, with the oxidation of fatty acids supplying most of the energy.

CARBOHYDRATE METABOLISM: ADIPOSE TISSUE

The insulin-dependent facilitated diffusion mechanism for glucose is found also in adipose tissue.

- Insulin acts primarily to stimulate glucose transport.
- Insulin activates glycogen synthetase and phosphofructokinase.
- The major end products of glucose metabolism in fat cells are fatty acids and alpha-glycerophosphate.
- The fat cell depends on glucose as a precursor of alpha-glycerophosphate, which is important in fat storage (because it forms esters with fatty acids to form triglycerides).

FAT METABOLISM: LIVER

- When insulin and carbohydrate are available, the human liver is quantitatively a more important site of fat synthesis than is adipose tissue.
- In the absence of insulin, the liver does not actively synthesize fatty acids, but it is capable of esterifying fatty acids with glycerol, which is phosphorylated by glycerokinase.

  - Glycerol must be phosphorylated before it can be used in the synthesis of fat.

  - In the absence of glycolytic breakdown of glucose to a-glycerophosphate, glycerokinase permits the esterification of fatty acids.
- In the absence of insulin, there is an increase in fat oxidation and in the production of ketone bodies. Insulin exerts a potent antiketogenic effect.

FAT METABOLISM: LIVER

Insulin promotes the synthesis and release of lipoprotein lipase, which is an extracellular enzyme that hydrolyzes both chylomicron and very-low-density lipoprotein (VLDL) triglyceride.

- **Lipoprotein lipase catalyzes the hydrolysis of circulating lipoprotein triglyceride to fatty acids and glycerol.**
- **Lipoprotein lipase is the key enzyme in the removal of lipoprotein triglyceride and thereby is important in the formation of both light and heavy lipoprotein.**
- **Lipoprotein lipase is active at the luminal surface of the capillary endothelial cell, and under normal conditions is completely absent from the circulation.**
- **The highest lipoprotein lipase activity is found in the heart, but lipoprotein lipase is distributed in adipose tissue, lactating mammary gland (and milk), lung, skeletal muscle, aorta, corpus luteum, brain, and placenta.**

FAT METABOLISM: ADIPOSE TISSUE

- Insulin deficiency also decreases the formation of fatty acids in adipose tissue.
- The major effect of insulin-stimulated glucose uptake in human fat cells is to provide alpha-glycerophosphate for esterification of free fatty acids. The absence of alpha-glycerophosphate formation from glycolysis during insulin deficiency prevents the esterification of free fatty acids, which are constantly released from triglycerides in the adipocytes.
- The lipolytic effect in the absence of insulin is caused by an increase in the hormone-sensitive lipase known as triglyceride lipase, the activity of which is normally inhibited by insulin.

AMINO ACID AND PROTEIN METABOLISM

Insulin is an important protein-anabolic hormone, and it is necessary for the assimilation of a protein meal. The protein-anabolic effect of insulin is not dependent on increased glucose transport.

- In diabetic patients, the muscle uptake of amino acids is reduced, and elevated postprandial blood levels are observed.
- During severe insulin deficiency, hyperaminoacidemia involving branched-chain amino acids (i.e., valine, leucine, and isoleucine) is present.

AMINO ACID AND PROTEIN METABOLISM

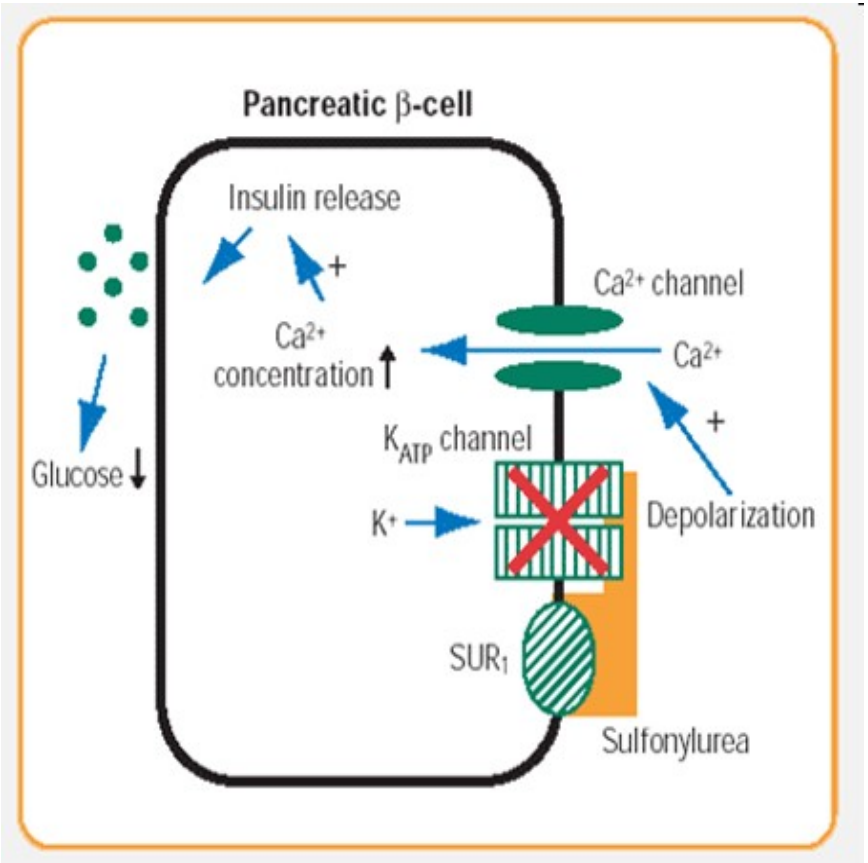
- **Insulin increases uptake of most amino acids into muscle and increases the incorporation of amino acids into protein.**
- **Insulin increases body protein stores through four mechanisms:**
  1. **Increased tissue uptake of amino acids**
  2. **Increased protein synthesis**
  3. **Decreased protein catabolism**
  4. **Decreased oxidation of amino acids.**

ELECTROLYTE METABOLISM

- **Insulin lowers serum K concentration. This hypokalemic action of insulin is caused by stimulation of K uptake by muscle and hepatic tissue.**
- **Diabetic patients have a proclivity toward developing hyperkalemia in the absence of acidosis.**
- **Insulin has an antinatriuretic effect.**

MEMBRANE POLARIZATION

- **Insulin decreases membrane permeability to both Na and K, but it decreases Na permeability to a greater extent, causing hyperpolarization of muscle.**
- **The membrane hyperpolarization produced by insulin is the cause, not the result, of the net shift of K from the extracellular to the intracellular space.**

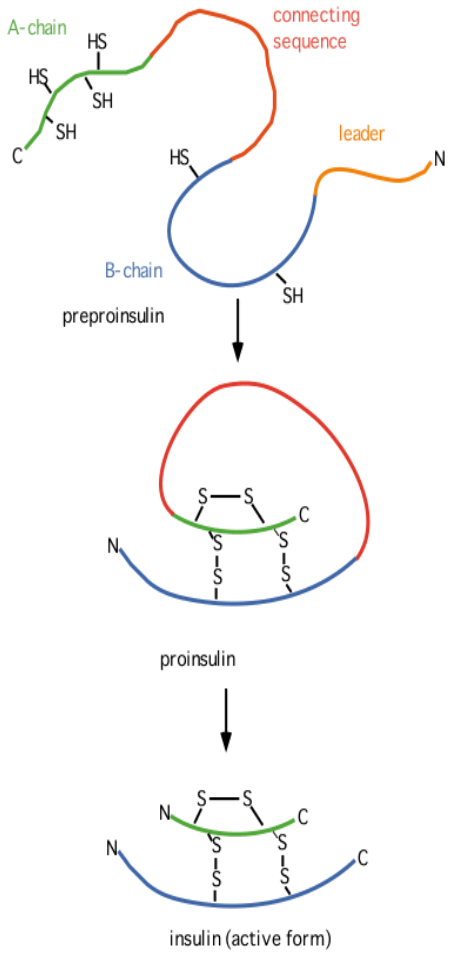


PHYSIOLOGIC ACTIONS OF INSULIN

Insulin is a very effective hypoglycemic hormone for two major reasons:

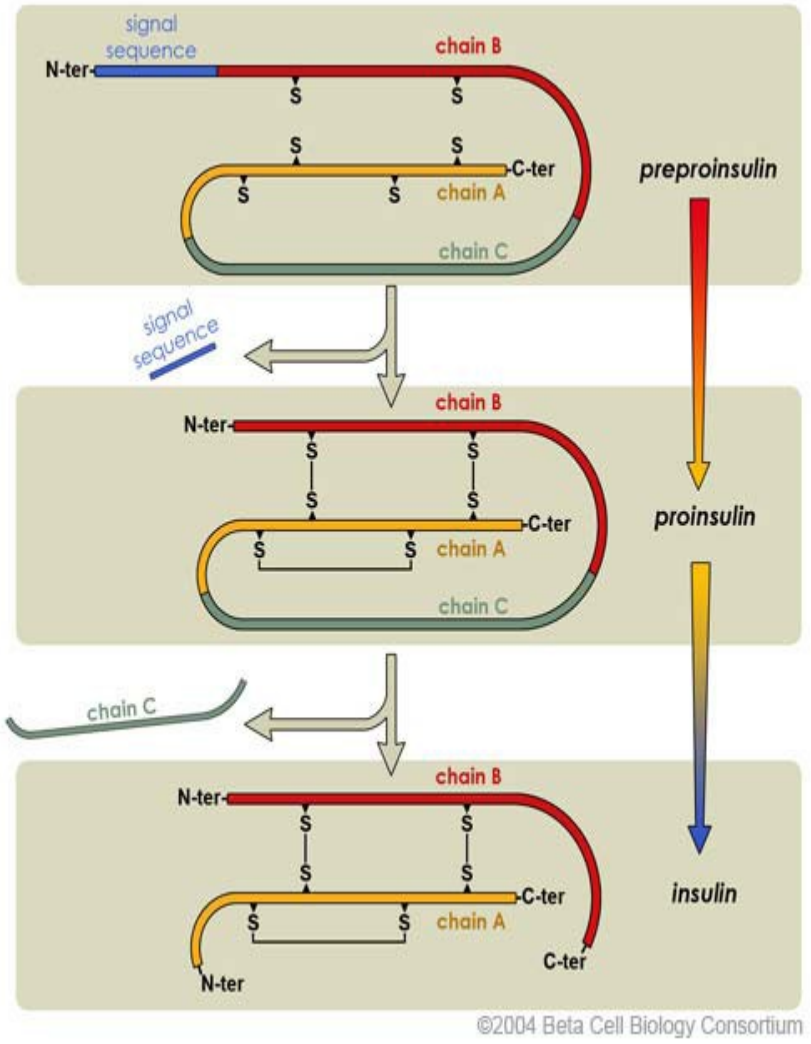
1. It promotes both hepatic and muscle glycogen deposition.

2. It enhances glucose utilization (glycolysis).



PHYSIOLOGIC ACTIONS OF INSULIN

For glucose transport, the major insulin-independent tissues are brain, erythrocytes, liver, and epithelial cells of the kidney and intestine.



INSULIN IS THE PRIMARY ANABOLIC HORMONE (REASONS)

1. Inhibition of hepatic gluconeogenesis decreases the hepatic requirement for amino acids.
2. The protein anabolic effect of insulin reduces the output of amino acids from muscle, thereby decreasing the availability of glucogenic amino acids for gluconeogenesis.
3. Glucose uptake by muscle is stimulated, providing an energy source that spares fatty acids, the release of which is inhibited by the antilipolytic action of insulin.

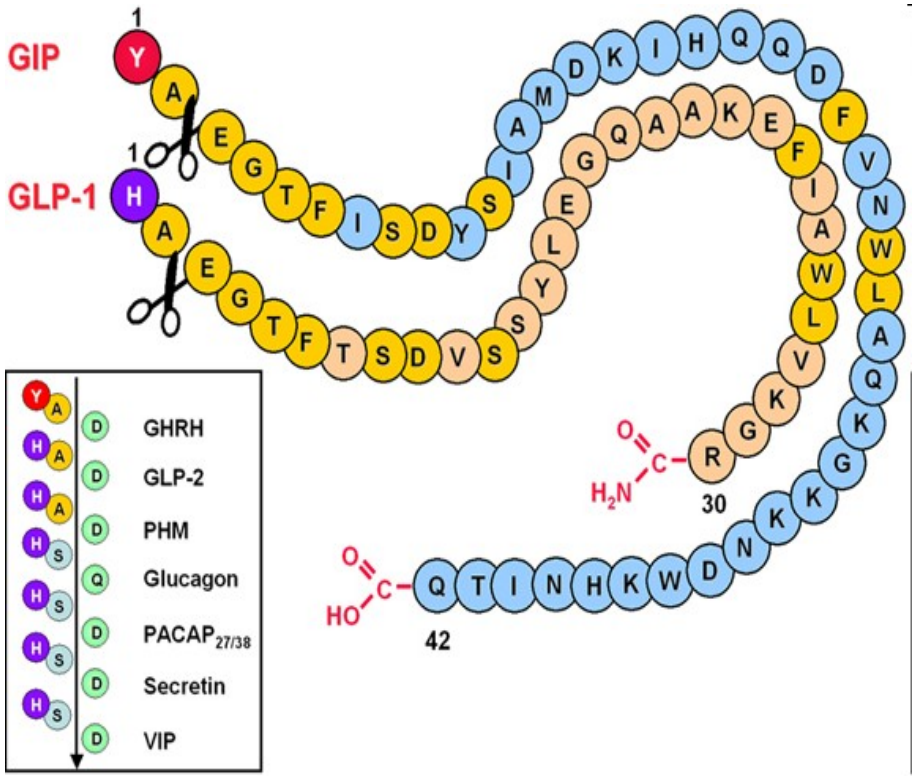
INSULIN IS THE PRIMARY ANABOLIC HORMONE (REASONS)

4. Fat accumulation is enhanced by increased hepatic lipogenesis.
5. The antilipolytic action of insulin (inhibition of hepatic oxidation of fatty acids) is a result of the formation of alpha-glycerophosphate from glucose in the fat cell.
6. The antilipolytic action of insulin at the level of the adipose cell reinforces the insulin-mediated inhibition of hepatic ketogenesis and gluconeogenesis by depriving the liver of precursor substrates for ketogenesis and the energy source (fatty acids) and cofactors (acetyl-CoA) necessary for gluconeogenesis.

CONTROL OF GLUCAGON SECRETION

1. Metabolic fuels

- Hypoglycemia stimulates glucagon secretion and hyperglycemia inhibits it.
- Amino acids (e.g., arginine, alanine) also are stimuli for glucagon release.
- Decreasing circulatory levels of fatty acids are associated with glucagon release.



CONTROL OF GLUCAGON SECRETION

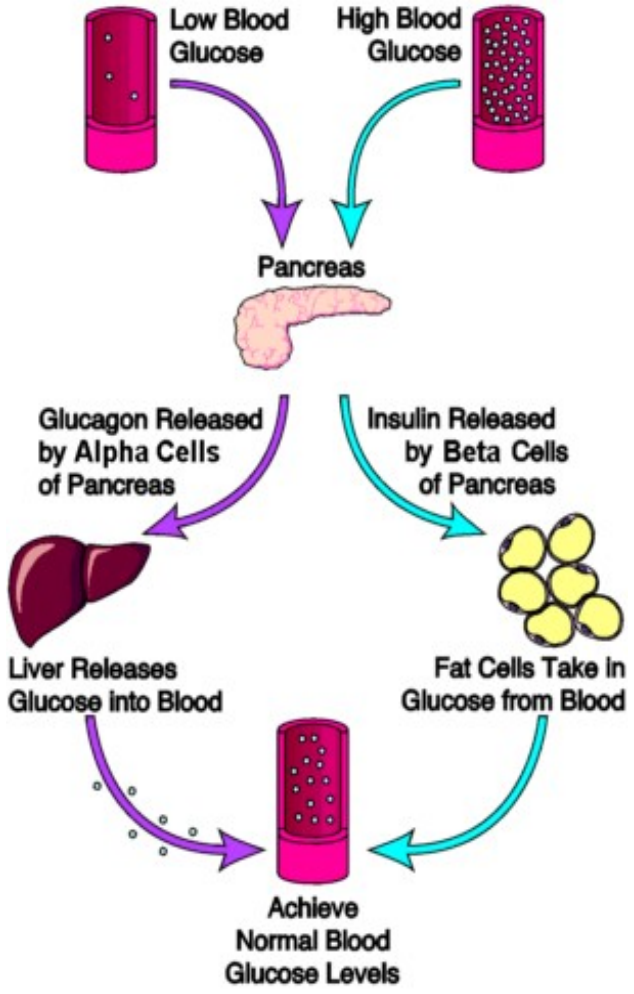
2. GI hormones

- CCK, gastrin, secretin, and gastric inhibitory peptide stimulate glucagon secretion.
- The potentiation of glucagon secretion by the ingestion of a protein meal is mediated via CCK secretion.

3. Fatty acids inhibit glucagon release.

ACTIONS OF GLUCAGON

- The major site of glucagon action is the liver.
- In almost all aspects the actions of glucagon are the exact opposite to those of insulin.



ACTIONS OF GLUCAGON

Carbohydrate metabolism

- **Glucagon has a hyperglycemic action, resulting primarily from stimulation of hepatic glycogenolysis.**
- **Glucagon is an important gluconeogenic hormone.**
- **The hyperglycemic action of epinephrine is amplified by its stimulation of glucagon secretion and its inhibition of insulin secretion.**
- **Suppression of glucagon secretion by glucose is not essential for normal glucose tolerance as long as insulin is available.**

ACTIONS OF GLUCAGON

Fat metabolism

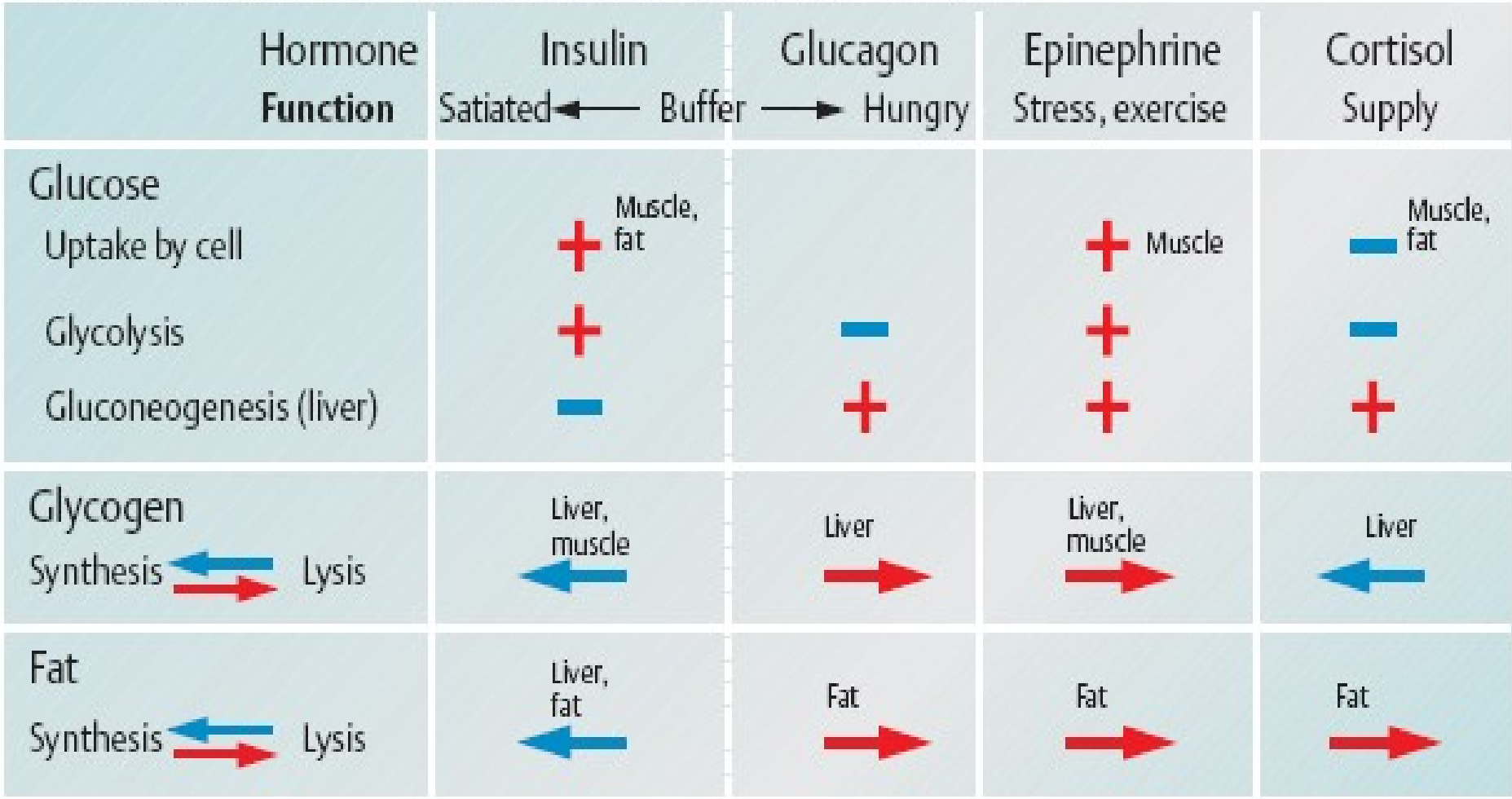
- **Glucagon is a lipolytic hormone because of its activation of hormone-sensitive lipase (triglyceride lipase) in adipose tissue by cyclic adenosine monophosphate.**
- **Glucagon causes an elevation in the plasma level of fatty acids and glycerol.**

  - Glycerol is utilized as a gluconeogenic substrate in the liver.

  - The oxidation of fatty acids as an energy substrate accounts for the glucose-sparing effect of glucagon.

  - Glucagon is essential for the ketogenesis brought about by the oxidation of fatty acids. In the absence of insulin, glucagon can accelerate ketogenesis, which leads to metabolic acidosis.

C. Hormonal effects on carbohydrate and fat metabolism



ACTIONS OF GLUCAGON

Protein metabolism

- **Glucagon has a net proteolytic effect in the liver (negative nitrogen balance).**
- **This peptide is gluconeogenic, an effect that leads to increased amino acid oxidation and urea formation.**
- **In addition to its protein catabolic effect, glucagon has an antianabolic effect - inhibition of protein synthesis.**

Figure 1

A

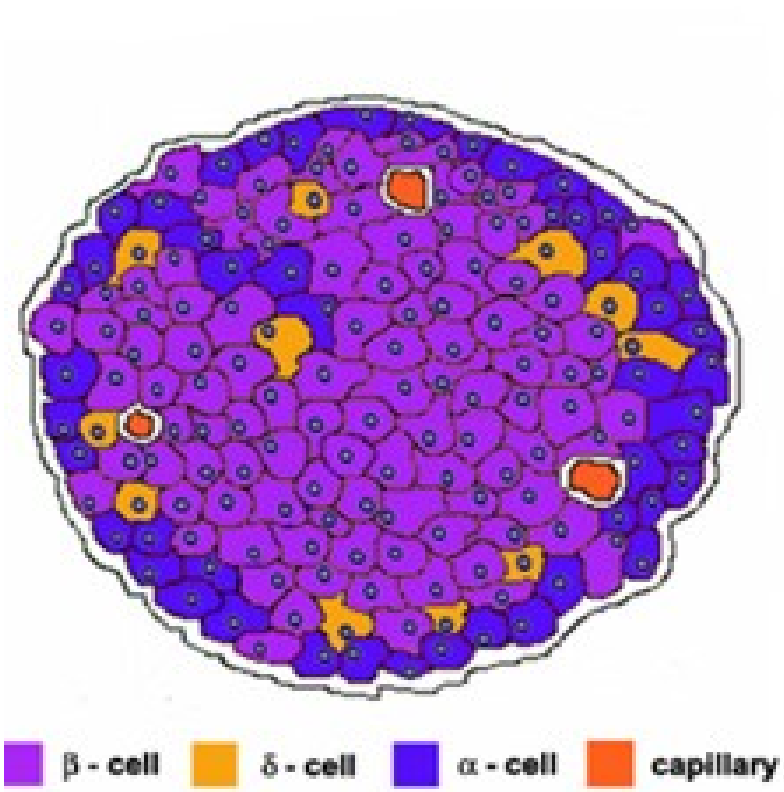
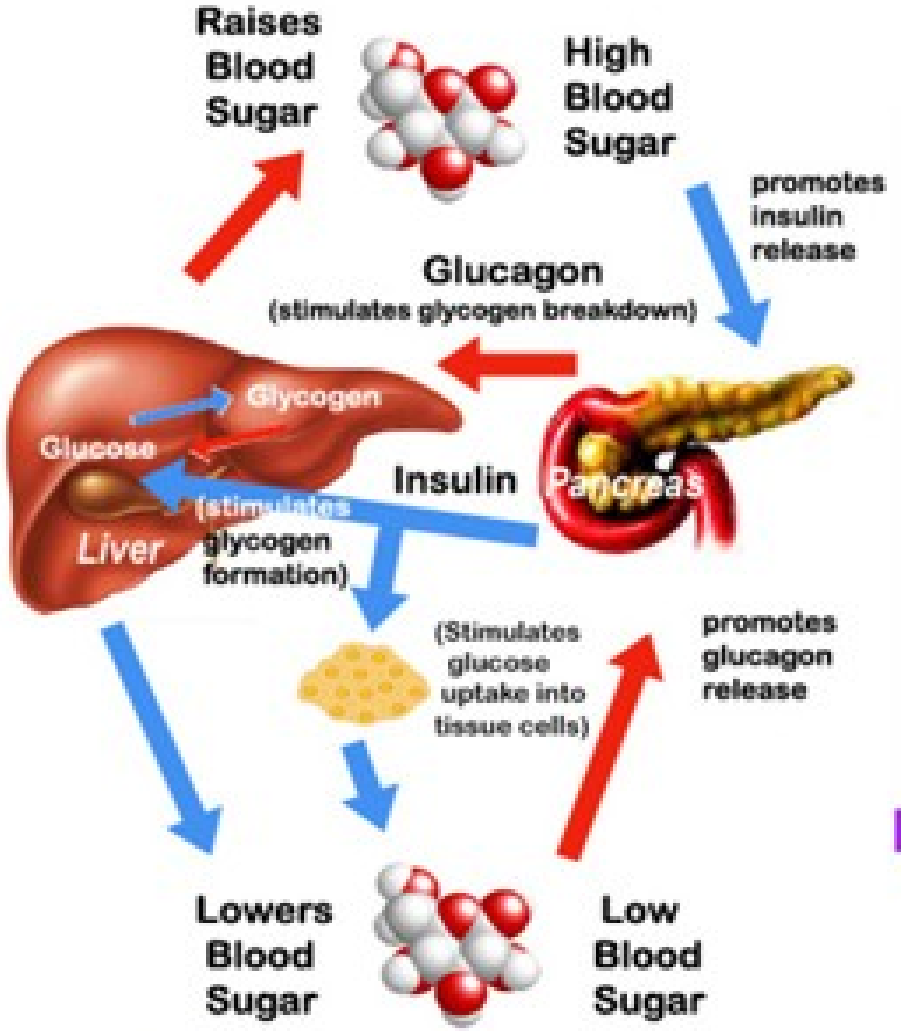


Illustration of the cellular composition of a pancreatic islet

B



The actions of insulin and glucagon to regulate blood sugar

CONTROL OF SOMATOSTATIN SECRETION

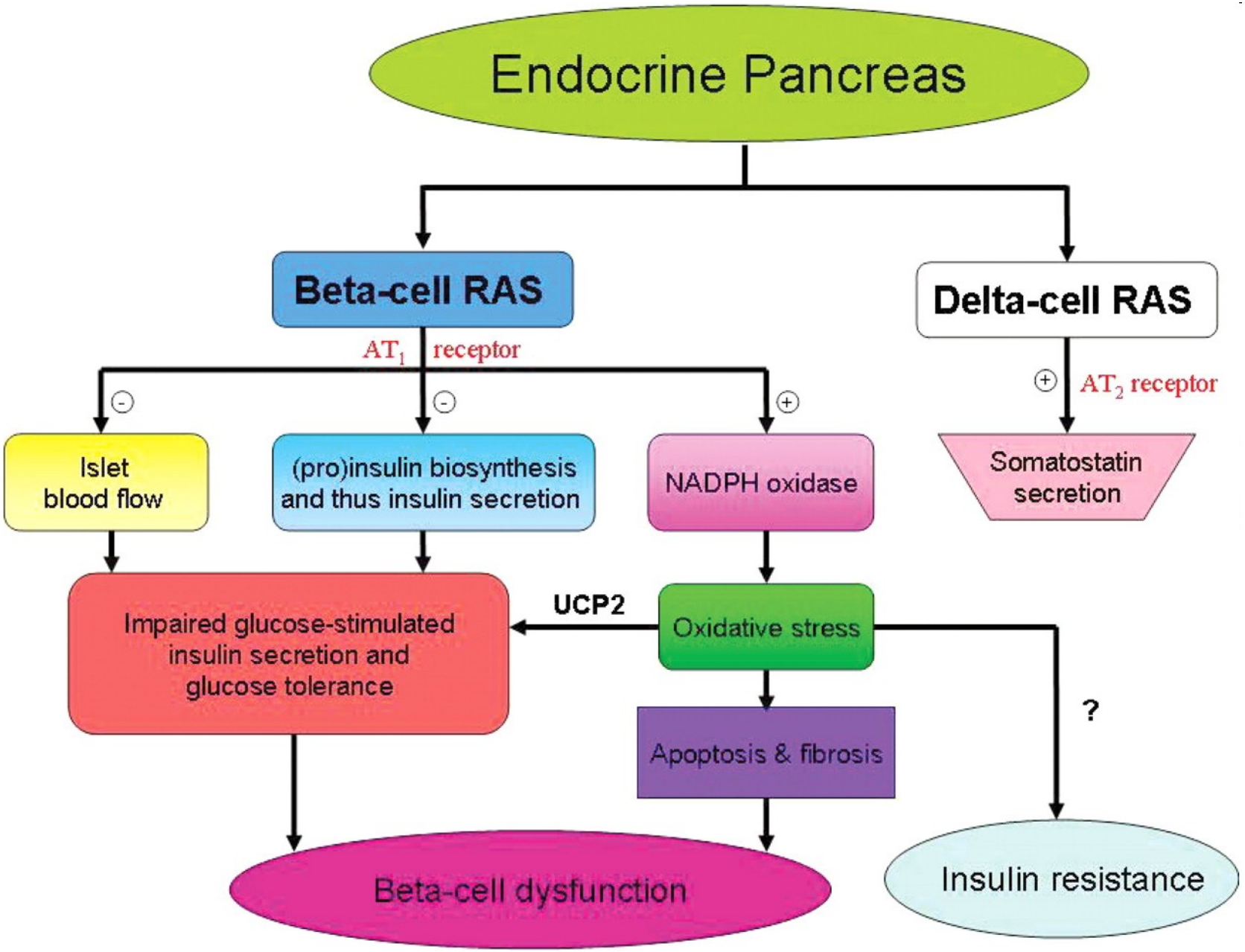
Somatostatin has many important physiologic actions in addition to inhibiting GH (somatotropin) secretion.

1. Somatostatin is a decapeptide synthesized in the delta cells of the pancreatic islets.
2. There is a parallelism between the agents that promote the secretion of somatostatin and those that stimulate the release of insulin, because the same metabolites and GI tract hormones promote the secretion of both hormones.
3. Somatostatin has been isolated from nerve terminals throughout the brain, spinal cord and peripheral ganglia, where it can function as a peptidergic neurotransmitter.

PHYSIOLOGIC ACTIONS OF SOMATOSTATIN

Somatostatin inhibits the secretion of both glucagon and insulin and produces a 30-50% decrease in blood glucose concentration.

1. Somatostatin elicits a parallel fall in hepatic glucose production.
2. The hypoglycemic effect is mediated by suppression of glucagon secretion, since somatostatin has no direct effect on glucose metabolism.
3. There are prevention of ketoacidosis and reduction of hyperglycemia by somatostatin.


Endocrine Pancreas
Beta-cell RAS
Delta-cell RAS
AT1 receptor
AT2 receptor
Islet blood flow
(pro)insulin biosynthesis and thus insulin secretion
NADPH oxidase
Somatostatin secretion
Impaired glucose-stimulated insulin secretion and glucose tolerance
UCP2
Oxidative stress
Apoptosis & fibrosis
?
Beta-cell dysfunction
Insulin resistance

CONTROL OF PANCREATIC POLYPEPTIDE (PP) SECRETION

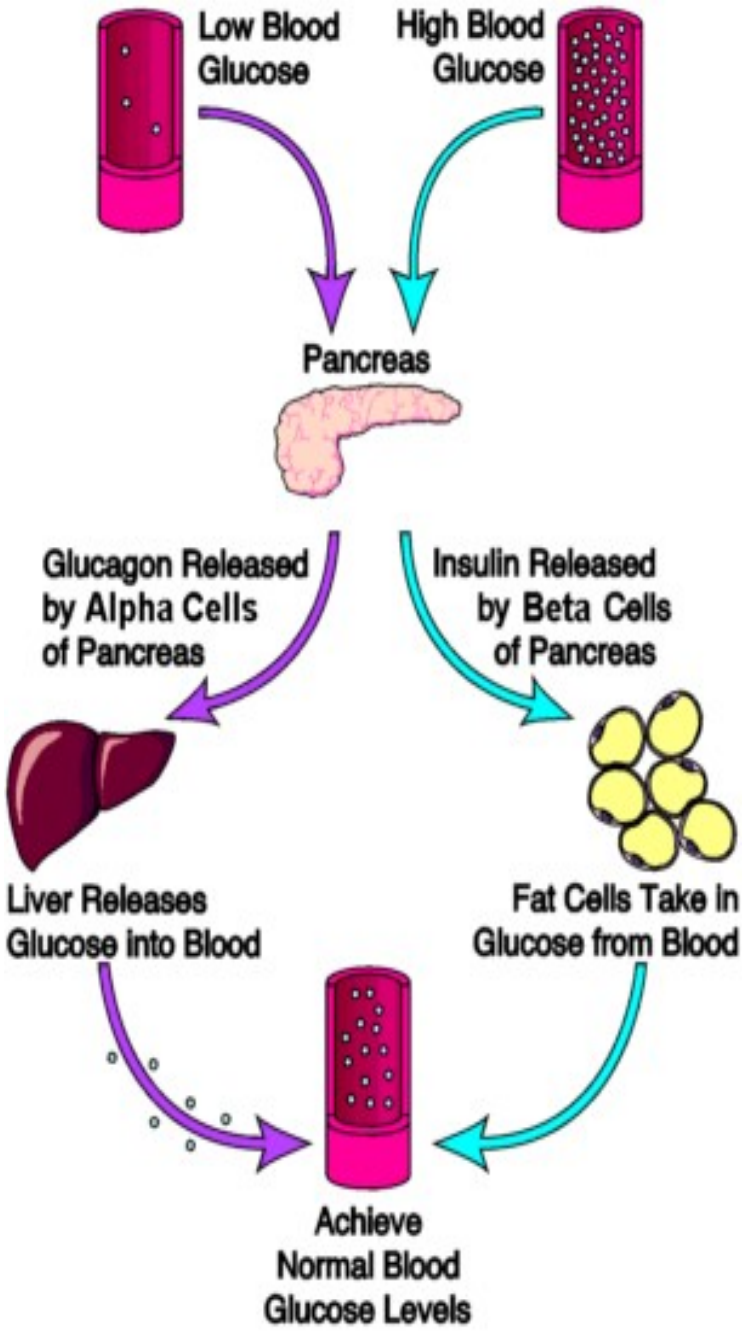
1. PP has been located in parts of the GI tract, but the pancreas is the major source of PP.
2. There is a marked hyperplasia of the PP cells (F cells) in type 1 diabetes of long duration.

CONTROL OF PANCREATIC POLYPEPTIDE (PP) SECRETION

3. The secretion of PP appears to be largely under the control of the autonomic nervous system, with the cholinergic stimulation via the vagus providing the major signal for secretion.
4. Blood nutrients and hormones may also play an important role in PP secretion.
5. Obesity causes a 50% decline in plasma PP levels.
6. Diabetes (type 1) is associated with an increased plasma concentration of PP.

PHYSIOLOGIC ACTIONS OF PP

1. PP inhibits the secretion of both insulin and somatostatin without affecting the release of glucagon.
2. PP also affects the exocrine pancreas by inhibiting trypsinogen and bicarbonate-ion secretion.
3. In general, PP slows down the digestive process.


Low Blood Glucose
High Blood Glucose
Pancreas
Glucagon Released by Alpha Cells of Pancreas
Insulin Released by Beta Cells of Pancreas
Liver Releases Glucose into Blood
Fat Cells Take in Glucose from Blood
Achieve Normal Blood Glucose Levels

DIABETES MELLITUS

3rd leading cause of death

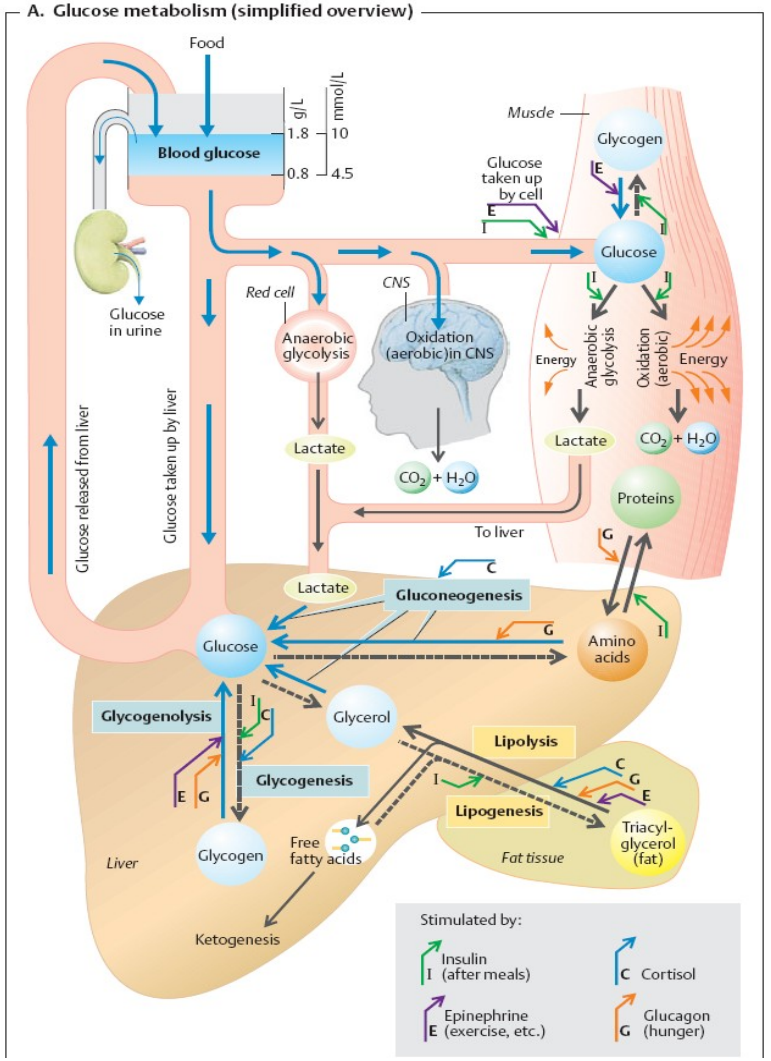
2nd leading cause of blindness

- **Two major types:**
  - **Juvenile onset (20% of all)**
  - **Maturity-onset diabetes (80% or more of all)**
- **Heredity plays an important role in each. It is caused by diminished rates of secretion of insulin by the beta cells of the islets of Langerhans.**

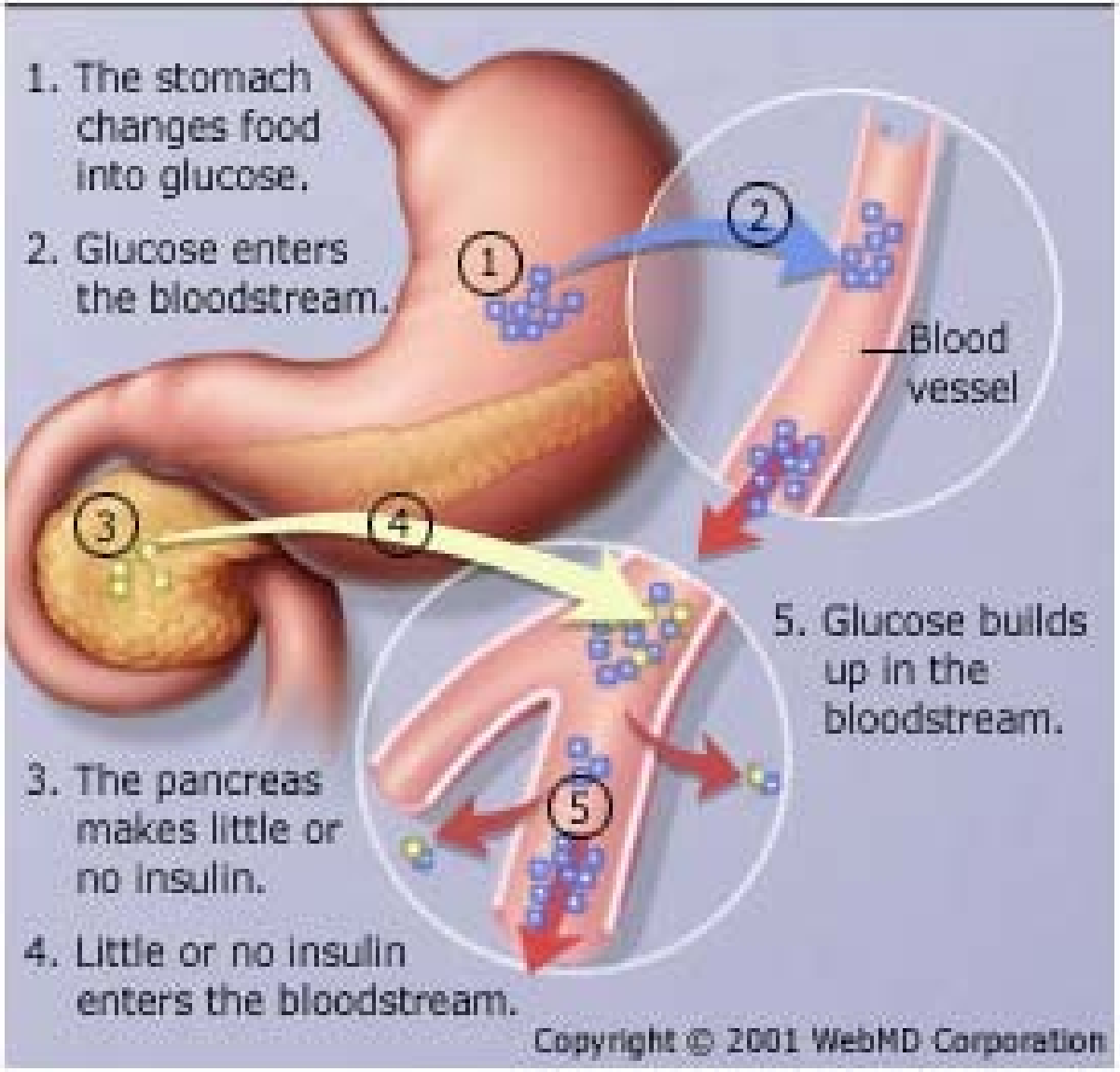
DIABETES MELLITUS: ABNORMALLY ELEVATED BLOOD GLUCOSE (HYPERGLYCEMIA)

Type 1:

- **beta cells destroyed - no insulin produced → chronic fasted state, "melting flesh", ketosis, acidosis, glucosurea, diuresis and coma**



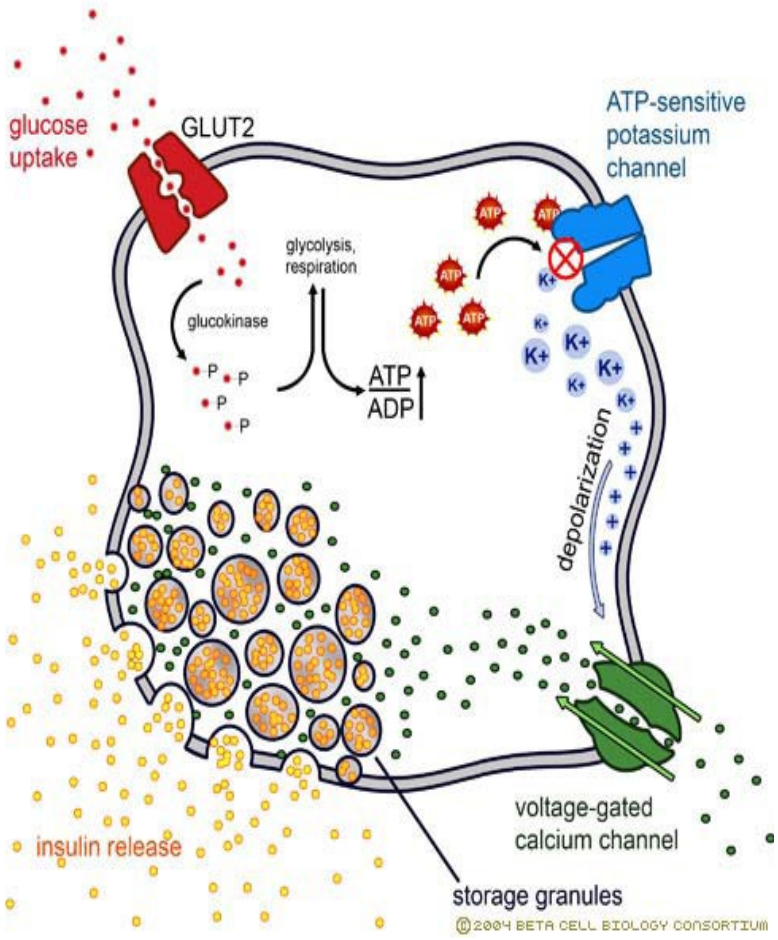
Type 1 Diabetes

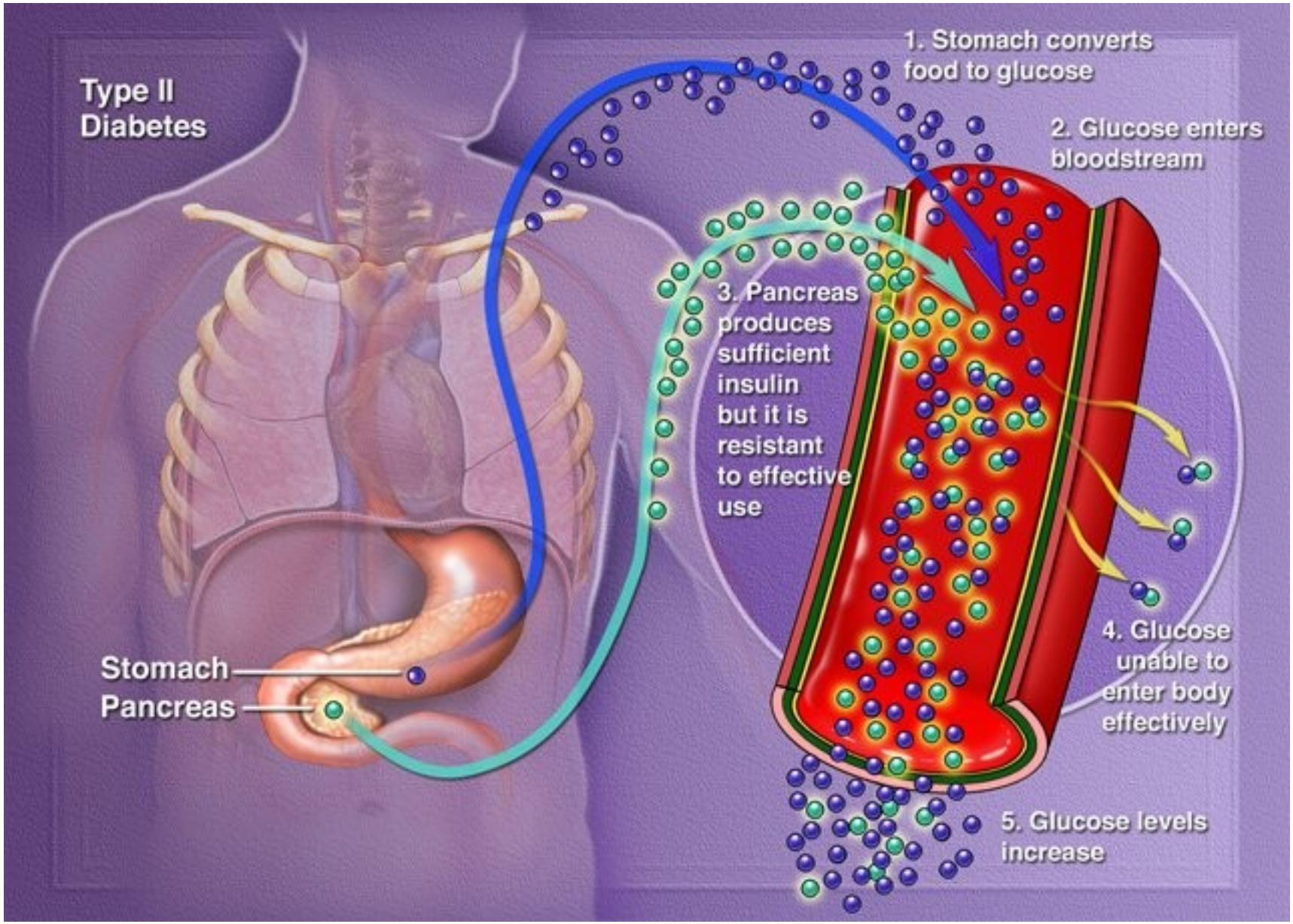


DIABETES MELLITUS: TYPE II A GROUP OF DISEASES

Type 2:

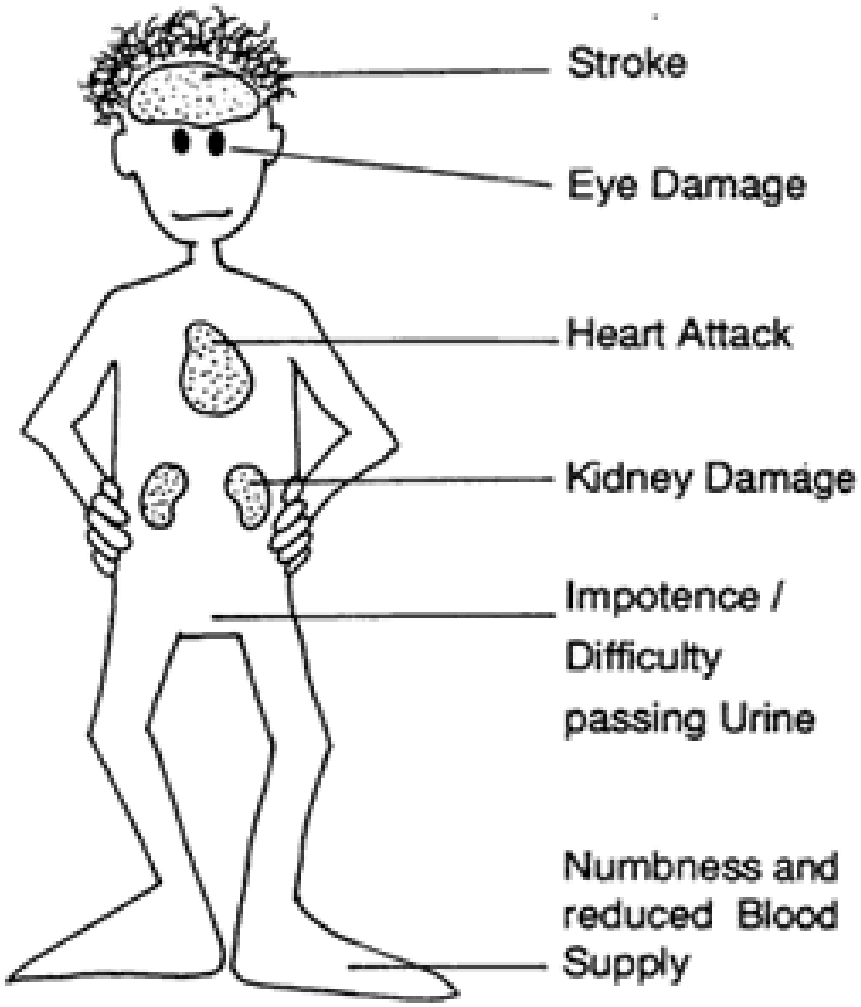
- Insulin resistance keeps blood glucose too high
- Problem with receptors, glucagons levels
- Chronic complications → atherosclerosis, renal failure and blindness

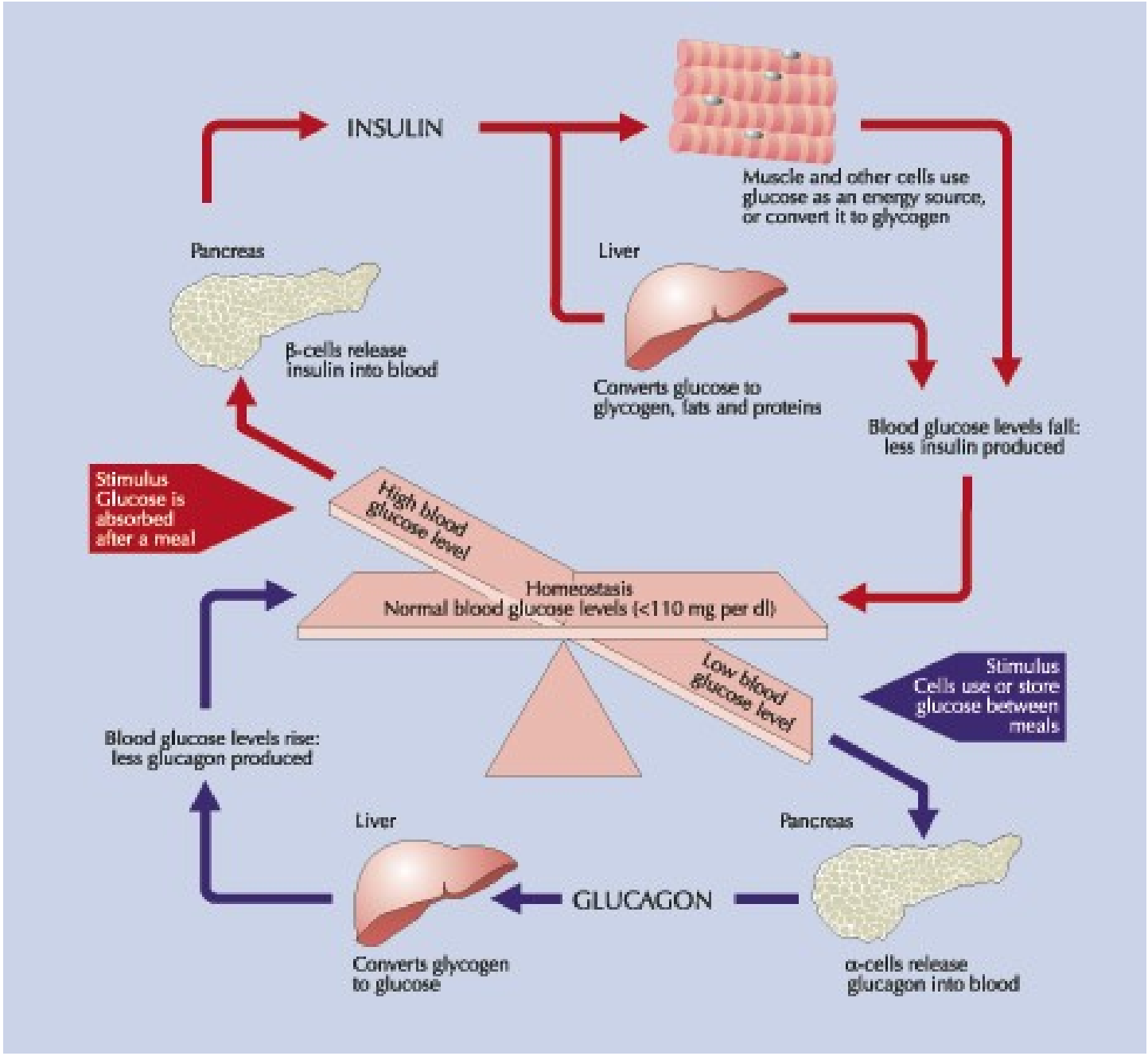



Type II
Diabetes
1. Stomach converts
food to glucose
2. Glucose enters
bloodstream
3. Pancreas
produces
sufficient
insulin
but it is
resistant
to effective
use
4. Glucose
unable to
enter body
effectively
5. Glucose levels
increase
Stomach
Pancreas

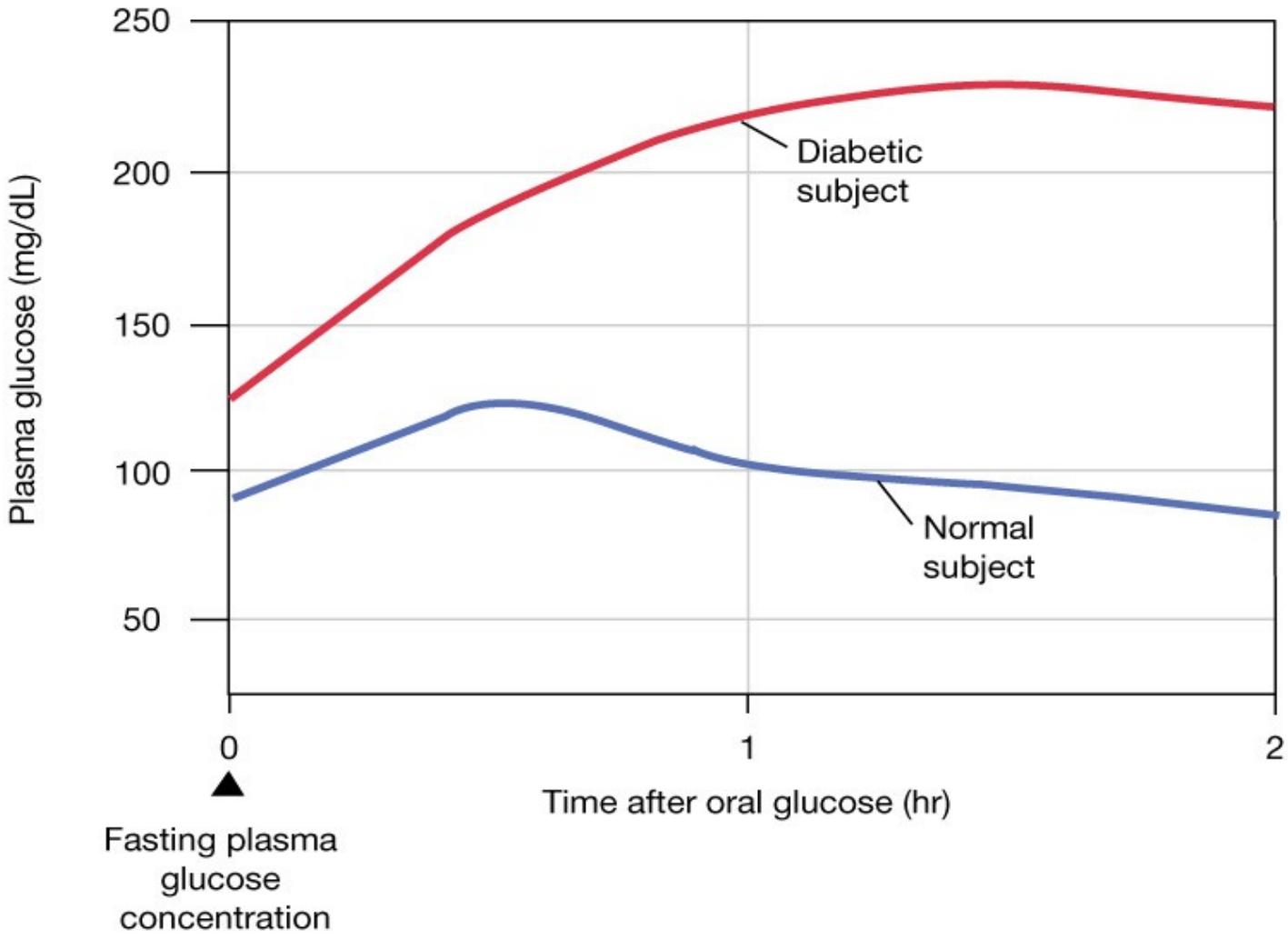
MAIN DIABETIC SYMPTOMS

- Polyuria (excess urine production)
- Polydipsia (excess drinking of water)
- Polyphagia (excessive eating)
- Loss of weight
- Asthenia (lack of energy)

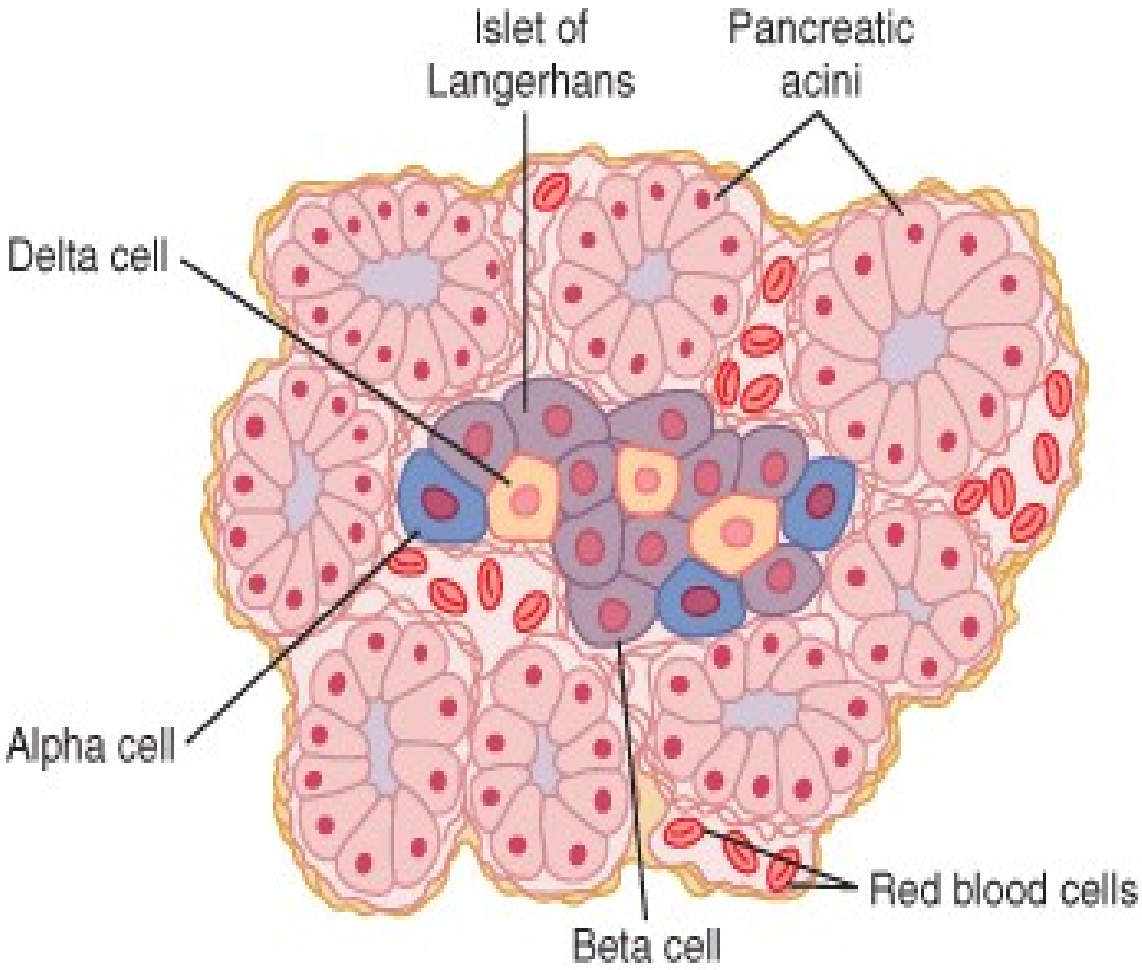


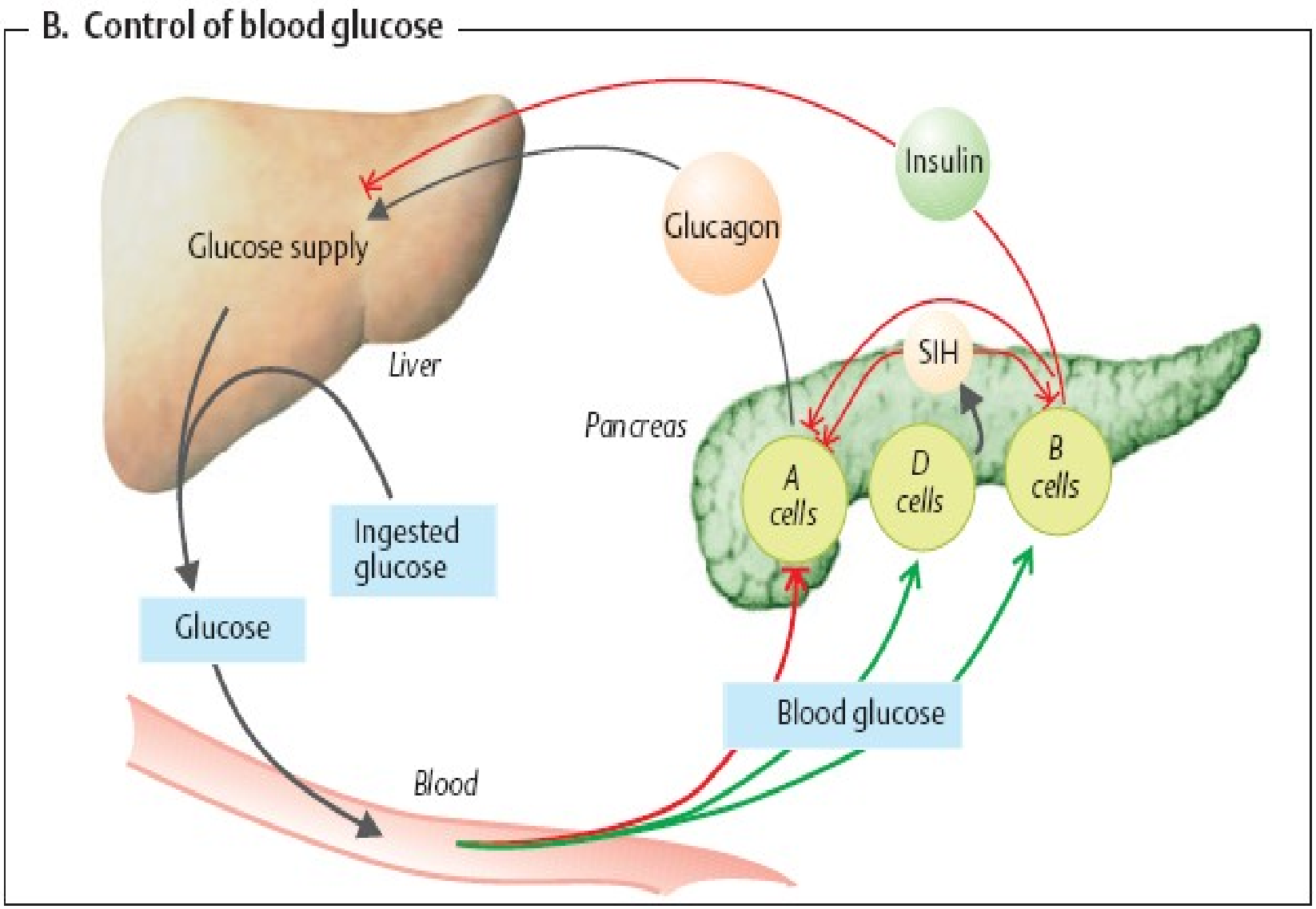

INSULIN
Muscle and other cells use glucose as an energy source, or convert it to glycogen
Pancreas
β-cells release insulin into blood
Liver
Converts glucose to glycogen, fats and proteins
Blood glucose levels fall: less insulin produced
Stimulus Glucose is absorbed after a meal
High blood glucose level
Homeostasis
Normal blood glucose levels (<110 mg per dl)
Low blood glucose level
Stimulus Cells use or store glucose between meals
Blood glucose levels rise: less glucagon produced
Liver
Converts glycogen to glucose
GLUCAGON
Pancreas
α-cells release glucagon into blood

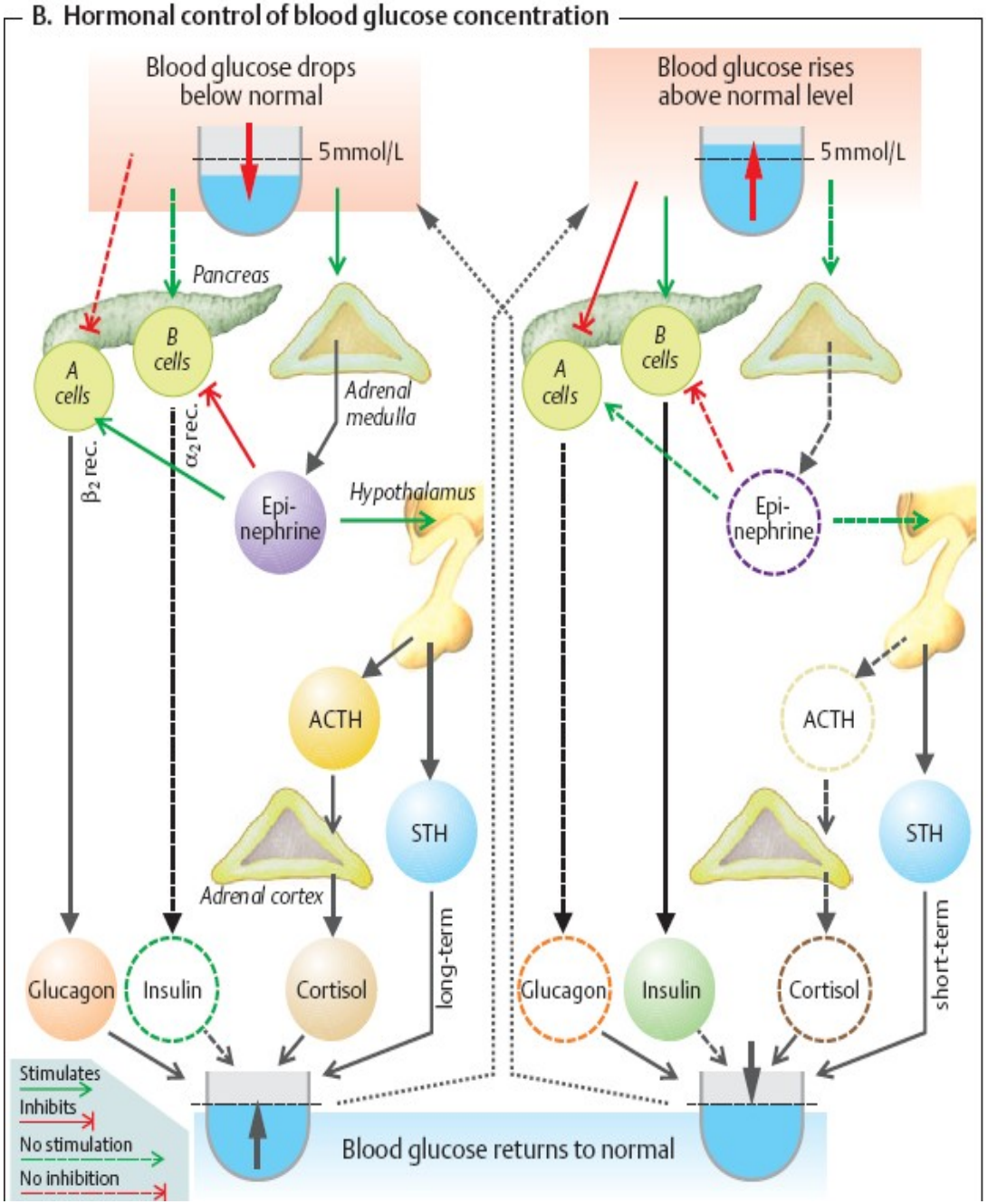
Diabetes Mellitus: Type II a Group of Diseases

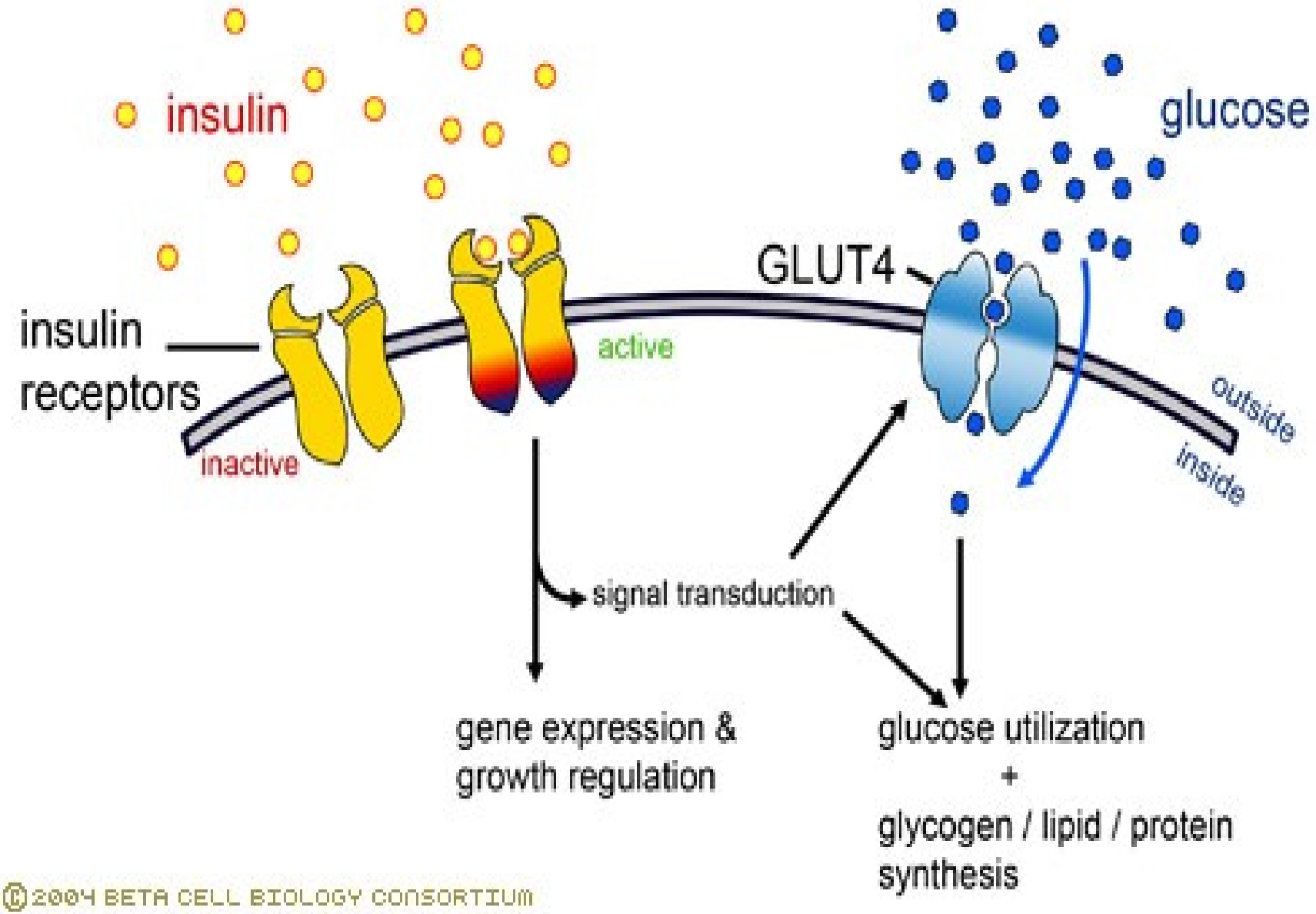


Normal and abnormal glucose tolerance tests



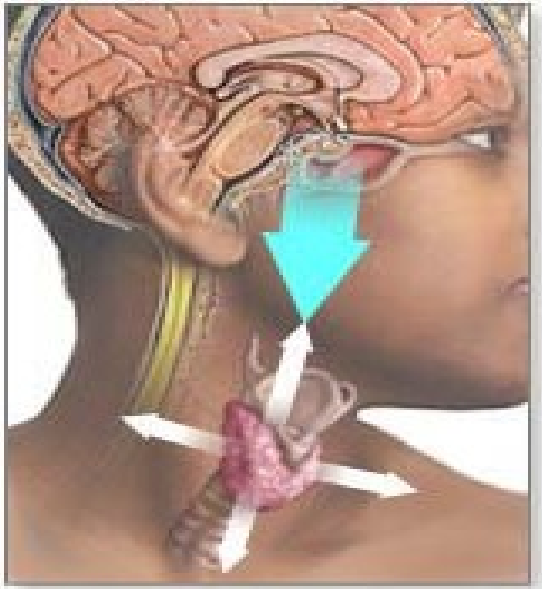

B. Control of blood glucose
Insulin
Glucagon
Glucose supply
Liver
SIH
Pancreas
A cells
D cells
B cells
Ingested glucose
Glucose
Blood glucose
Blood


B. Hormonal control of blood glucose concentration
Blood glucose drops below normal
5 mmol/L
Blood glucose rises above normal level
5 mmol/L
Pancreas
A cells
B cells
Adrenal medulla
β2 rec.
α2 rec.
Epi-nephrine
Hypothalamus
ACTH
STH
Adrenal cortex
Glucagon
Insulin
Cortisol
long-term
short-term
Stimulates
Inhibits
No stimulation
No inhibition
Blood glucose returns to normal

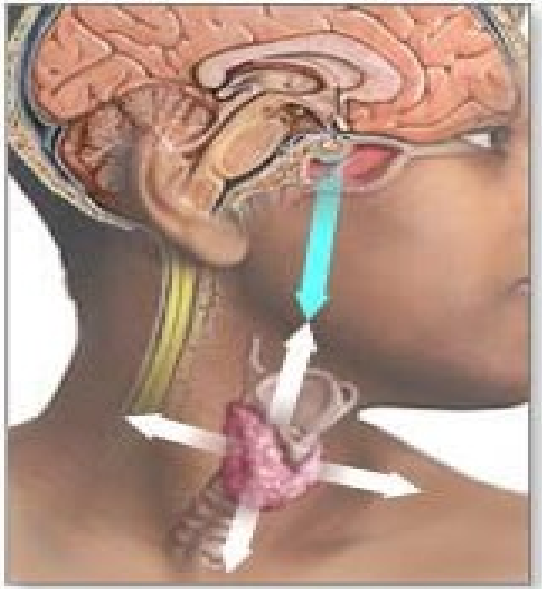


I thank all of you for your patience!

THYROID PHYSIOLOGY



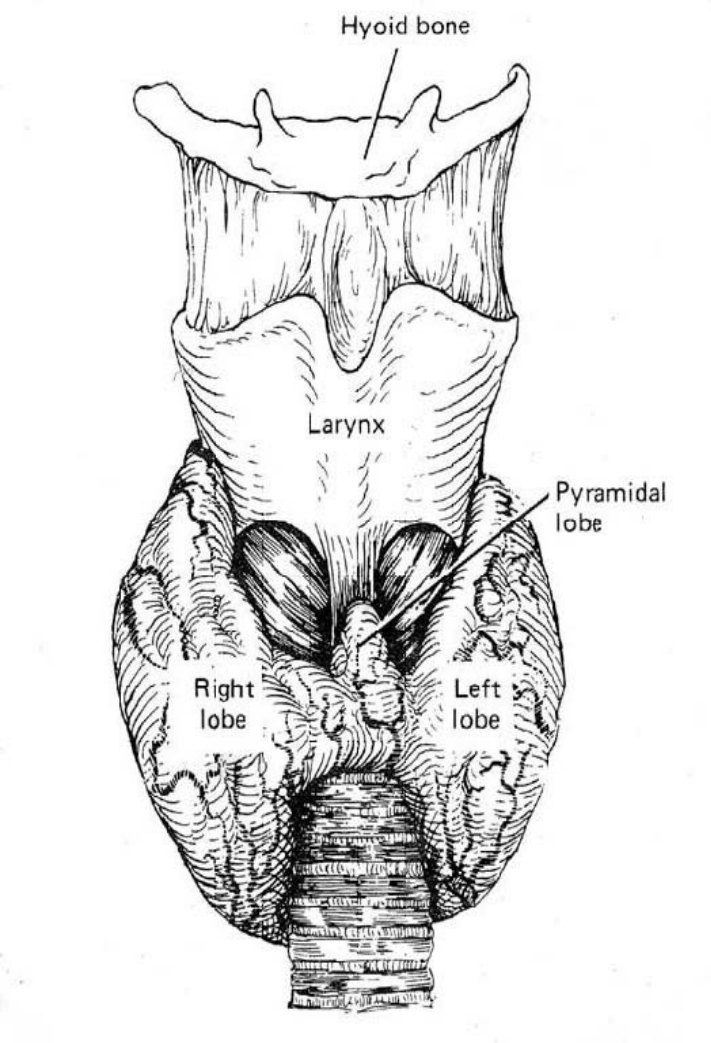
Primary hypothyroidism: thyroid can't produce amount of hormones pituitary calls for



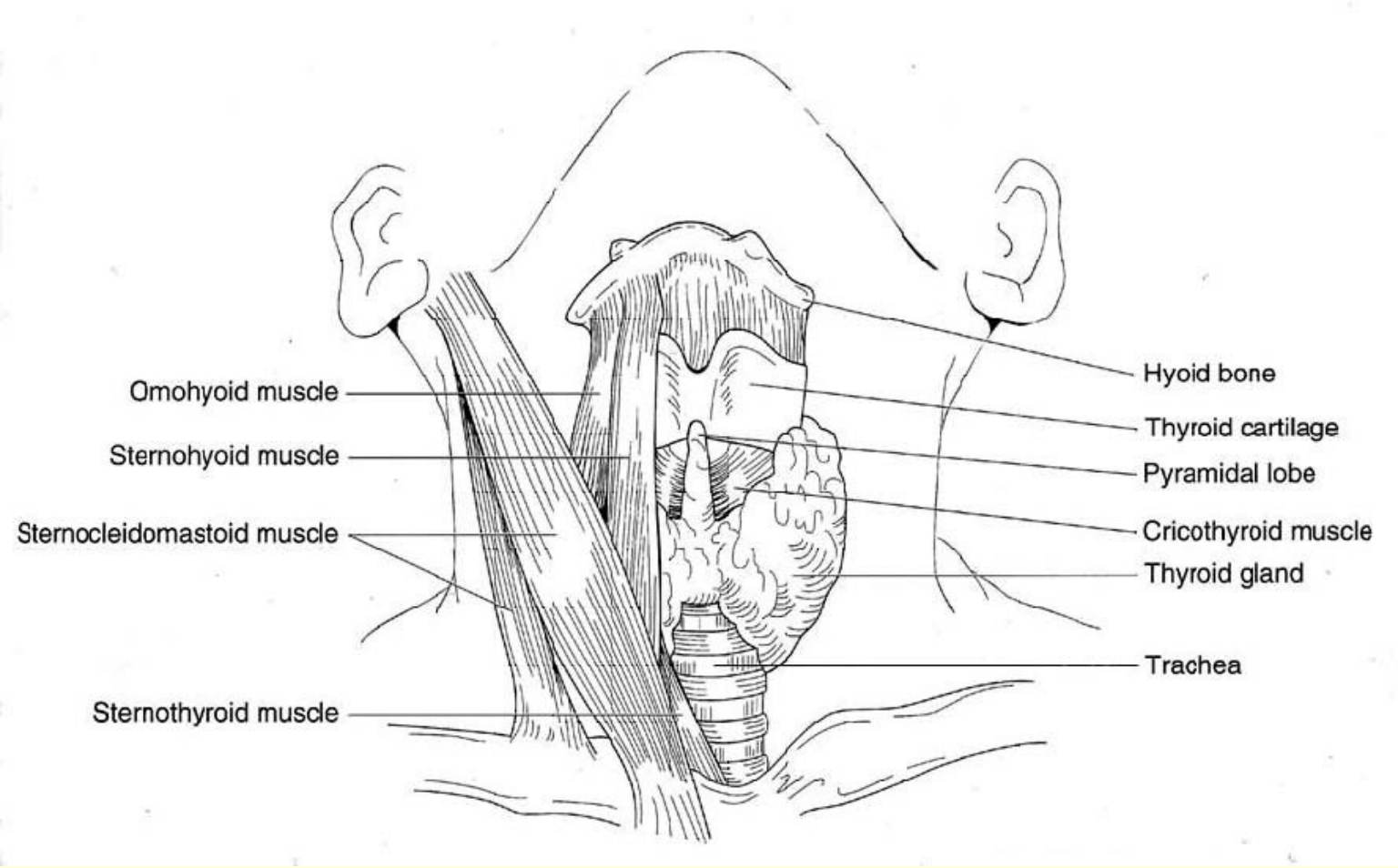
Secondary hypothyroidism: thyroid isn't being stimulated by pituitary to produce hormones

THYROID GLAND

- The thyroid gland is situated in front of the neck.
- It has two lobes on either side connected by an isthmus which lies at the level of second, third and fourth tracheal rings.
- The gland is highly vascular.
- It is composed of large number of follicles and there are parafollicular cells in between the follicles.



THYROID GLAND TOPOGRAPHY

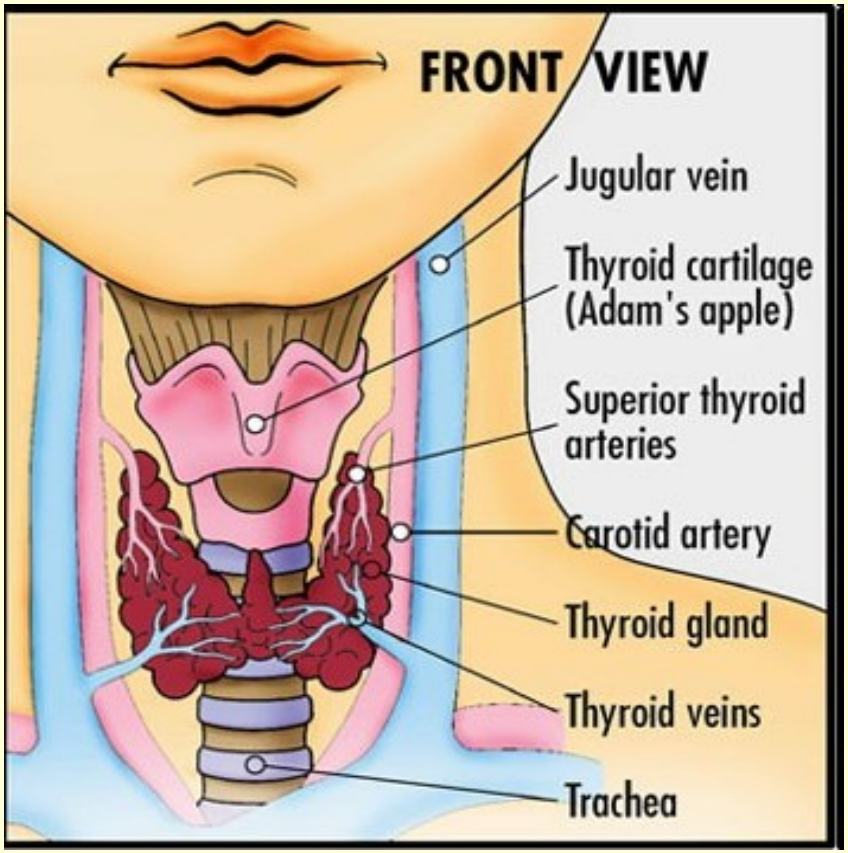


HISTORY

“The thyroid is a bag of worms whose eggs and occasionally themselves crossed for digestive purpose into esophagus”

Vercelloni, 1711

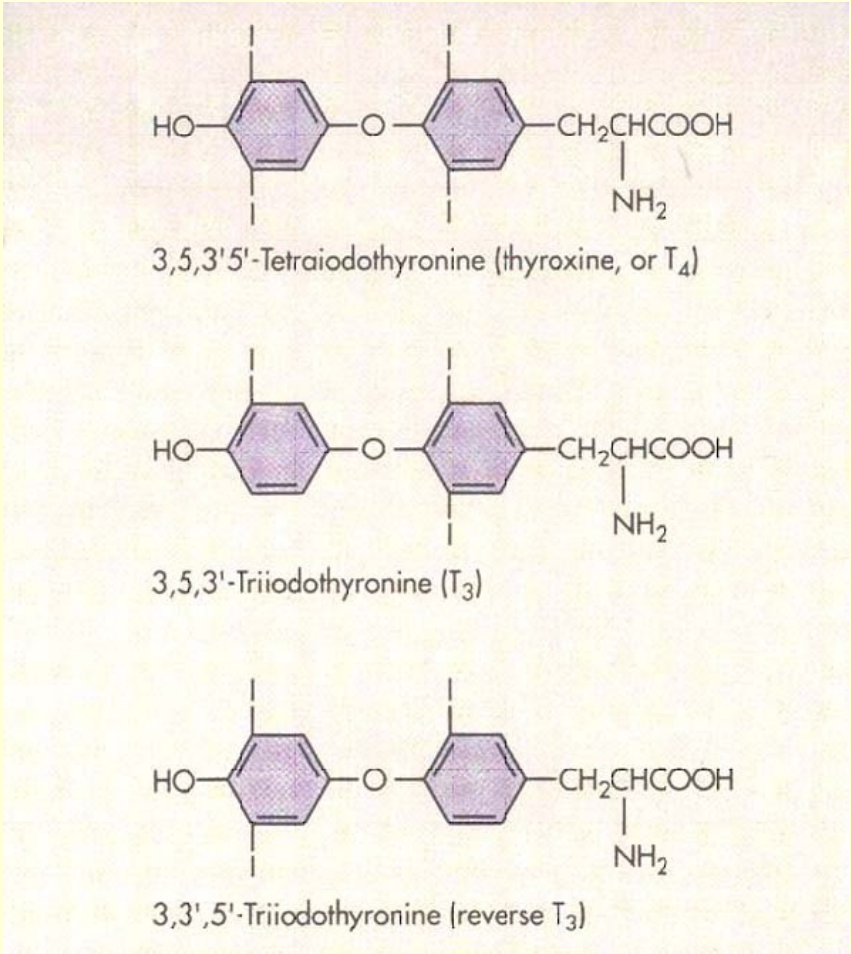
THYROID GLAND



- Thyroid gland derives from the floor of embryonic pharynx
- Thyroid development is largely completed between 10-20 weeks of gestation
- Abrupt rise of TSH causes an increase of serum T4 and T3 within 24 hours of birth
- Thyroid gland size increase gradually by 1 g/year until age of 15 years were it achieves adult size (15-20 g)

THYROID GLAND HORMONES

1. Tetra-iodothyronine [Thyroxine] (T4)
2. Tri-iodothyronine (T3)
3. Thyrocalcitonin
   - T3 and T4 are secreted from the follicular cells
   - Thyrocalcitonin from the parafollicular cells.



THYROID GLAND HORMONES

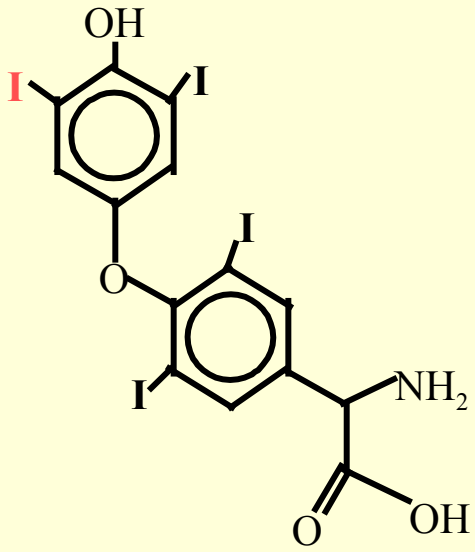
- Thyroid gland normally secretes mainly T4
- 70 % of T3 derived from T4 in peripheral tissues
- T4 is converted to T3 by 5-deiodinase enzyme

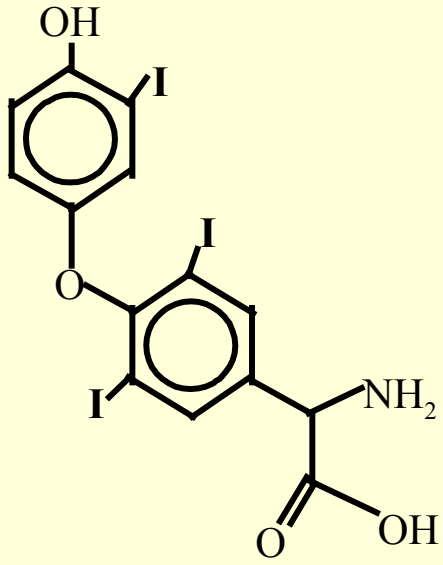
Both T4 and T3 are in bound form (TBG - thyroxine-binding globulin, pre albumin and albumin)

- Only 0.025% of T4 and 0.35% of T3 are free
- Free hormone concentration best correlates with thyroid status
- T4 production is 5-6 μg/kg/day in infancy with gradual decrement to 1.5 μg/kg/day in adult

THYROID HORMONES

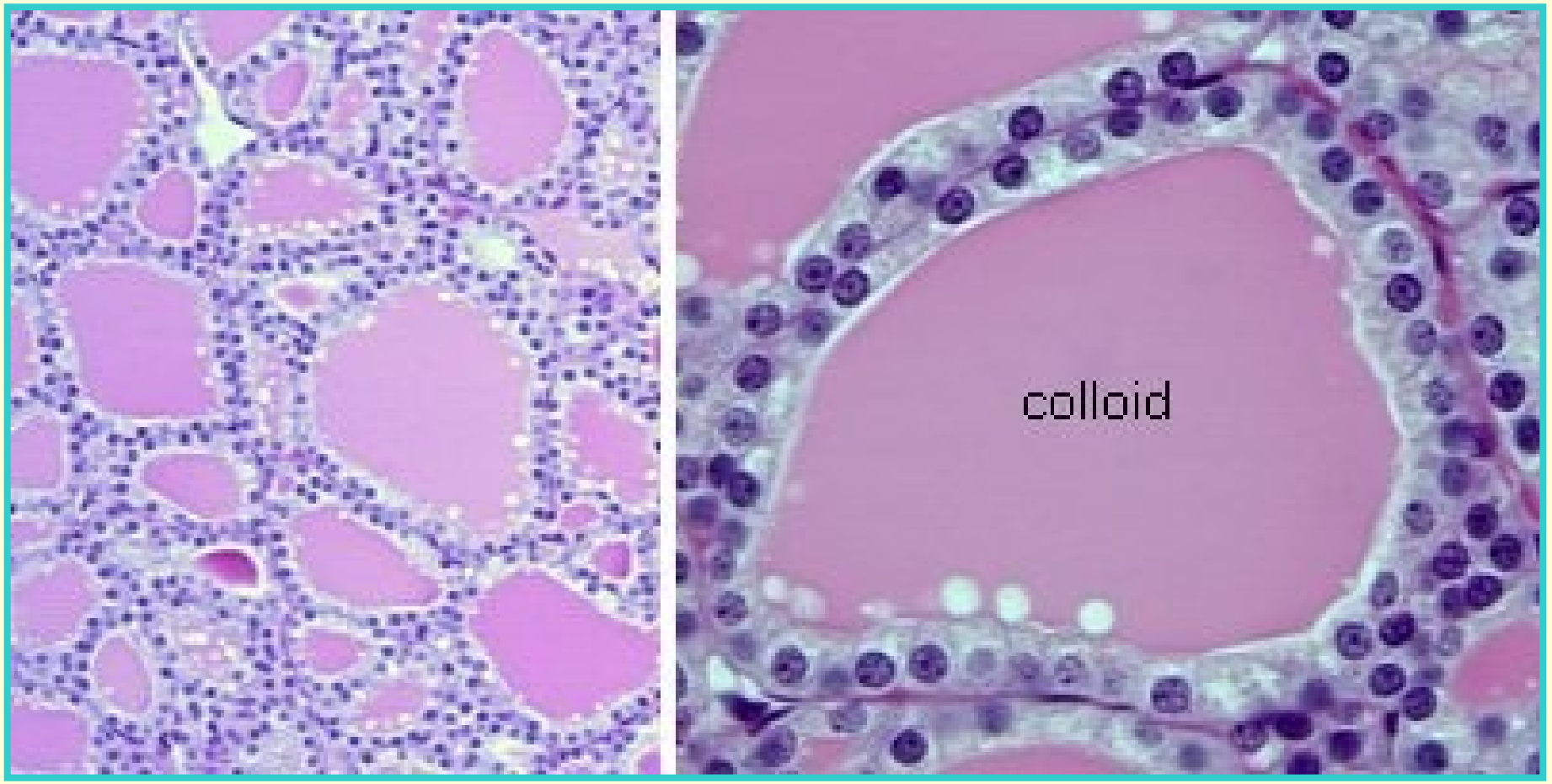
Thyroxine (T4)





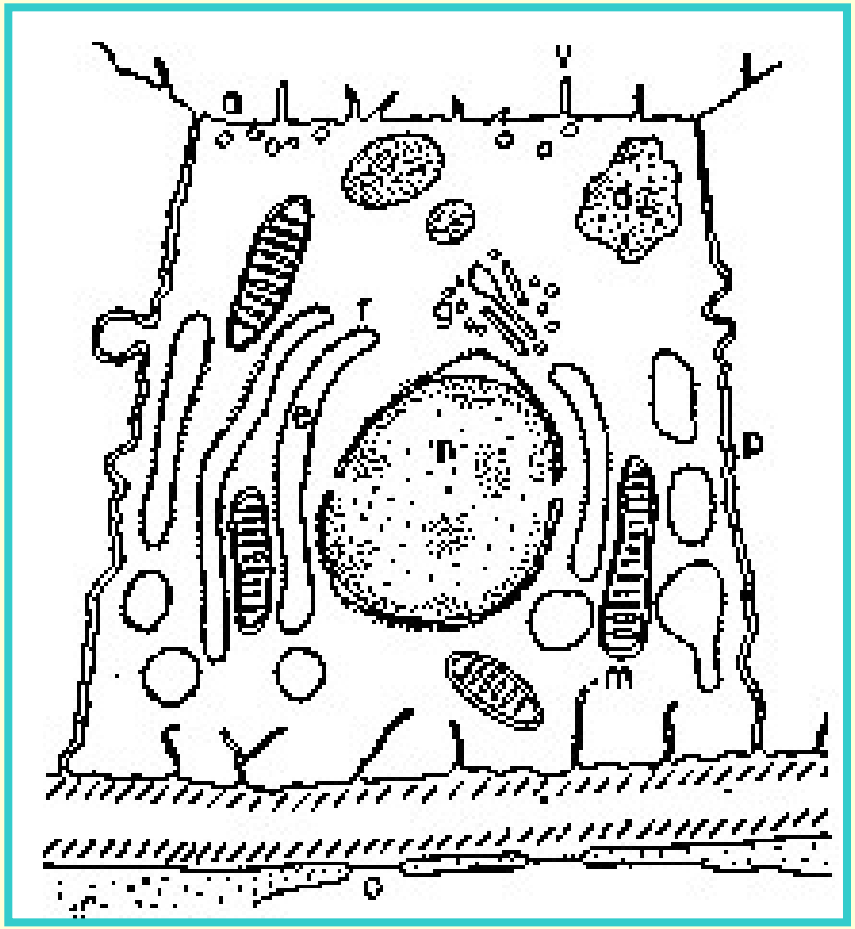
3,5,3'-Triiodothyronine (T_3)

THYROID GLAND HISTOLOGY



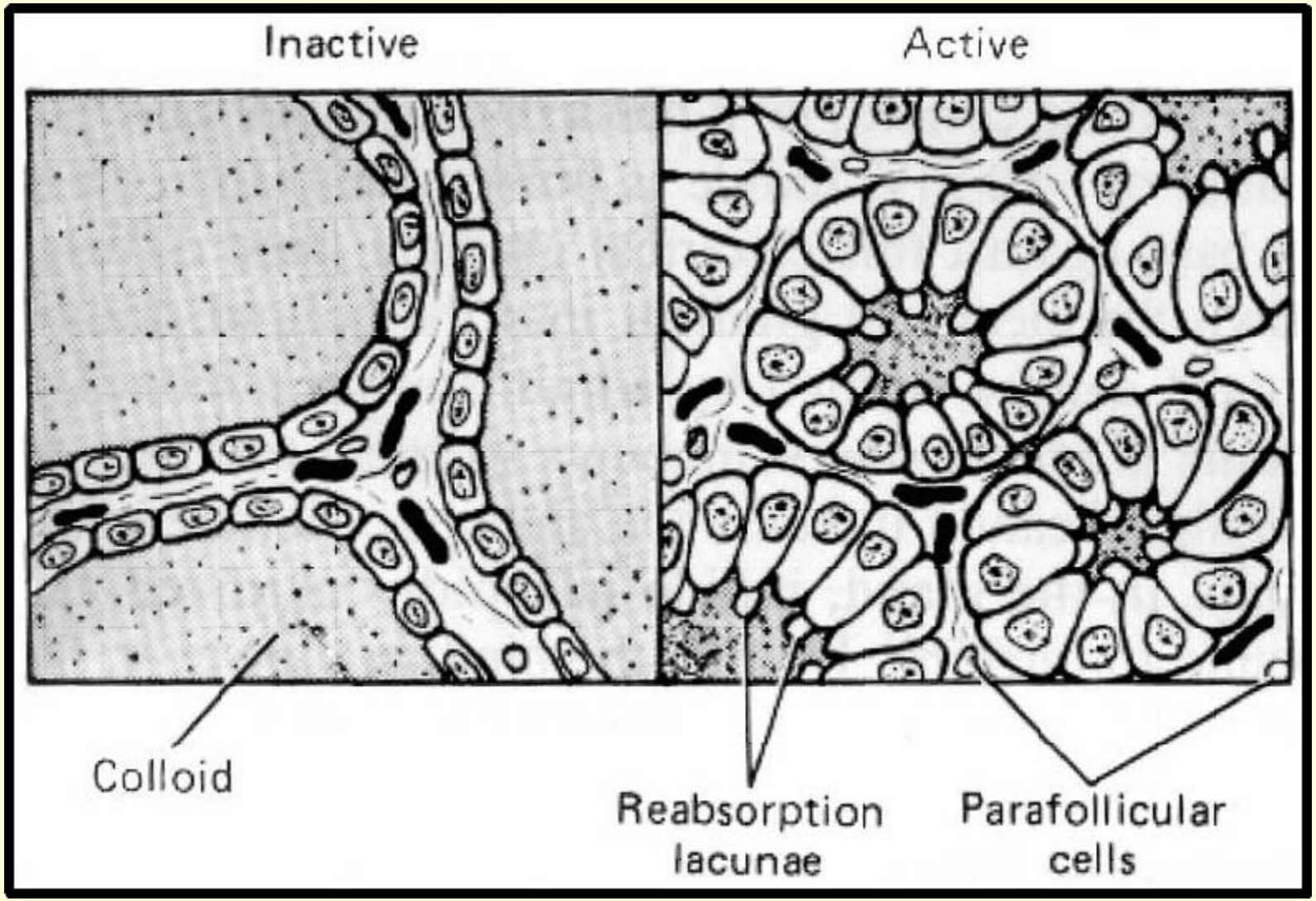
SYNTHESIS OF THYROID HORMONES

Thyroid hormones are synthesised within the acinar cells by iodination of the tyrosine residues within the thyroglobulin molecules which are also synthesised in the acinar cells. Iodine for this purpose is obtained from blood.



ACINAR CELLS

- The follicles are spherical structures (acini) lined by a single layer of glandular epithelium (acinar cell) and are filled with colloid, a homogenous substance mainly containing a protein, called thyroglobulin.
- The acinar cells are normally cubical. When the amount of colloid in the acini of a gland increases, the acinar cells become flat.
- The acinar cells become tall columnar when the amount of colloid decreases.
- The colloid increases in an inactive gland but decreases in an active gland.


Inactive
Active
Colloid
Reabsorption lacunae
Parafollicular cells

THYROGLOBULIN SYNTHESIS

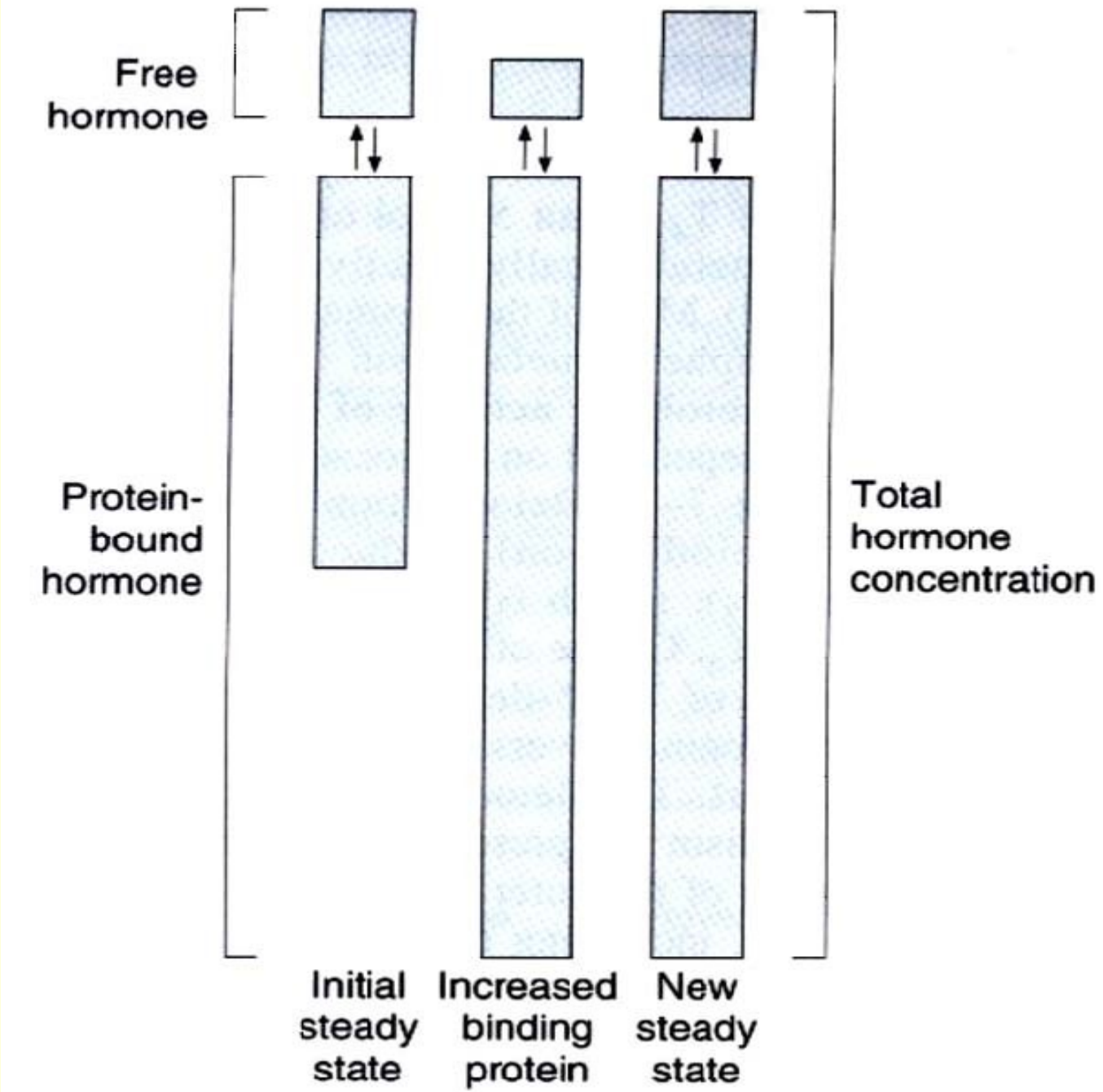
- Thyroglobulin is a glycoprotein synthesised by the follicular cells and is secreted into the colloid. It provides tyrosine residues for synthesis of the thyroid hormones.
- T3 and T4 synthesised in the acinar cells, remain attached to the thyroglobulin molecule and are stored in the colloid.
- Thyroglobulin is also found in circulation.

THYROID HORMONE SYNTHESIS

1. <u>Iodide pump</u>
   - rate–limiting step in thyroid hormone synthesis which needs energy
   - normal thyroid: serum iodine is 30-40:1
2. <u>Iodide oxidation to iodine and organification</u>
   - Both processes are catalyzed by thyroid peroxidase, then iodination of tyrosyl residue on thyroglobulin to form MIT and DIT

THYROID HORMONE SYNTHESIS

3. Coupling
   - Occurs within TG molecule
   - Also catalyzes by thyroid peroxidase
   - MIT +DIT = T3; DIT + DIT = T4
4. Deiodination
   - TG hydrolysis during secretion and iodide enters intracellular iodide pool which accounts for 70-80% of daily thyroidal iodine supply
5. Thyroid hormone secretion
   - Initially into follicular cells then into blood


Free hormone
Protein-bound hormone
Total hormone concentration
Initial steady state
Increased binding protein
New steady state

THYROID HORMONES IN THE BLOOD

- Approximately 99.98% of T_4 is bound to 3 serum proteins:
  - thyroid binding globulin (TBG) ~75%
  - thyroid binding prealbumin (TBPA or transthyretin) 15-20%
  - albumin ~5-10%
- Only ~0.02% of the total T_4 in blood is unbound or free.
- Only ~0.4% of total T_3 in blood is free.

Protein	Plasma Concentration (mg/dL)	Amount of Circulating Hormone Bound (%)	
		T_4	T_3
Thyroxine-binding globulin (TBG)	2	67	46
Thyroxine-binding prealbumin (TBPA)	15	20	1
Albumin	3500	13	53

DEGRADATION OF THYROID HORMONES

- Both the thyroxine and the tri-iodothyronine are disposed from the body after their action is over.
- Normally there is a balance between formation and degradation of the hormones.
- They are conjugated and excreted by liver as glucuronides and major part of the hormones are excreted through urine as tetrac and triac

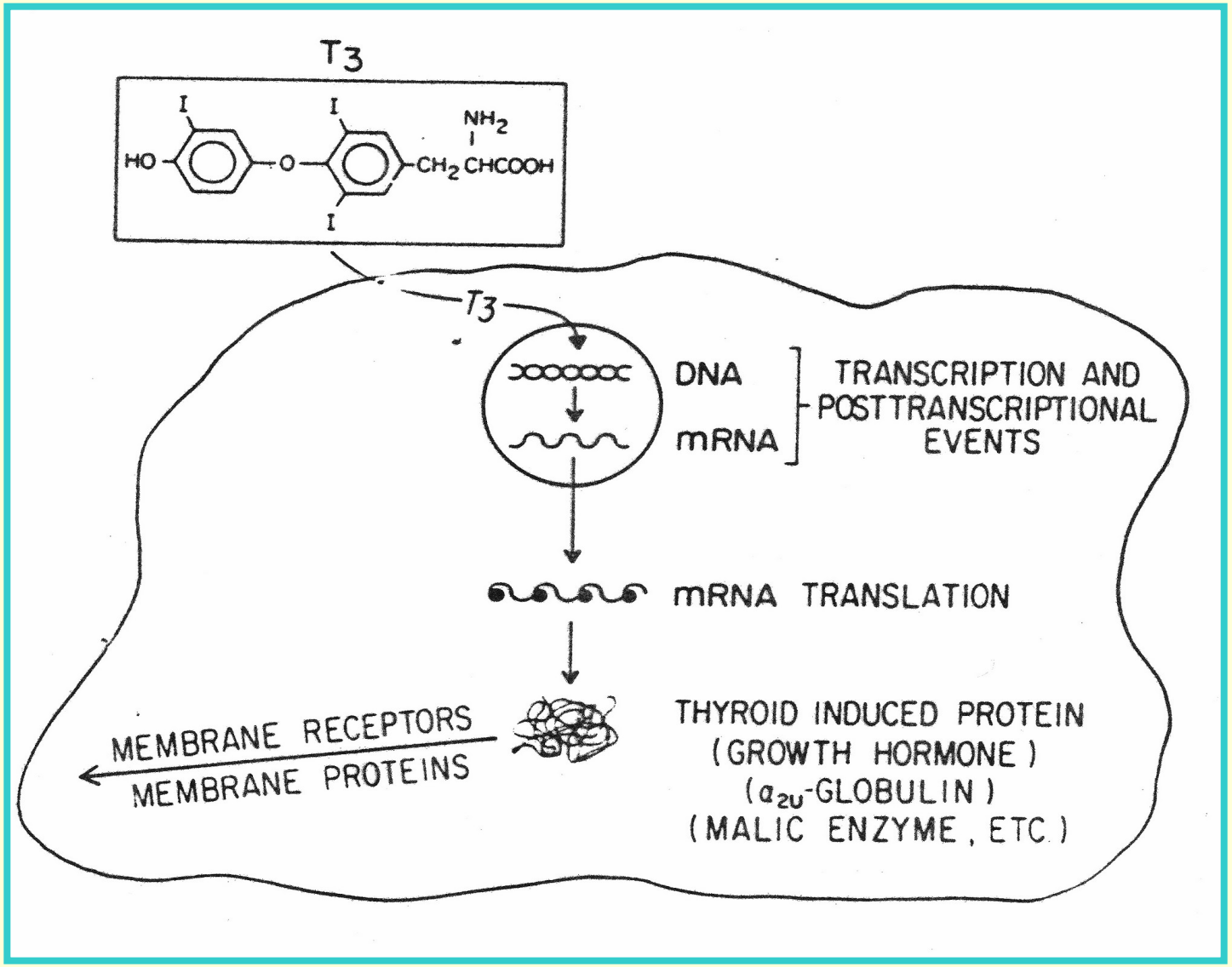
(Tetrac = tetra-iodothyro acetic acid,

Triac = tri-iodothyro acetic acid)

MECHANISM OF THYROID HORMONES ACTION

- Thyroid hormones bind to their intracellular receptors in the target organs. T3 binds to these receptors more avidly than T4, this may be the cause of T3 being more active than T4.
- These receptors are present in the nuclear chromatin and binding with the hormone results in gene expression and transcription. The mRNAs formed thus lead to protein synthesis.
- These proteins bring about all the intracellular actions of thyroid hormone. These proteins may be structural proteins, Na-K-ATPase, mitochondrial enzymes, adrenergic receptors.
- Hormone-receptor complex may also decrease expression of genes of some enzymes.
- Receptors for thyroid hormones are also present in cytosol.

BASICS OF THYROID HORMONE ACTION IN THE CELL



THYROID HORMONES FUNCTIONS

ON GENERAL GROWTH AND DEVELOPMENT

- THs (thyroid hormones) are very much essential for general growth.
- THs are required for synthesis of somatomedins.
- THs stimulate secretion of growth hormone (GH) and potentiate its action.
- THs cause increased synthesis of proteins, which also include the structural proteins.
- THs are necessary for differentiation and maturation, e.g., for ossification of epiphyseal centres and epiphyseal closure.

THYROID HORMONES FUNCTIONS

CALORIGENIC ACTION

- **THs increase metabolic rate, hence in cases of increased secretion there is increased BMR. So, the body temperature is also raised.**
- **Increased heat production is partially explained on the basis of increased number and also activity of Na-K-ATPase and increased ATP breakdown by them. This increases O_2 consumption in all the tissues except brain, anterior pituitary, testes, lymph nodes and spleen.**
- **There are other mechanism also to explain this increased O_2 consumption, e.g., increased intracellular reactions may be a cause.**

THYROID HORMONES FUNCTIONS

METABOLIC ACTIONS: CARBOHYDRATE METABOLISM

- THs increase blood sugar level by:
  - increased absorption of glucose from gut
  - increased gluconeogenesis
  - increased glycogenolysis.
- These are partly due to its permissive action on epinephrine.
- THs have inhibitory role on insulin action through the mediation of cAMP. On the other hand, THs increase peripheral utilisation of glucose.
- Mucopolysaccharide metabolism is also influenced by the thyroid hormones, particularly of hyaluronic acid, under the skin (e.g., myxoedema).

THYROID HORMONES FUNCTIONS

METABOLIC ACTIONS: LIPID METABOLISM

THs stimulate all the aspects of lipid metabolism, I.e., synthesis, mobilisation and degradation. THs increase lipolysis mainly due to its permissive influence on other hormones and to some extent by themselves. They can lower the serum cholesterol level by enhancing its catabolism and also by increasing the number of LDL receptors in liver.

METABOLIC ACTIONS: PROTEIN METABOLISM

THs are essential for protein synthesis and growth, but a high level of thyroid hormones results in protein catabolism. On the other hand, a normal level leads to positive nitrogen balance.

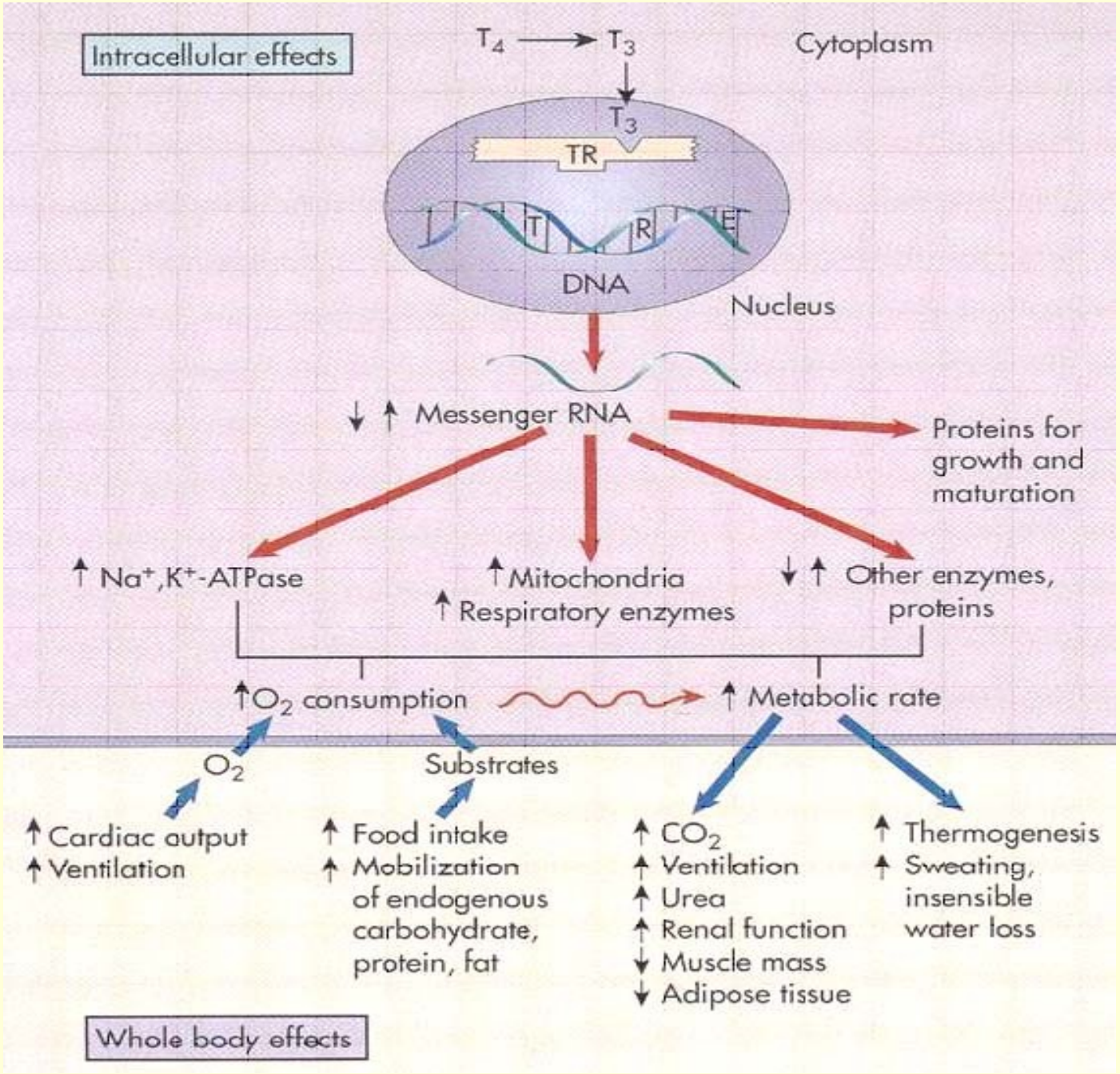
THYROID HORMONES FUNCTIONS

METABOLIC ACTIONS: MINERAL METABOLISM

THs are also related to Ca^{2+} and PO_4^{3-} metabolism. When there is excess secretion of thyroid hormones there is a negative balance of Ca^{2+} and PO_4^{3-} and results in osteoporosis.

METABOLIC ACTIONS: VITAMIN METABOLISM

THs help in conversion of carotene to a vitamin A. They also help in absorption of vitamin B_{12} from gut.


Intracellular effects
T_4 → T_3
Cytoplasm
T_3
TR
T
R
E
DNA
Nucleus
↓ ↑ Messenger RNA
Proteins for growth and maturation
↑ Na^+,K^+-ATPase
↑ Mitochondria
↑ Respiratory enzymes
↓ ↑ Other enzymes, proteins
↑ O_2 consumption
↑ Metabolic rate
O_2
Substrates
↑ Cardiac output
↑ Ventilation
↑ Food intake
↑ Mobilization of endogenous carbohydrate, protein, fat
↑ CO_2
↑ Ventilation
↑ Urea
↑ Renal function
↓ Muscle mass
↓ Adipose tissue
↑ Thermogenesis
↑ Sweating, insensible water loss
Whole body effects

EFFECTS OF THYROID HORMONES

ON THE CARDIOVASCULAR SYSTEM

- Increase heart rate
- Increase force of cardiac contractions
- Increase stroke volume
- Increase cardiac output
- Up-regulate catecholamine receptors

EFFECTS OF THYROID HORMONES

ON THE RESPIRATORY SYSTEM

- **Increase resting respiratory rate**
- **Increase minute ventilation**
- **Increase ventilatory response to hypercapnia and hypoxia**

ON THE RENAL SYSTEM

- **Increase blood flow**
- **Increase glomerular filtration rate**

EFFECTS OF THYROID HORMONES

ON OXYGEN CARRYING CAPACITY

- Increase RBC mass
- Increase oxygen dissociation from hemoglobin

ON INTERMEDIARY METABOLISM

- Increase glucose absorption from the GI tract
- Increase carbohydrate, lipid and protein turnover
- Down-regulate insulin receptors
- Increase substrate availability

EFFECTS OF THYROID HORMONES

IN GROWTH AND TISSUE DEVELOPMENT

- **Increase growth and maturation of bone**
- **Increase tooth development and eruption**
- **Increase growth and maturation of epidermis, hair follicles and nails**
- **Increase rate and force of skeletal muscle contraction**
- **Inhibits synthesis and increases degradation of mucopolysaccharides in subcutaneous tissue**

EFFECTS OF THYROID HORMONES

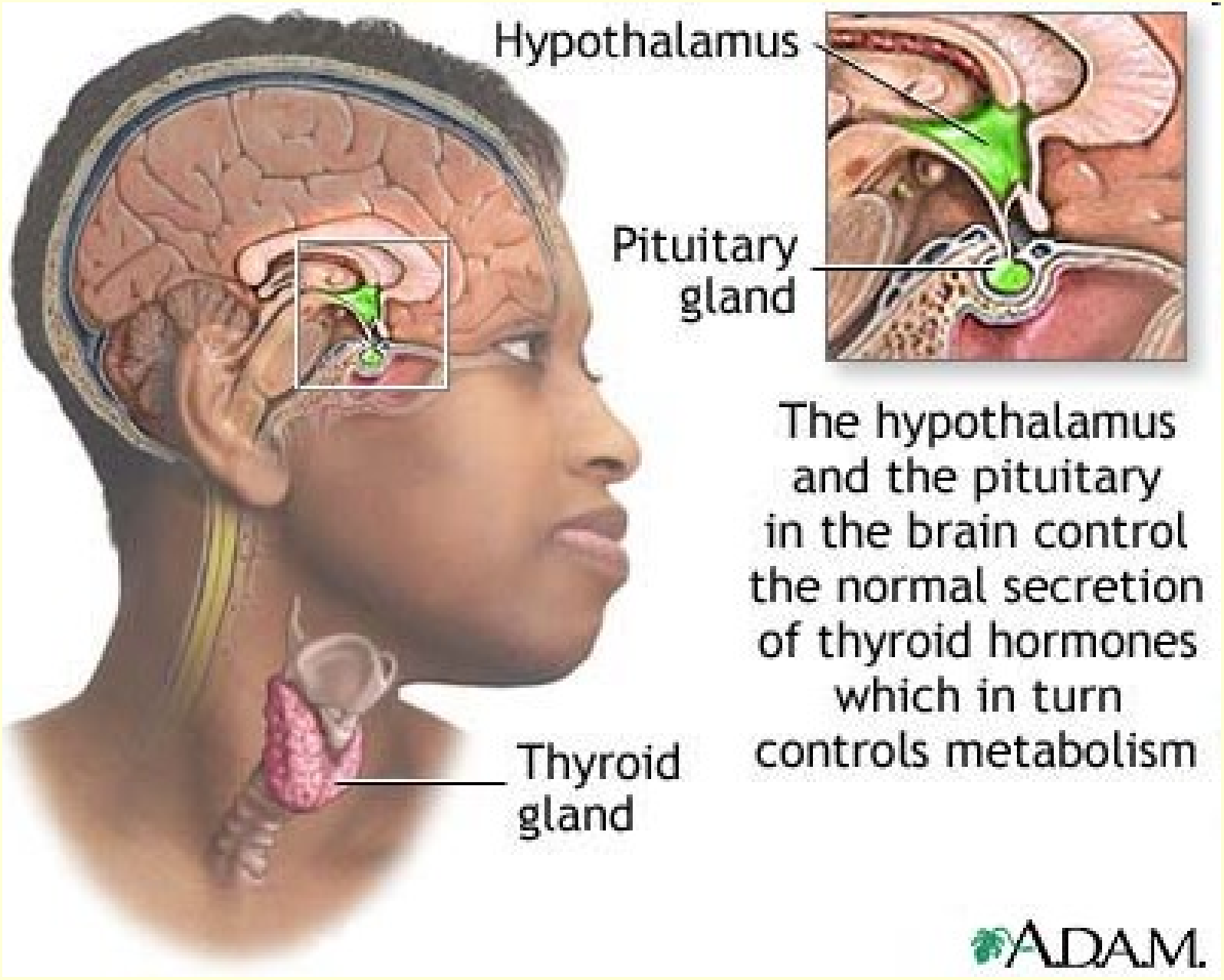
ON THE NERVOUS SYSTEM

- Critical for normal CNS neuronal development
- Enhances wakefulness and alertness
- Enhances memory and learning capacity
- Required for normal emotional tone
- Increase speed and amplitude of peripheral nerve reflexes

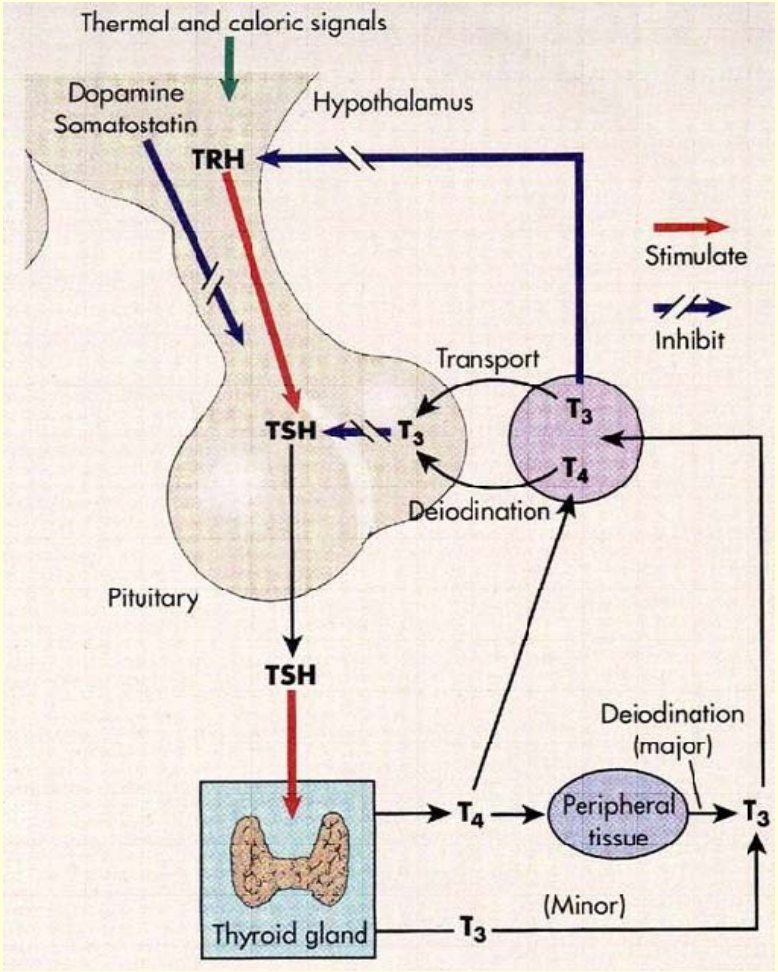
EFFECTS OF THYROID HORMONES

ON THE REPRODUCTIVE SYSTEM

- **Required for normal follicular development and ovulation in the female**
- **Required for the normal maintenance of pregnancy**
- **Required for normal spermatogenesis in the male**

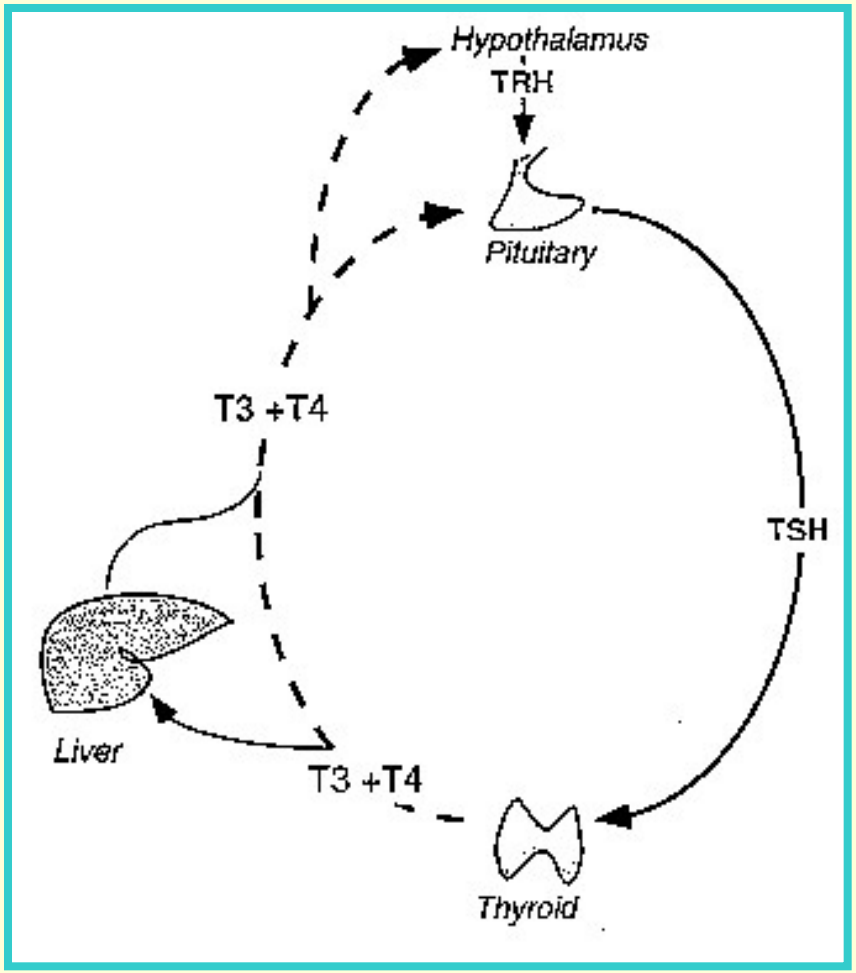

Hypothalamus
Pituitary gland
Thyroid gland
The hypothalamus and the pituitary in the brain control the normal secretion of thyroid hormones which in turn controls metabolism
A.D.A.M.

HYPOTHALAMIC-PITUITARY REGULATION



- TSH stimulates thyroid cell growth and metabolism
- TSH binds to thyroid membrane receptor and its action is mediated through cAMP
- TSH stimulates both I^- uptake and iodination of tyrosine resides on thyroglobulin
- T4 is produced mainly from the thyroid gland
- 30% of T3 produced from thyroid gland

PITUITARY-THYROID AXIS



<u>Key players for the thyroid include</u>:

- **TRH - Thyrotrophin Releasing Hormone**
- **TSH - Thyroid Stimulating Hormone**
- **T4/T3 - Thyroid hormones**

REGULATION OF SECRETION

Regulation of thyroid hormone secretion occurs in the following way :

1. TRH (thyrotrophin releasing hormone) from hypothalamus increases secretion of TSH (thyroid stimulating hormone) from the anterior pituitary. TSH in turn stimulates secretion of thyroid hormones. Secretion of TRH increases in cold and decreases in warmth but TRH secretion definitely decreases in stress. SS (somatostatin) and DA (dopamine) both inhibit TSH secretion and thus secretion of thyroid hormones.

REGULATION OF SECRETION

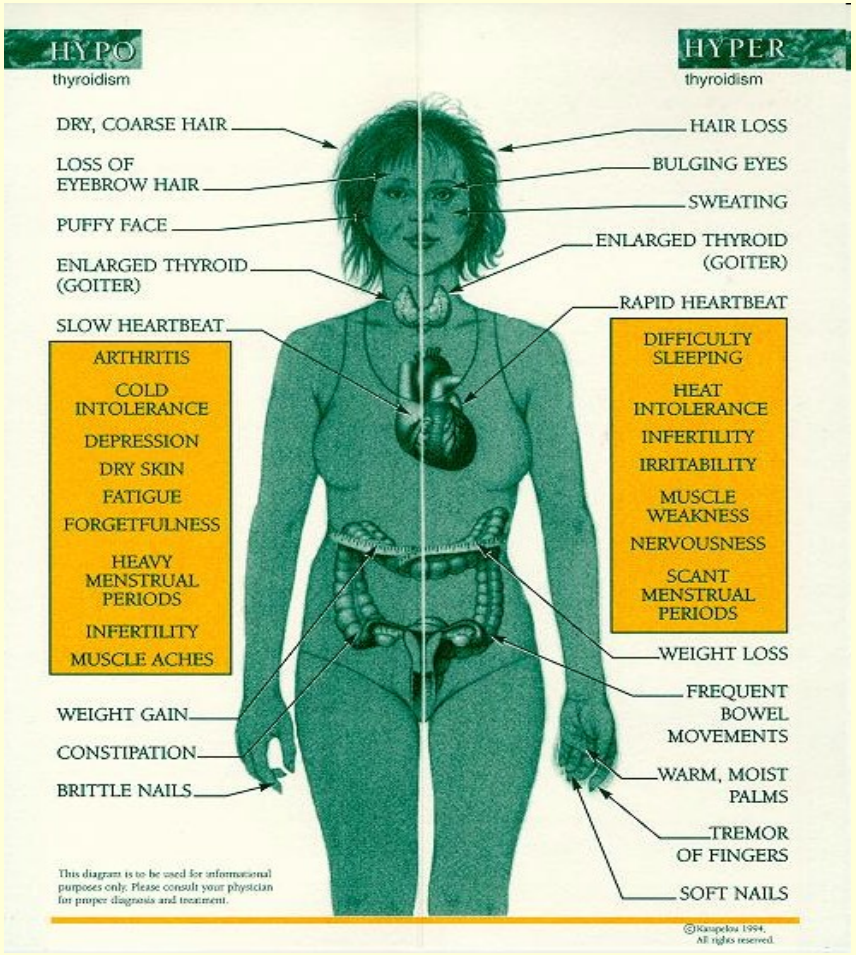
2. T3, and T4 feedback action is the most important mode of regulation of thyroid hormone secretion in normal condition. THs act both on pituitary as well as on hypothalamus. Increased secretion of T3, and T4 leads to inhibition of TSH secretion and also reduction of TRH receptors on pituitary. In this respect T3 is more potent and in pituitary T4 is converted into T3 by 5'-deiodinase enzyme.

REGULATION OF SECRETION

3. There is some autoregulation of the activity of thyroid gland depending on the availability of iodine in the body. When the iodine content increases, the thyroid gland is depressed, whereas it becomes hyperactive when there is a decrease in iodine supply. This mechanism help to maintain a normal secretion rate even if there is change in iodine supply.

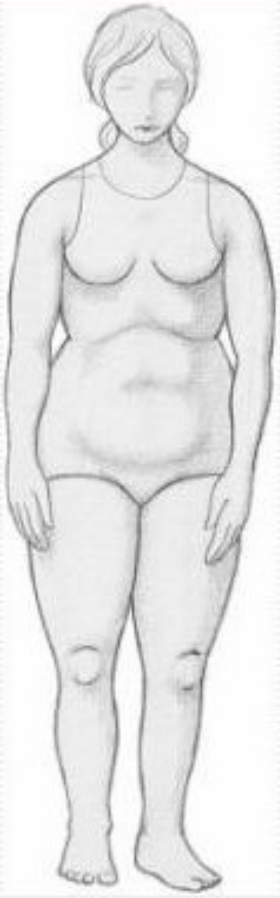
HYPOTHYROIDISM - HYPERTHYROIDISM

- When there is a decrease in thyroid secretion and deficiency signs develop, it is called hypothyroidism.
- On the other hand, hyperthyroidism means more than normal activity of the gland with increased levels of thyroid hormone.
- Euthyroid state indicates normal function of the gland.
- Both hyper- and hyposecretion occur frequently in the population.



Thyroid-related symptoms

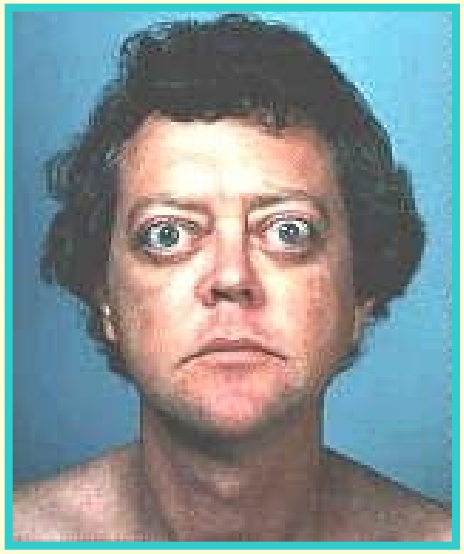
- **Decreased Metabolic Activity**
- Decreased mental processes
- Cholesterol Problems
- Need for vitamins
- Loose skin
- Dry skin, dry hair
- **Sleepiness, Depression, Fatigue**



- Decreased libido
- **Inflammation of the tendons & joints**
- Cold internally
- **Overall weight gain more evenly distributed**
- Weak heart
- **Fat & Carbohydrate Metabolism Altered**

EXAMPLES OF THYROID DISEASES

Hypothyroidism



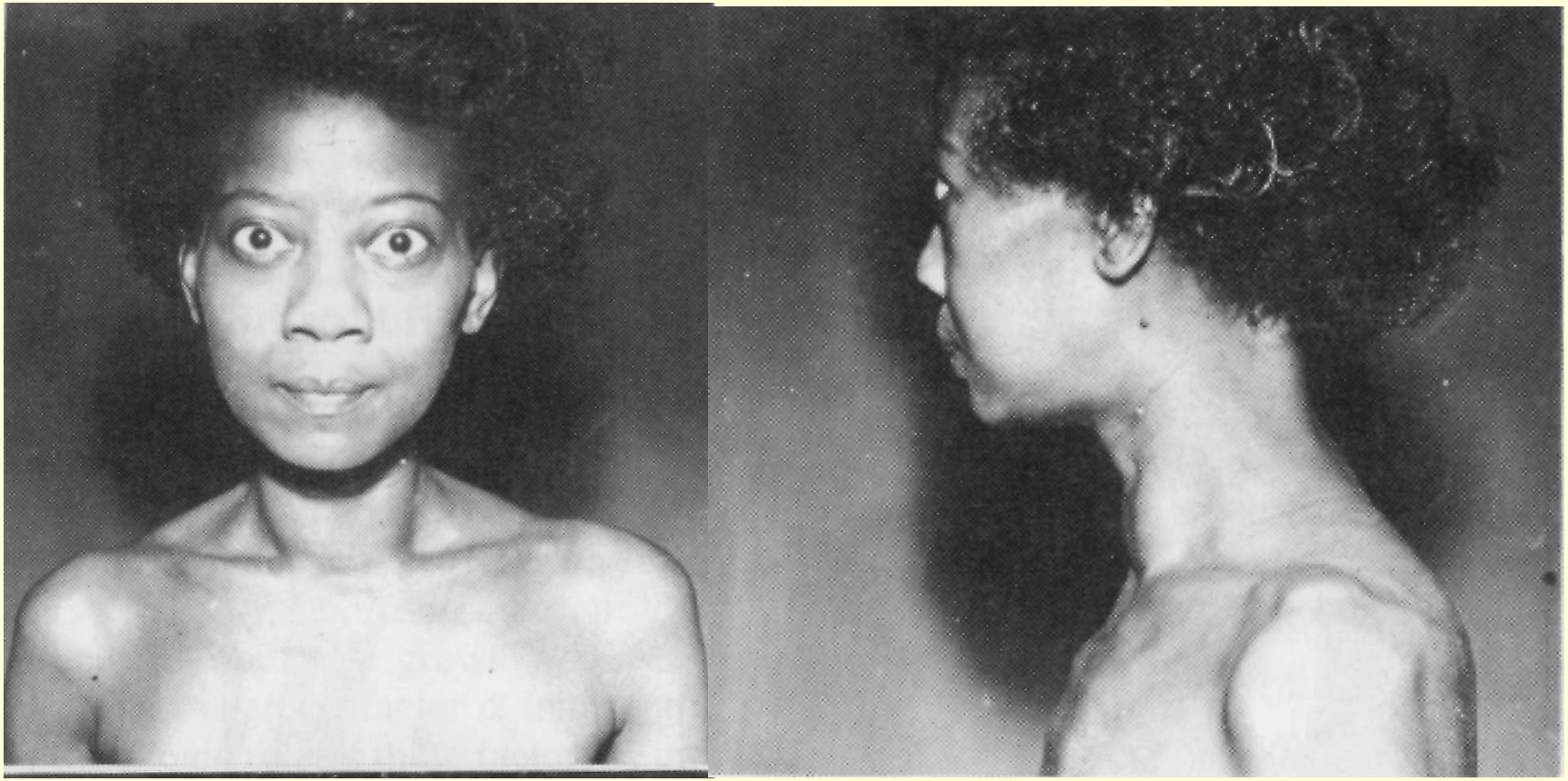
Hyperthyroidism

EXAMPLES OF THYROID DISEASES

Cretinism (congenital hypothyroidism)

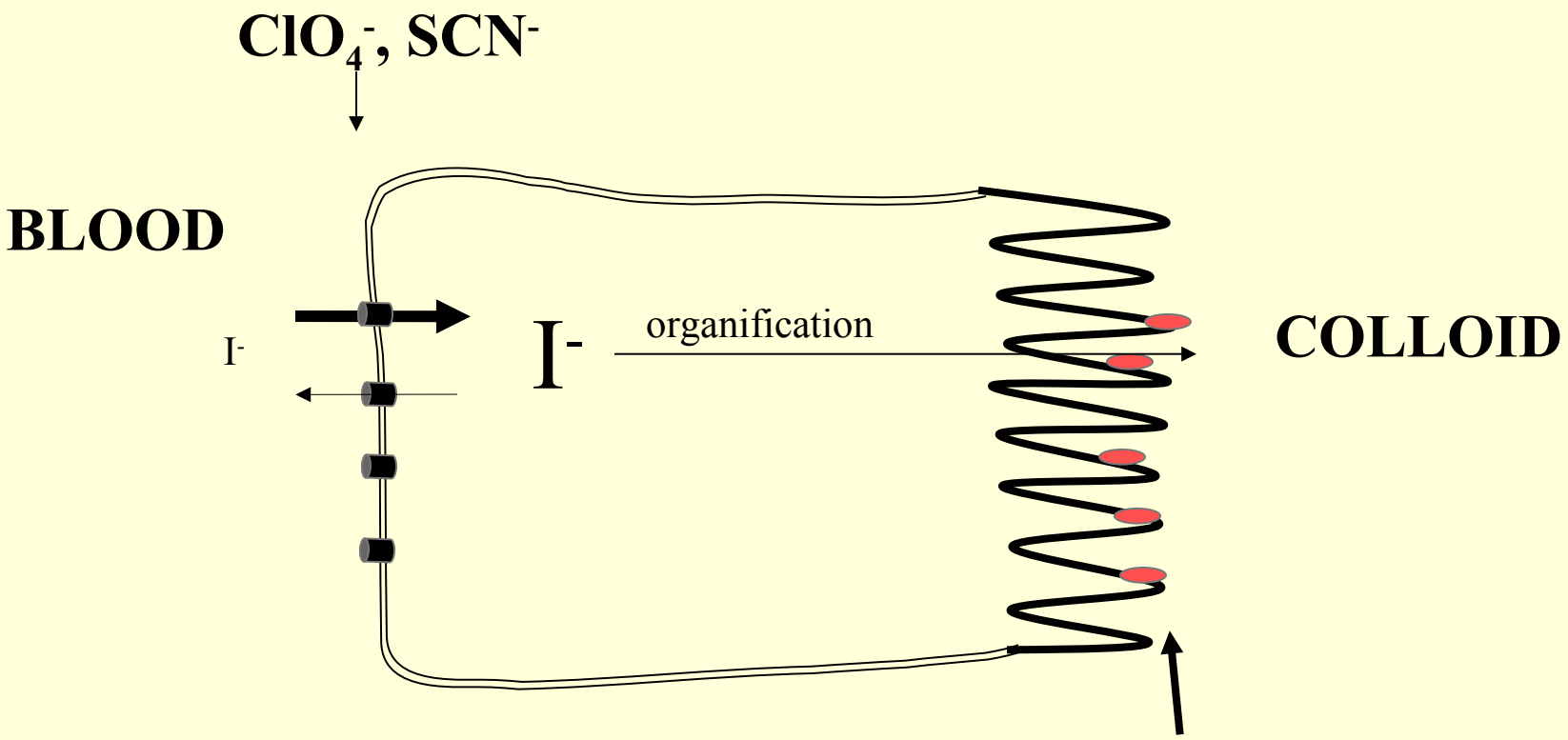
is the term for the constellation of defects resulting from untreated neonatal hypothyroidism.

EXAMPLES OF THYROID DISEASES



Hyperthyroidism

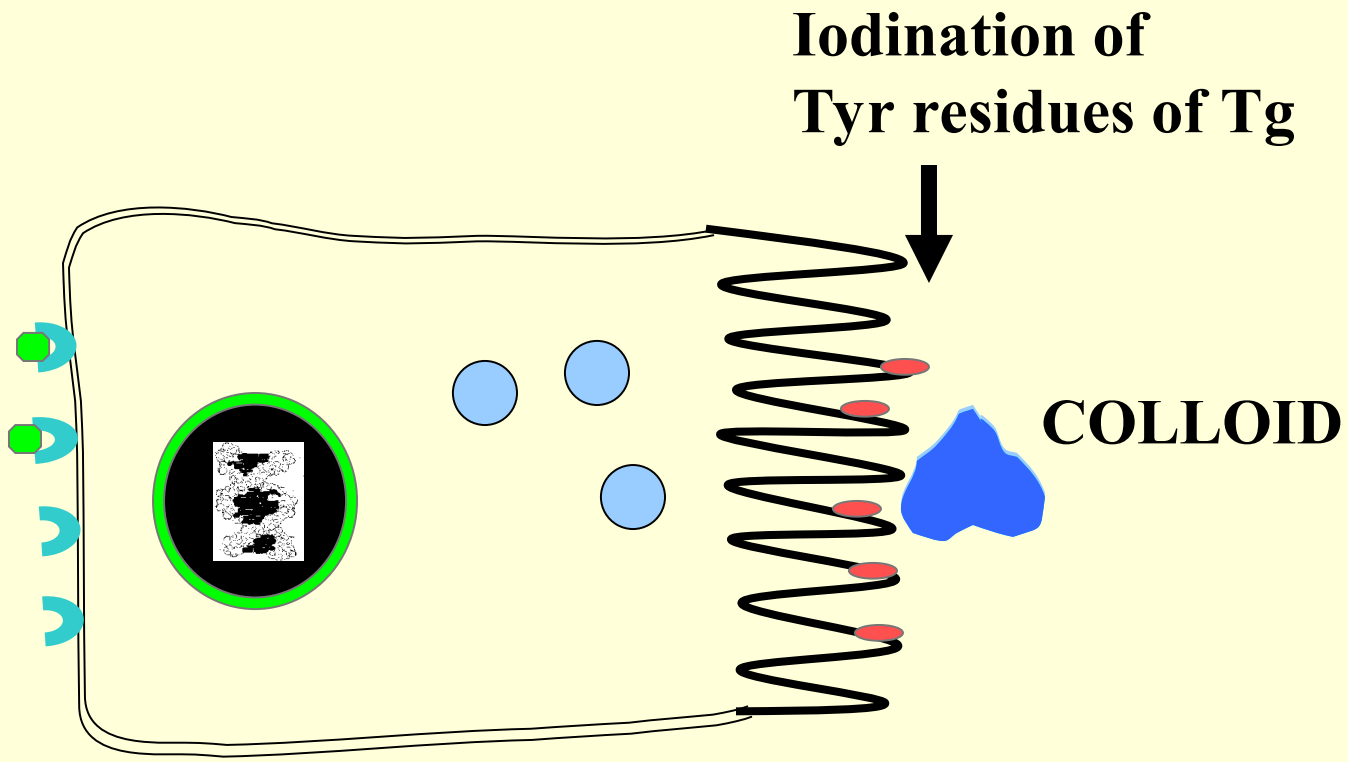
ION TRANSPORT BY THE THYROID FOLLICULAR CELL



- **NaI symporter (NIS)**
- **Thyroid peroxidase (TPO)**

Propylthiouracil (**PTU**) blocks iodination of thyroglobulin

THYROGLOBULIN SYNTHESIS IN THE THYROID FOLLICULAR CELL

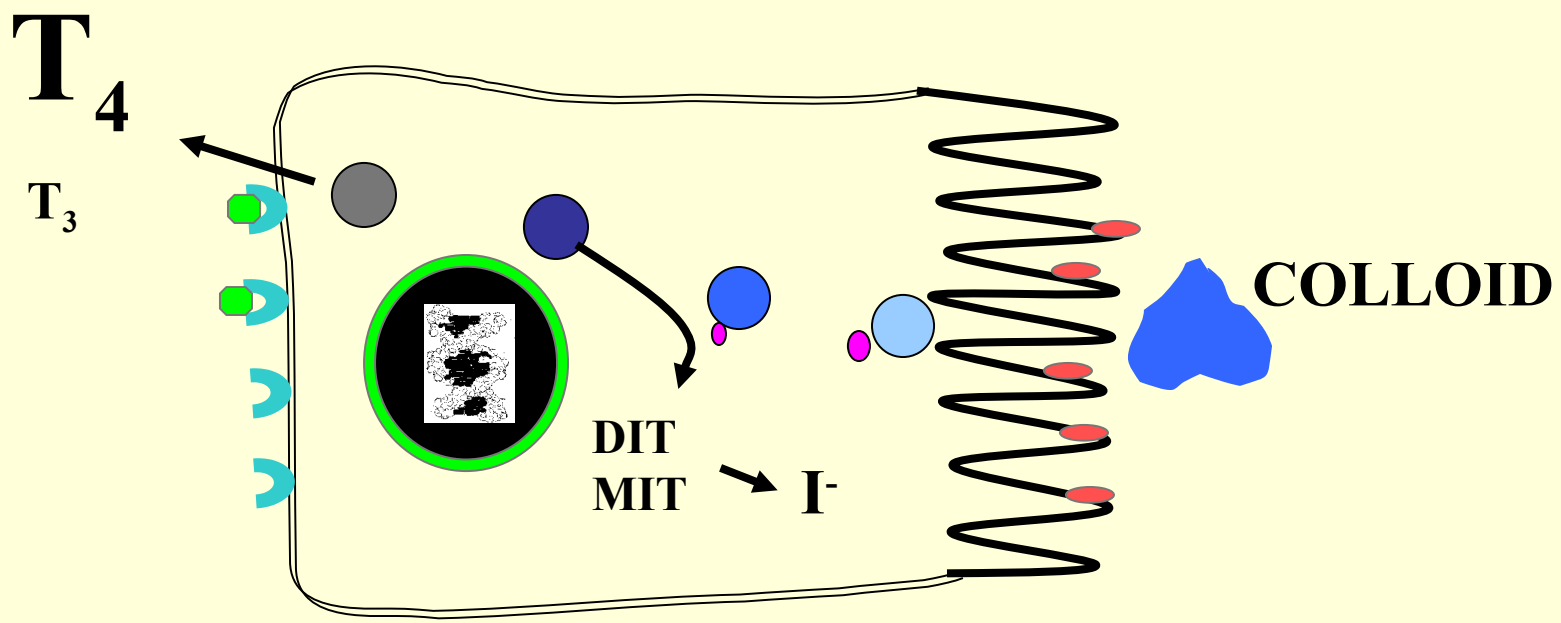


TSH

TSH receptor

TPO

THYROID HORMONE SECRETION BY THE THYROID FOLLICULAR CELL



TSH

TSH receptor

Hormone production: "Classic" glands

Hypothalamus:
- GHRH, CRH, TRH, GnRH
- Somatostatin
- ADH

Pituitary:
- Growth hormone
- Prolactin
- ACTH, MSH
- TSH
- FSH & LH

- Oxytocin
- ADH

Pancreas:
- Insulin
- Glucagon

Ovaries:
- Estrogens
- Progesterone

Epiphysis:
- Melatonin

Thyroid gland:
- T3, T4
- Calcitonin

Parathyroid glands:
- Parathyroid h.

Adrenal cortex:
- Cortisol
- Aldosterone
- Androgens

Adrenal medulla:
- Catecholamines


I thank
all of you
for your
patience!