# Diabetes Mellitus

A biochemical/biomedical overview

# Diabetes Mellitus :

a group of diseases characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both

- 20.8 million in US ( 7% of population)
- estimated 14.6 million diagnosed (only 2/3)
- Consists of 3 types:
- 1) Type 1 diabetes
- 2) Type 2 diabetes
- 3) Gestational diabetes

Complications :

- Stroke
- Heart attack
- Kidney disease
- Eye Disease
- Nerve Damage

# Diabetes Mellitus

- ## Type 1 Diabetes

  - cells that produce insulin are destroyed
  - results in insulin dependence
  - commonly detected before 30

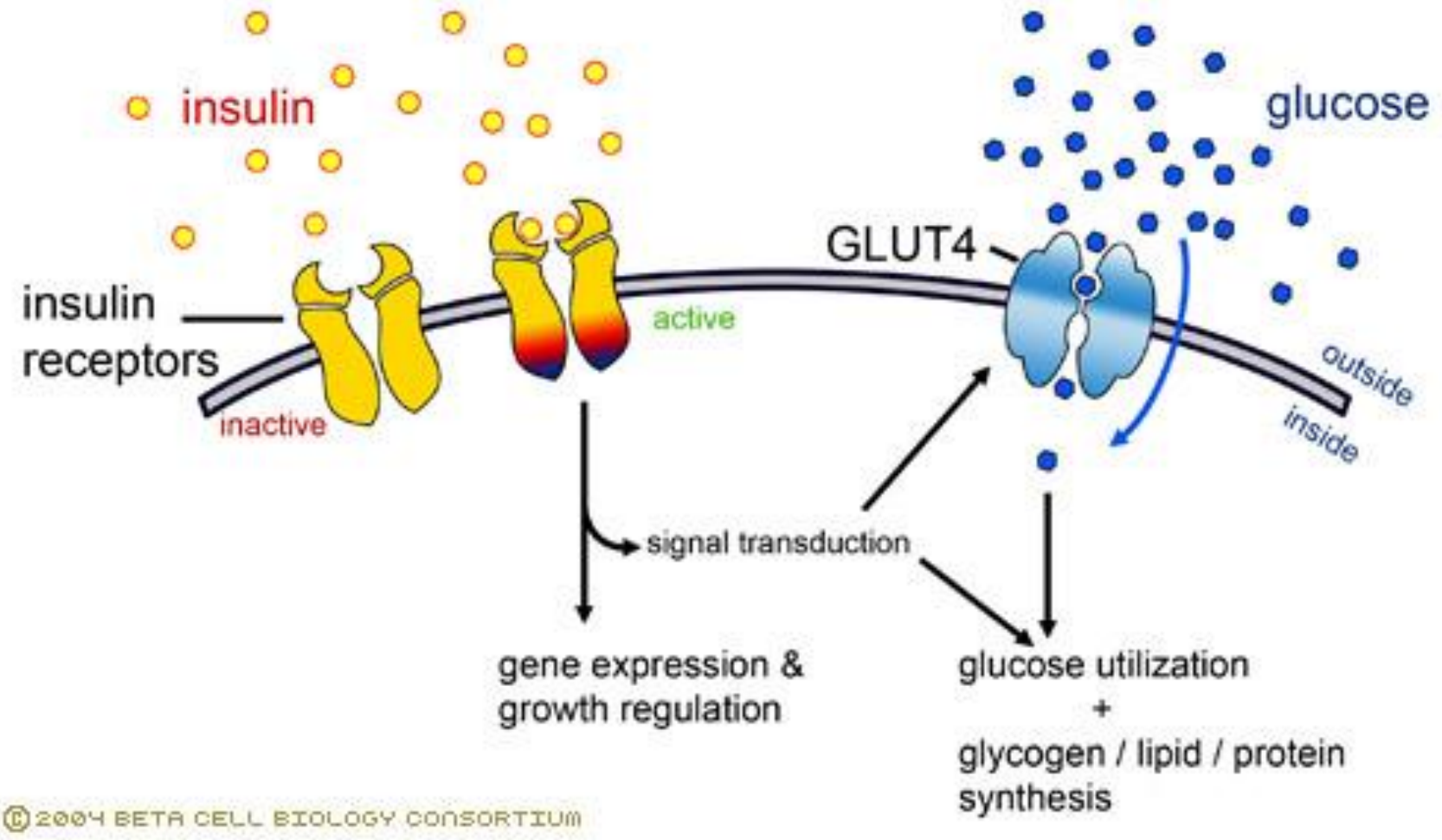
- ## Type 2 Diabetes

  - blood glucose levels rise due to
    1) Lack of insulin production
    2) Insufficient insulin action (resistant cells)
  - commonly detected after 40
  - effects > 90%
  - eventually leads to β-cell failure (resulting in insulin dependence)

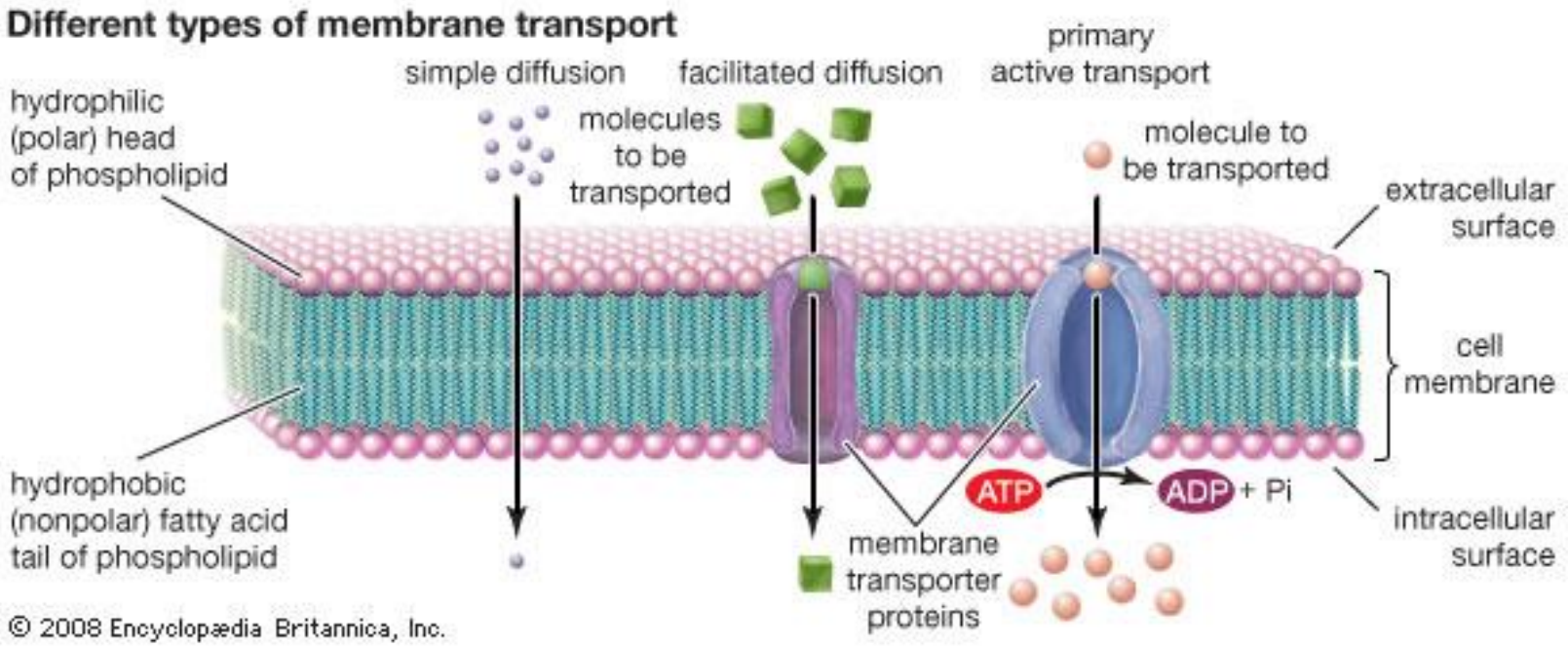
## Gestational Diabetes

3-5% of pregnant women in the US develop gestational diabetes

A depiction of insulin receptors (active and not active) and the glucose cell transport system. More on this later…



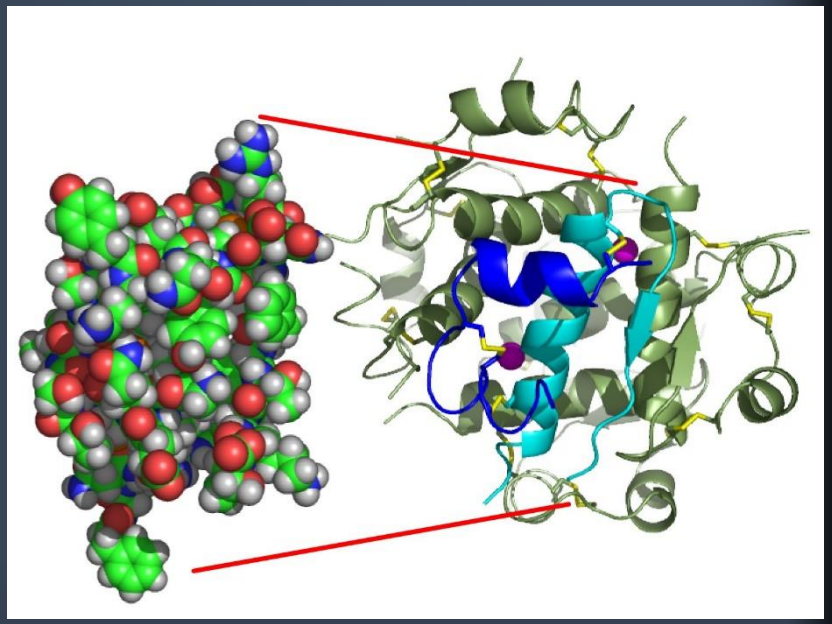
We will cover the ‘membrane transport system’ later in the Biotech course, but this is how glucose gets admitted to the cell (or not)



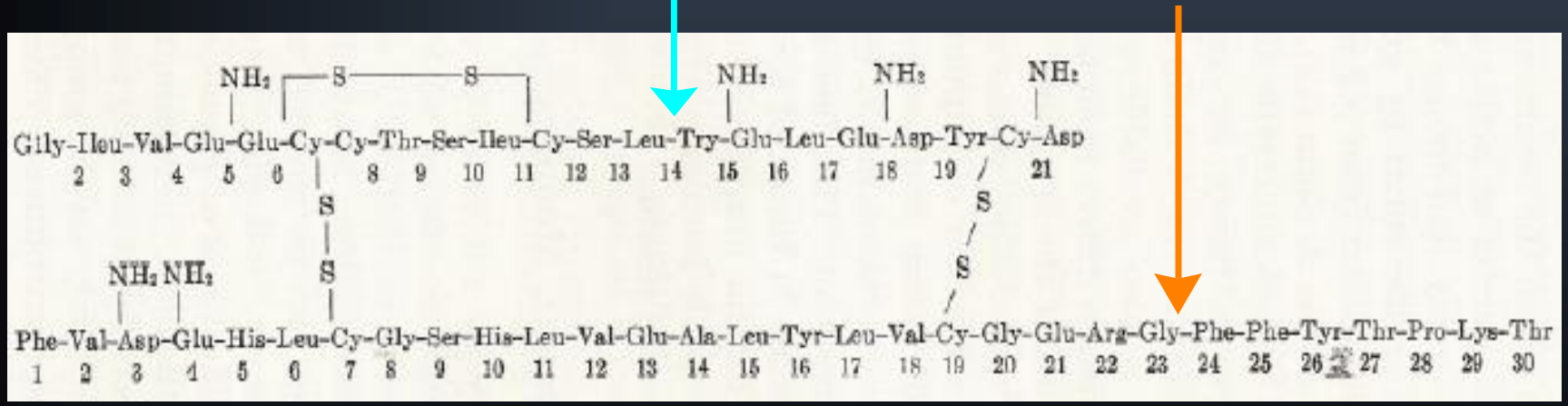
# Insulin

- Discovered in 1921 by Banting and Best
- Consist of A & B chains linked by 2 disulfide bonds

  (plus additional disulfide in A)



- A = 21amino acids  B = 30 amino acids



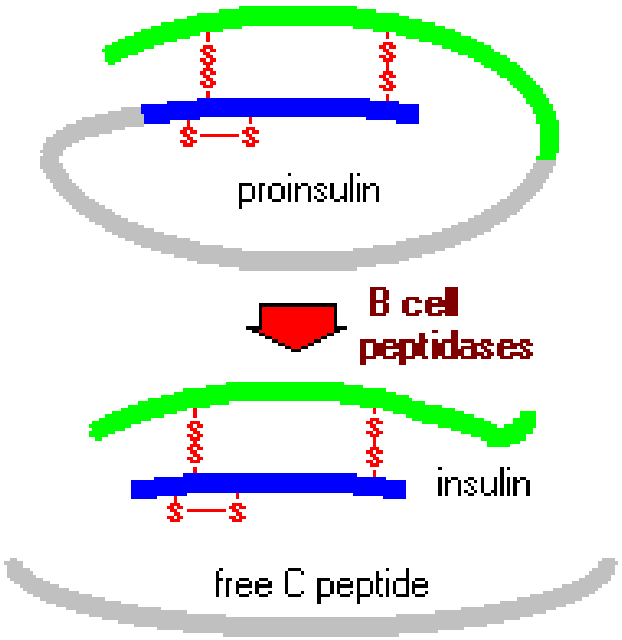
Insulin differs slightly among animals. Pig insulin was pretty close, and relatively easy to get.

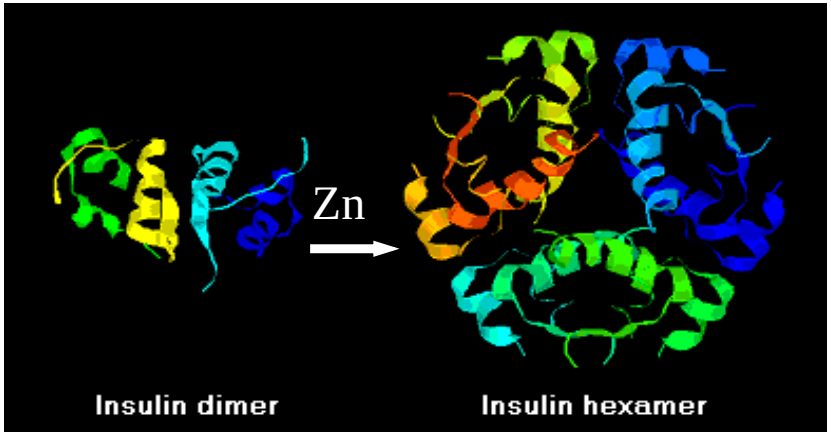
*Amino acid differences among mammalian insulins in A 8, 9, 10 and B 30*

| | A 8 | A 9 | A 10 | B 30 |
|---|---|---|---|---|
| Beef | Ala | Ser | Val | Ala |
| Sheep | Ala | Gly | Val | Ala |
| Pig | Thr | Ser | Ileu | Ala |
| Sperm whale | Thr | Ser | Ileu | Ala |
| Sei whale | Ala | Ser | Thr | Ala |
| Human subject | Thr | Ser | Ileu | Thr |
| Rabbit | Thr | Ser | Ileu | Ser |
| Horse | Thr | Gly | Ileu | Ala |

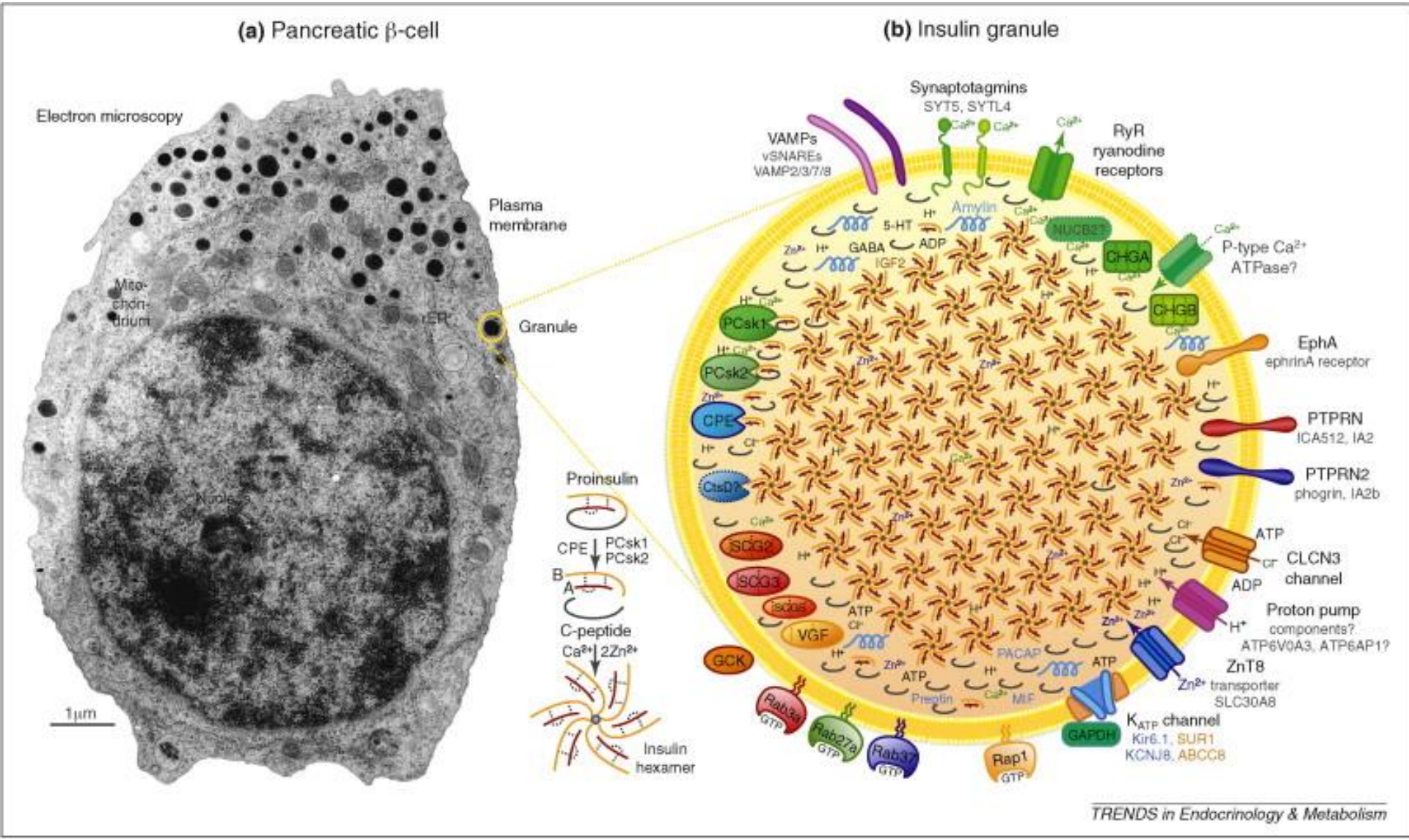
# Insulin synthesis in the body

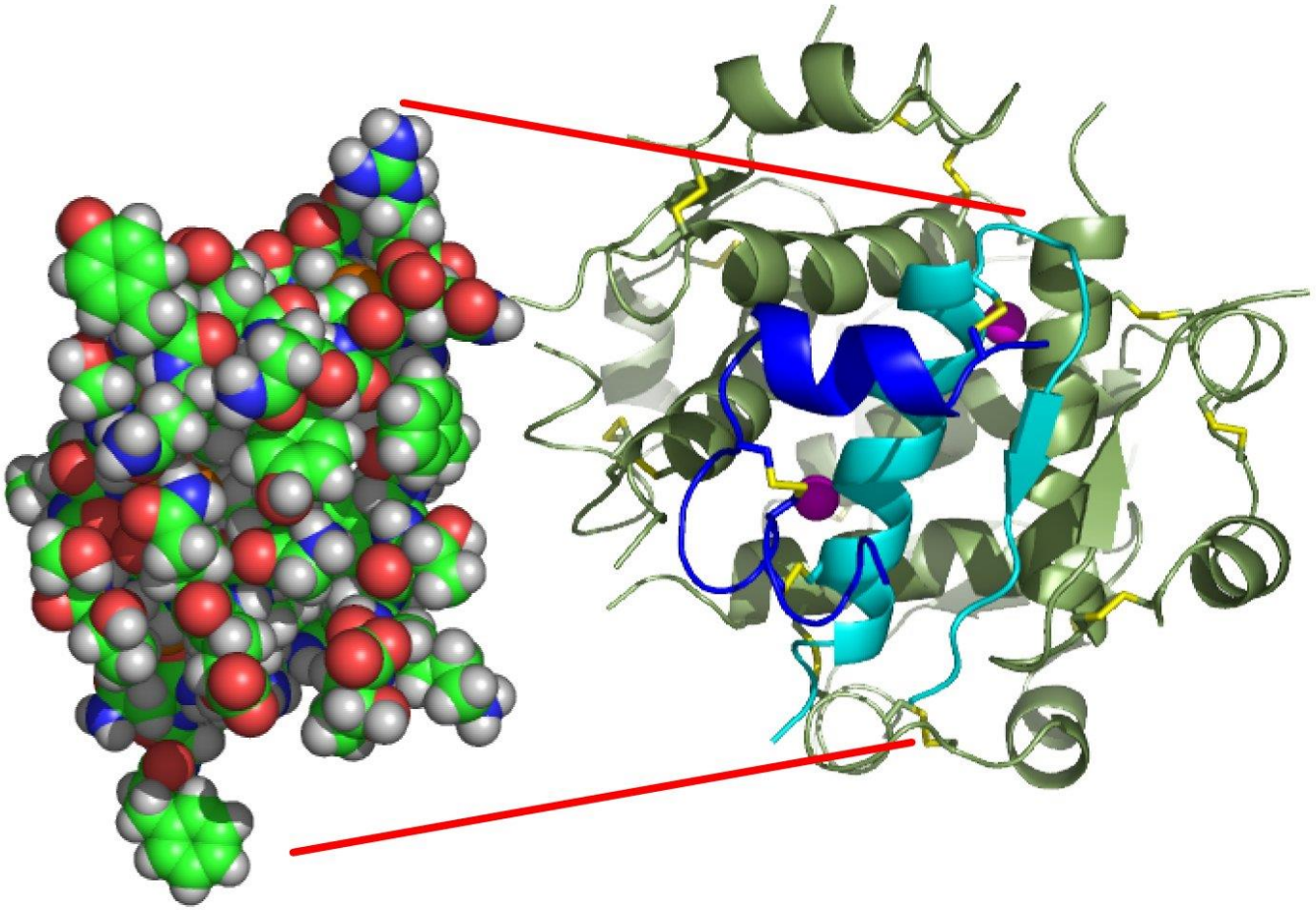
- Produced within the pancreas by β cells → islets of Langerhans
- Insulin mRNA is translated as a single chain precursor called preproinsulin
- Removal of signal peptide during insertion into the endoplasmic reticulum generates proinsulin (signal peptides are 15-30 amino acid extensions which direct the insertion of the protein into the ER membrane)
- Within the endoplasmic reticulum, proinsulin is exposed to several specific endopeptidases which excise the C peptide, thereby generating the mature form of insulin
- Stored as β granules in the pancreas (see next slide)



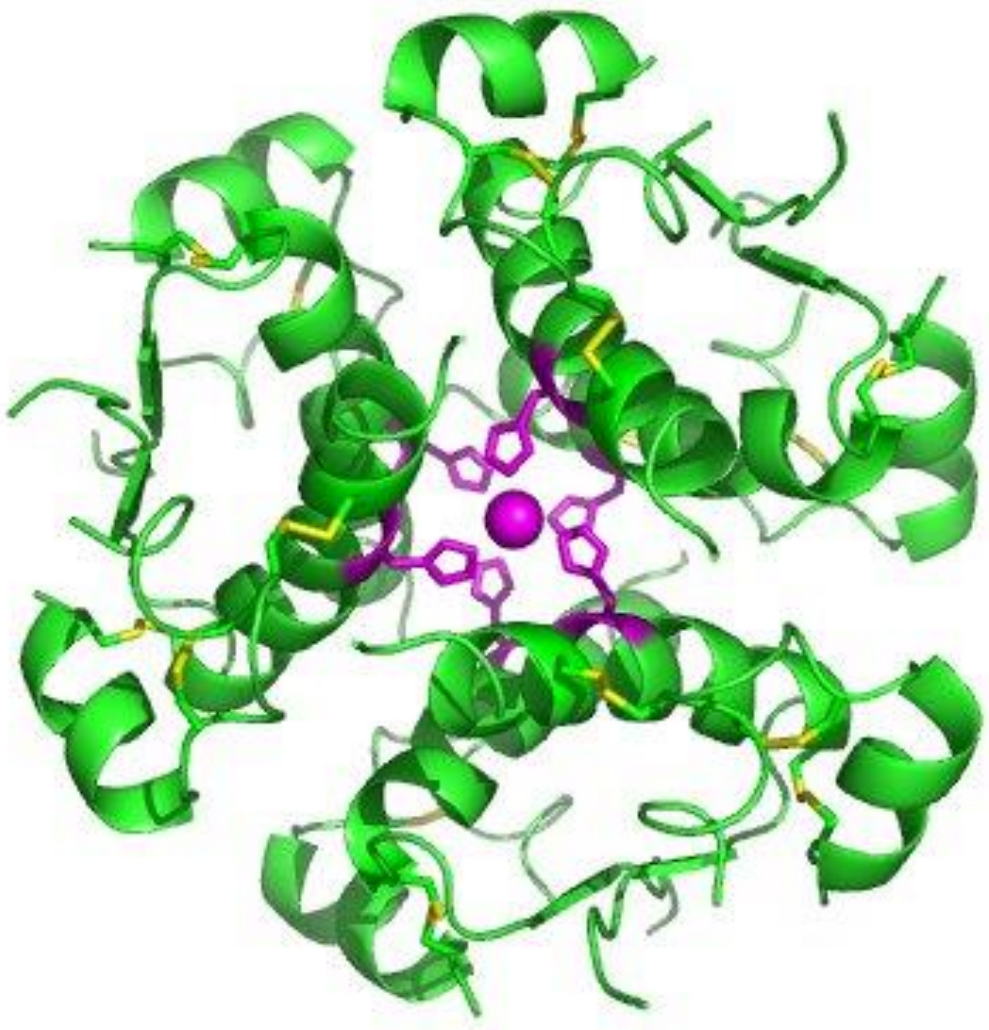



# Insulin beta granules





**The structure of insulin.** The left side is a space-filling model of the insulin monomer, believed to be biologically active. Carbon is green, hydrogen white, oxygen red, and nitrogen blue. On the right side is a ribbon diagram of the insulin hexamer, believed to be the stored form. A monomer unit is highlighted with the A chain in blue and the B chain in cyan. Yellow denotes disulfide bonds, and magenta spheres are zinc ions.



High-resolution model of six insulin molecules assembled in a hexamer, highlighting the threefold symmetry, the zinc ion holding it together (pink sphere), and the histidine residues (pink sticks) involved in zinc binding.

Inactive insulin is stored in the body as a hexamer, while the active form is the monomer

# Types of Diabetes

- Type 1 Diabetes Mellitus
- Type 2 Diabetes Mellitus
- Gestational Diabetes
- Other types:
  - LADA (
  - MODY (maturity-onset diabetes of youth)
  - Secondary Diabetes Mellitus

# Type 1 diabetes

- **Was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes.**
- **Type 1 diabetes develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin that regulates blood glucose.**
- **This form of diabetes usually strikes children and young adults, although disease onset can occur at any age.**
- **Type 1 diabetes may account for 5% to 10% of all diagnosed cases of diabetes.**
- **Risk factors for type 1 diabetes may include autoimmune, genetic, and environmental factors.**

# Type 2 diabetes

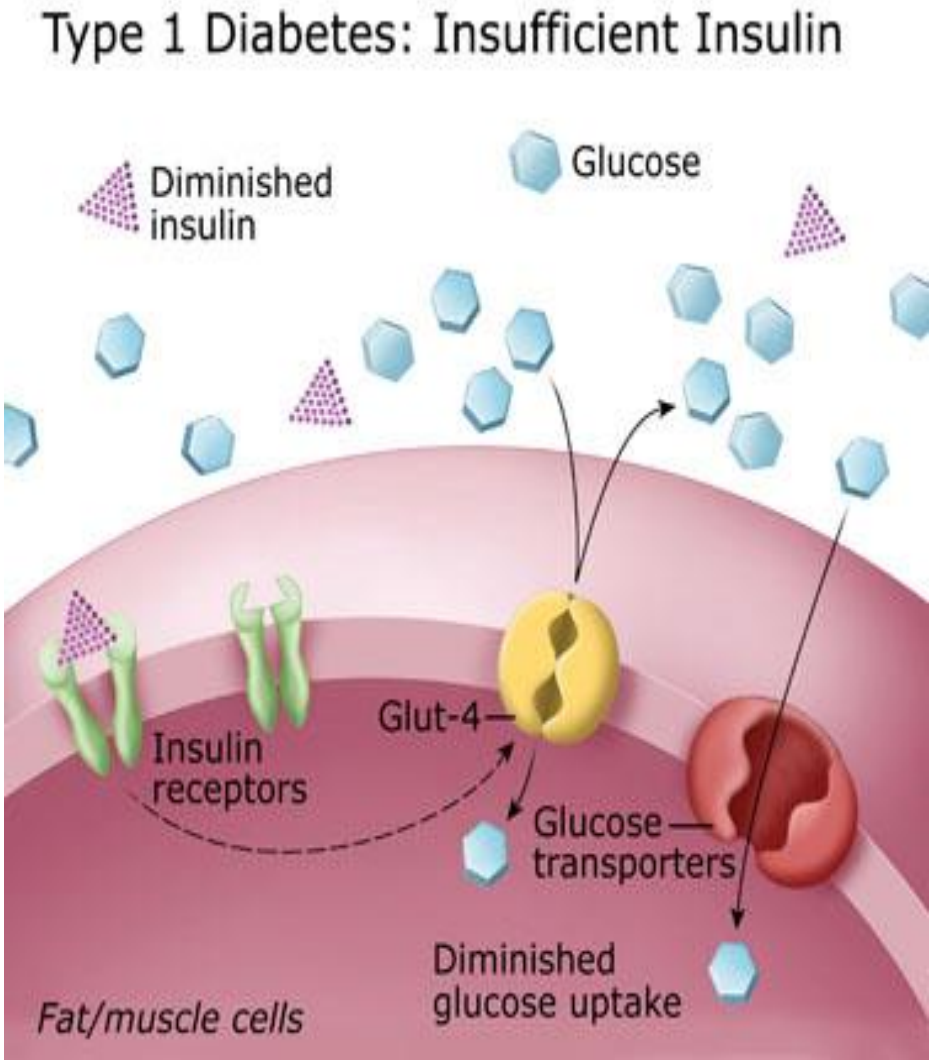
- **Was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes.**
- **Type 2 diabetes may account for about 90% to 95% of all diagnosed cases of diabetes.**
- **It usually begins as insulin resistance, a disorder in which the cells do not use insulin properly. As the need for insulin rises, the pancreas gradually loses its ability to produce insulin.**
- **Type 2 diabetes is associated with older age, obesity, family history of diabetes, history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity.**
- **African Americans, Hispanic/Latino Americans, American Indians, and some Asian Americans and Native Hawaiians or Other Pacific Islanders are at particularly high risk for type 2 diabetes.**
- **Type 2 diabetes is increasingly being diagnosed in children and adolescents.**

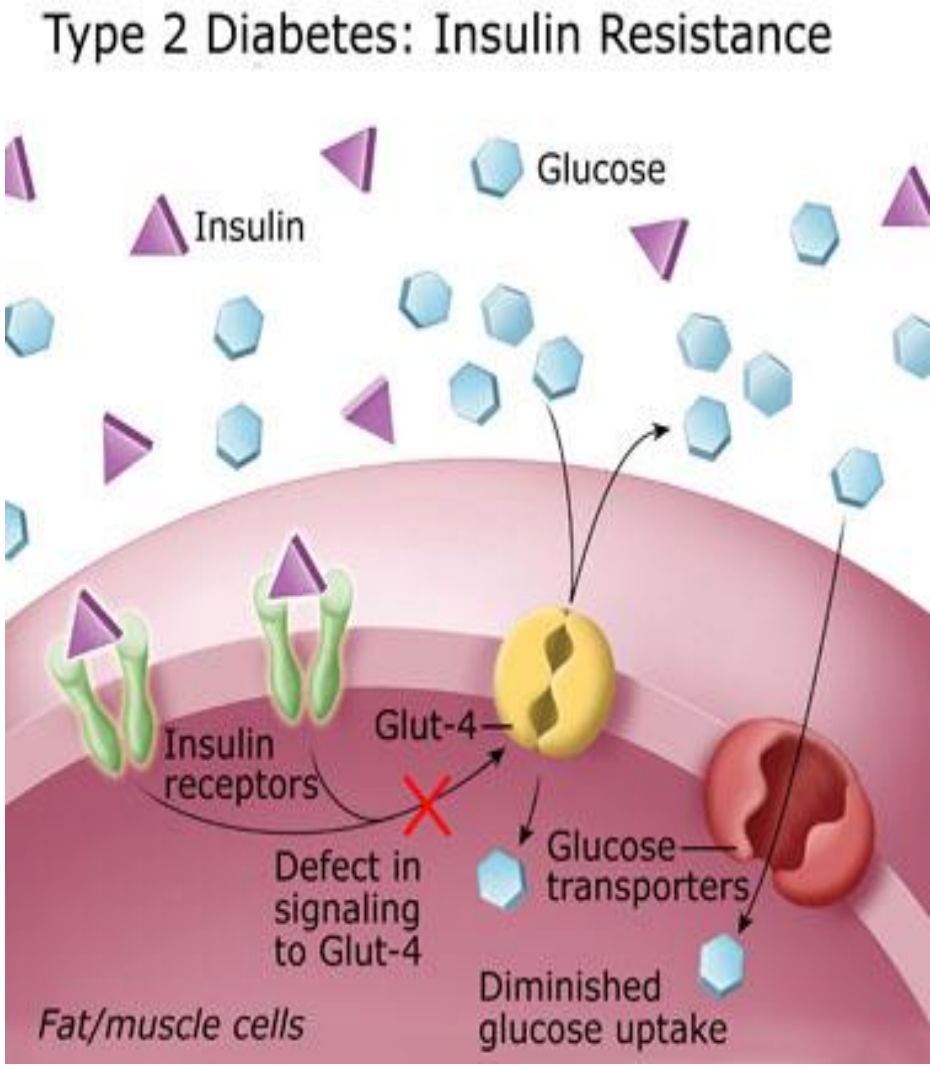
# Other types of DM

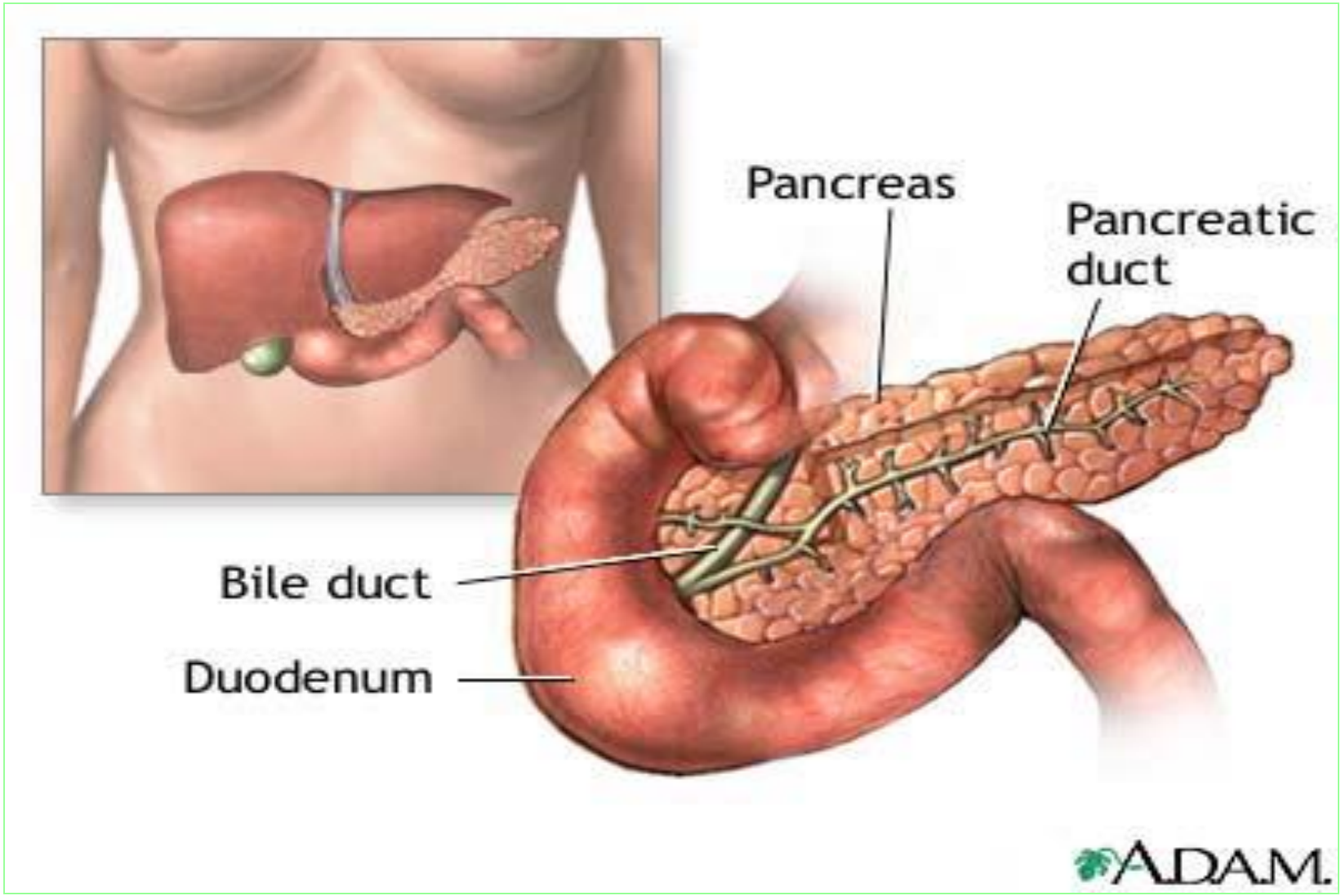
- Other specific types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, drugs, malnutrition, infections, and other illnesses.

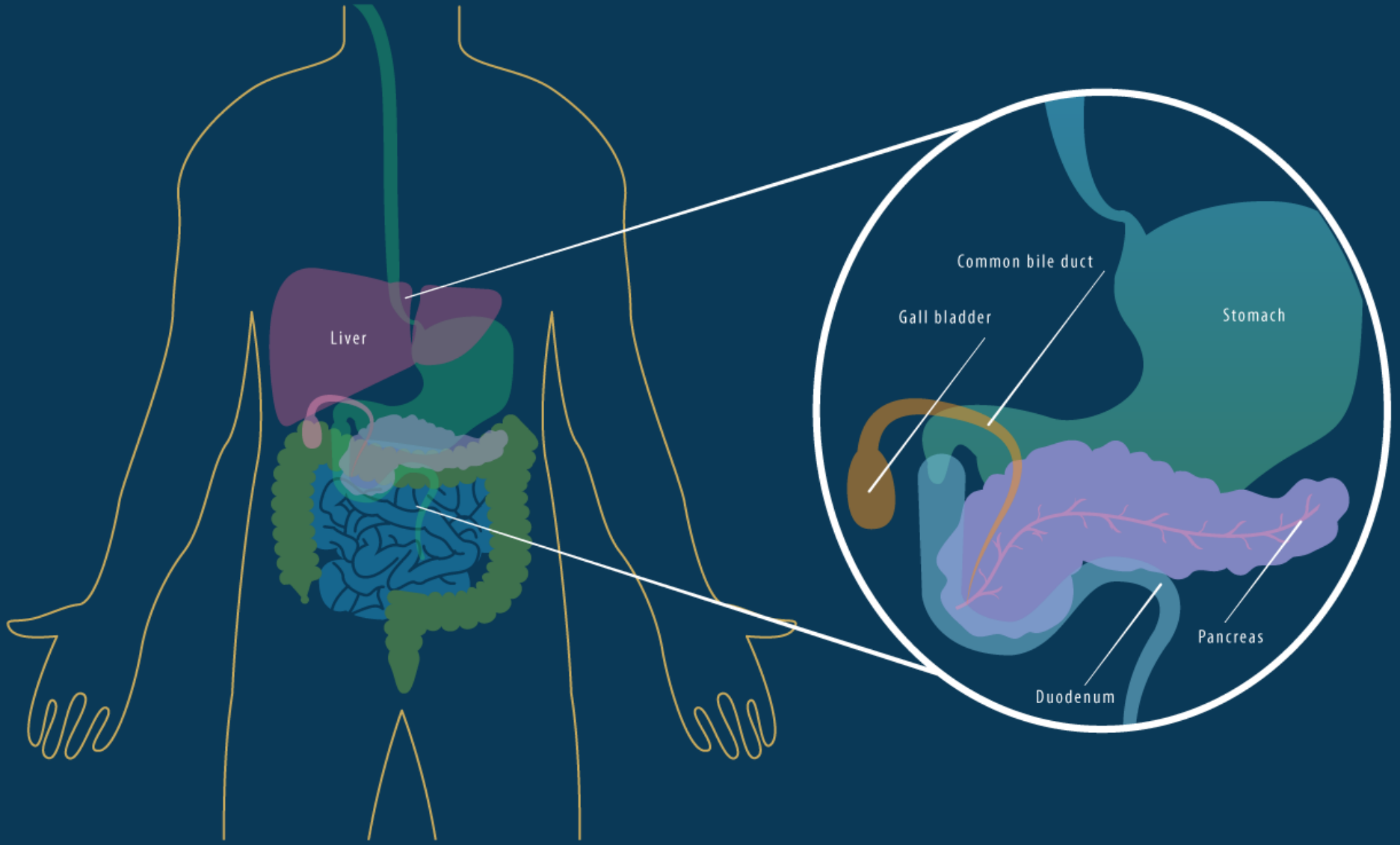
- Such types of diabetes may account for 1% to 5% of all diagnosed cases of diabetes.

# Now back to the cell transport system….




Pancreas
Pancreatic duct
Bile duct
Duodenum
A.D.A.M.

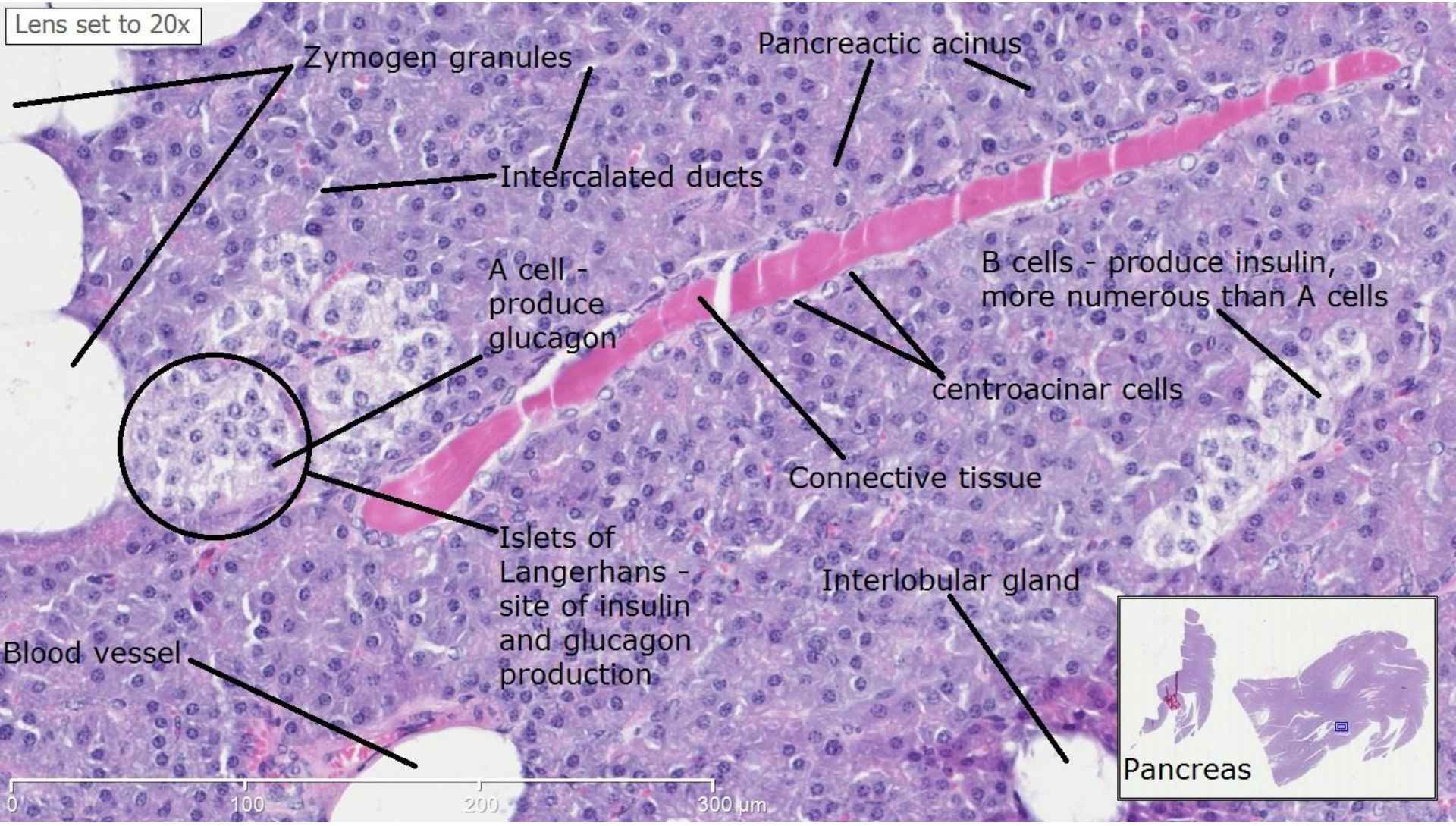


**The pancreas is an amazing chemical factory:**

The bulk of the pancreas is an exocrine gland secreting pancreatic fluid into the duodenum after a meal.

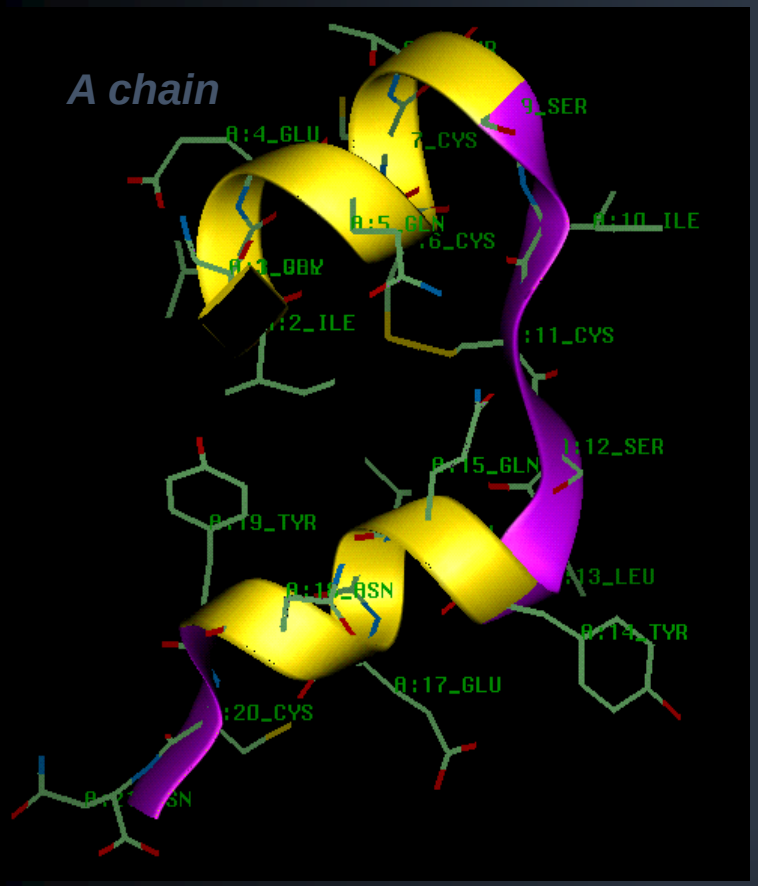
Inside the pancreas are millions of clusters of cells called islets of Langerhans. The islets are endocrine tissue containing four types of cells. In order of abundance, they are:

- Beta cells, which secrete insulin and amylin
- Alpha cells, which secrete glucagon
- Delta cells, which secrete somatostatin
- Gamma cells, which secrete a polypeptide

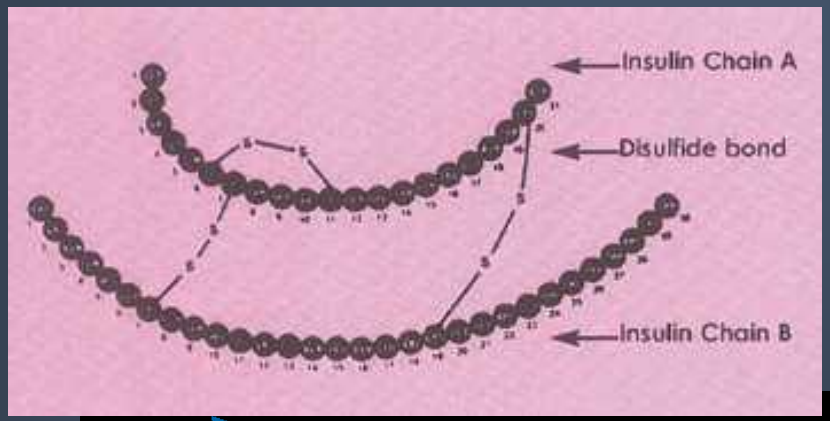

Lens set to 20x
Zymogen granules
Pancreactic acinus
Intercalated ducts
A cell - produce glucagon
B cells - produce insulin, more numerous than A cells
centroacinar cells
Connective tissue
Islets of Langerhans - site of insulin and glucagon production
Interlobular gland
Blood vessel
Pancreas
0
100
200
300 µm

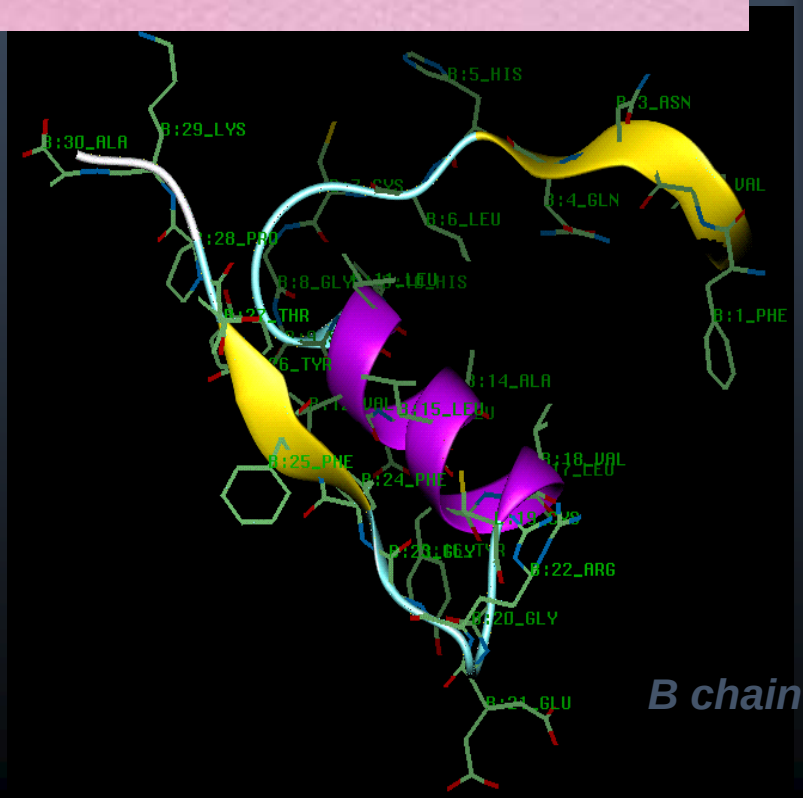
## Pancreatic Hormones

- **Insulin** – allows your cells to take up glucose
- Amylin – slows gastric emptying, thus serving to curtail the onslaught of glucose into the bloodstream
- Glucagon – raises glucose in the bloodstream (opposite of insulin)
- Somatostatin – inhibits the secretion of other hormones, including insulin
- Pancreatic Polypeptide – another metabolic regulator. Exact function still uncertain.



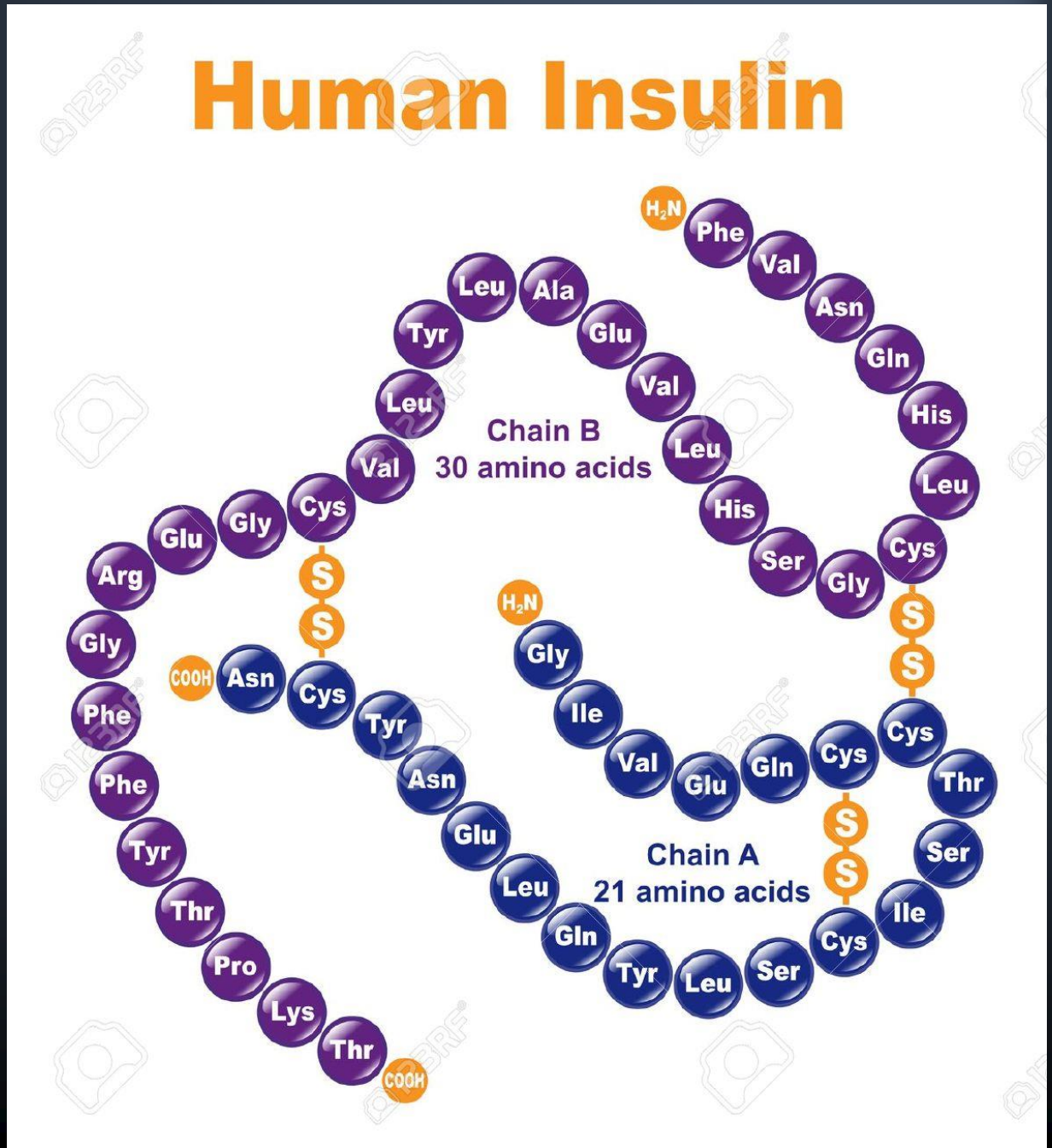

**Insulin** is a small protein consisting of an A chain of 21 amino acids linked by two disulfide (S—S) bridges to a B chain of 30 amino acids.



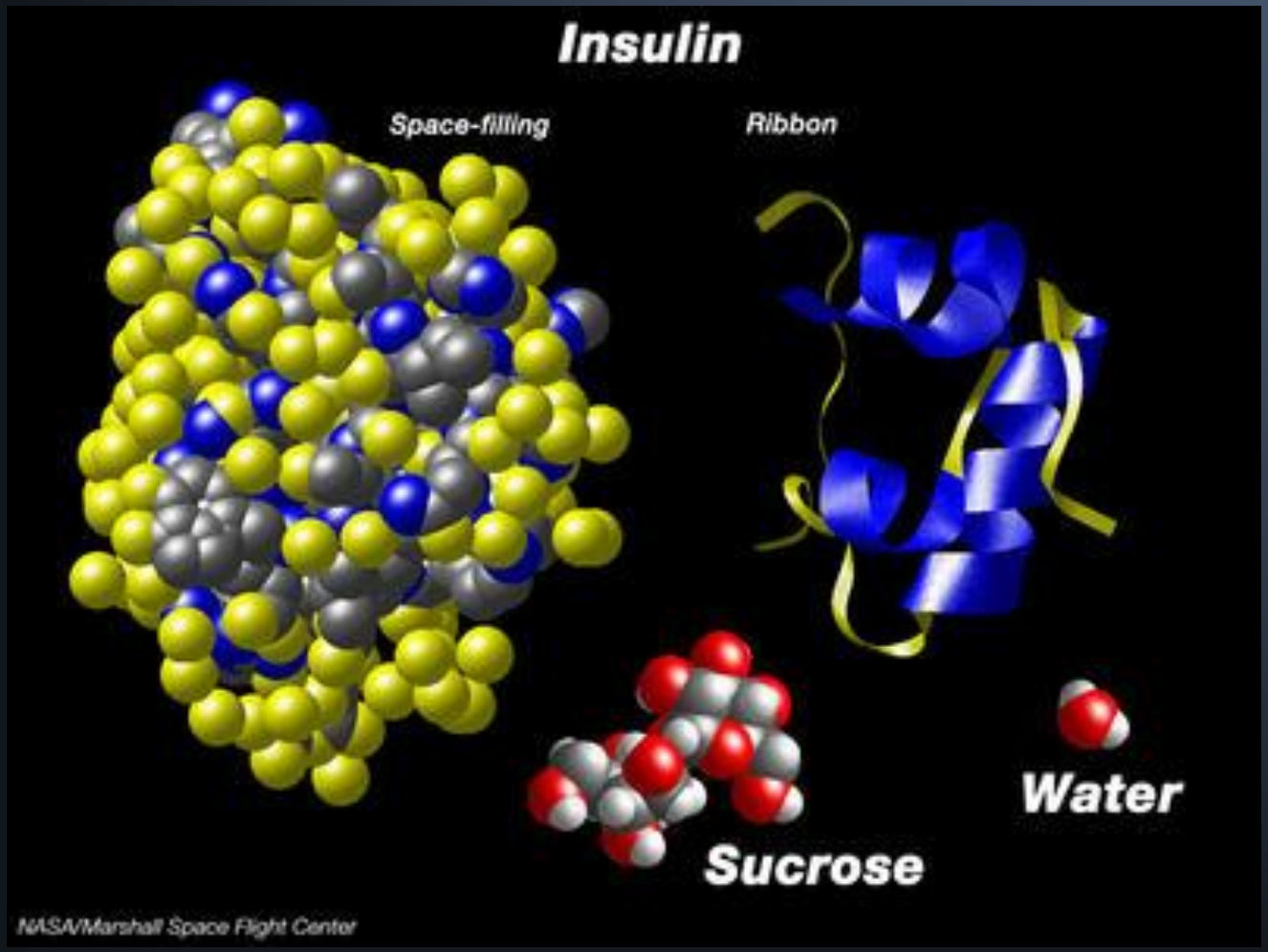




Beta cells have channels in their plasma membrane that serve as glucose detectors. Beta cells secrete insulin in response to a rising level of circulating glucose.

Another diagram of the amino acid sequence



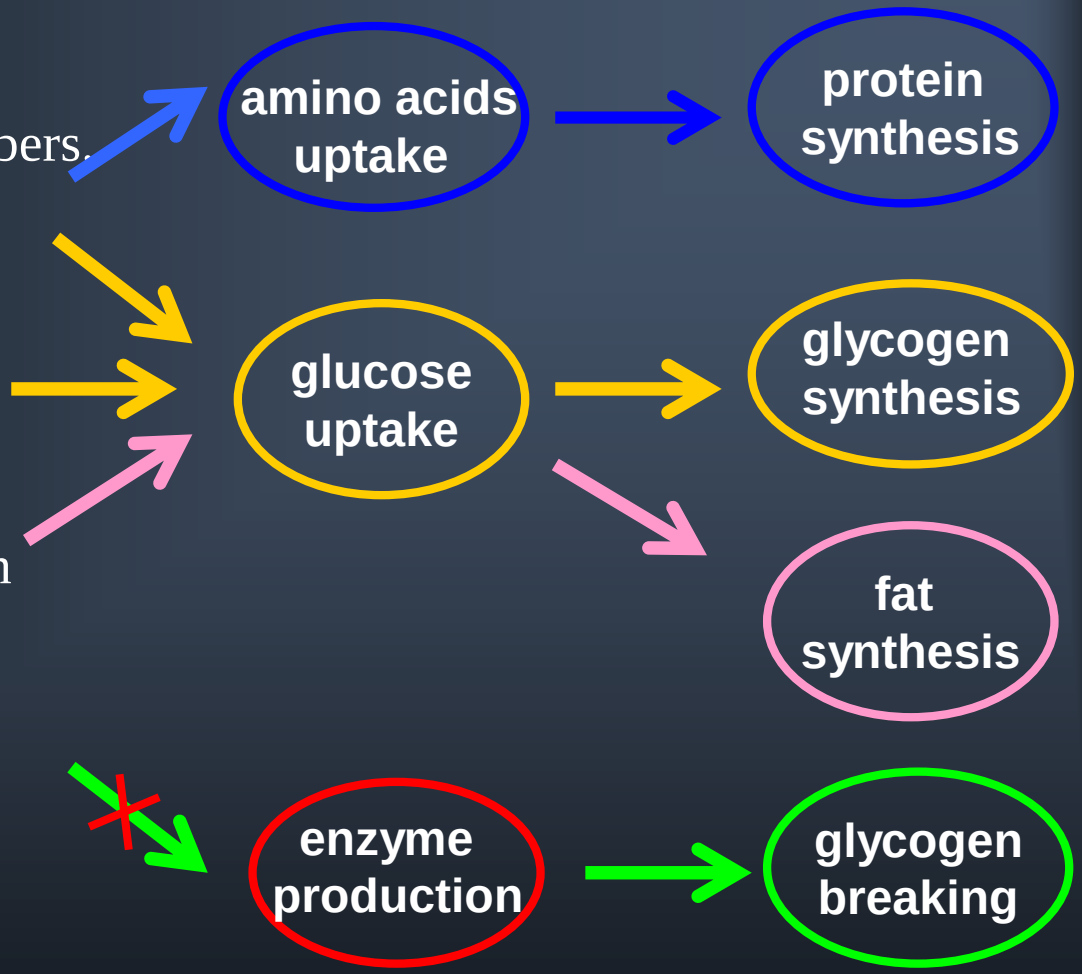
# Here's some relative sizes



**Insulin affects many organs:**

- It stimulates skeletal muscle fibers.
- It stimulates liver cells.
- It acts on fat cells
- It inhibits production of certain enzyme.

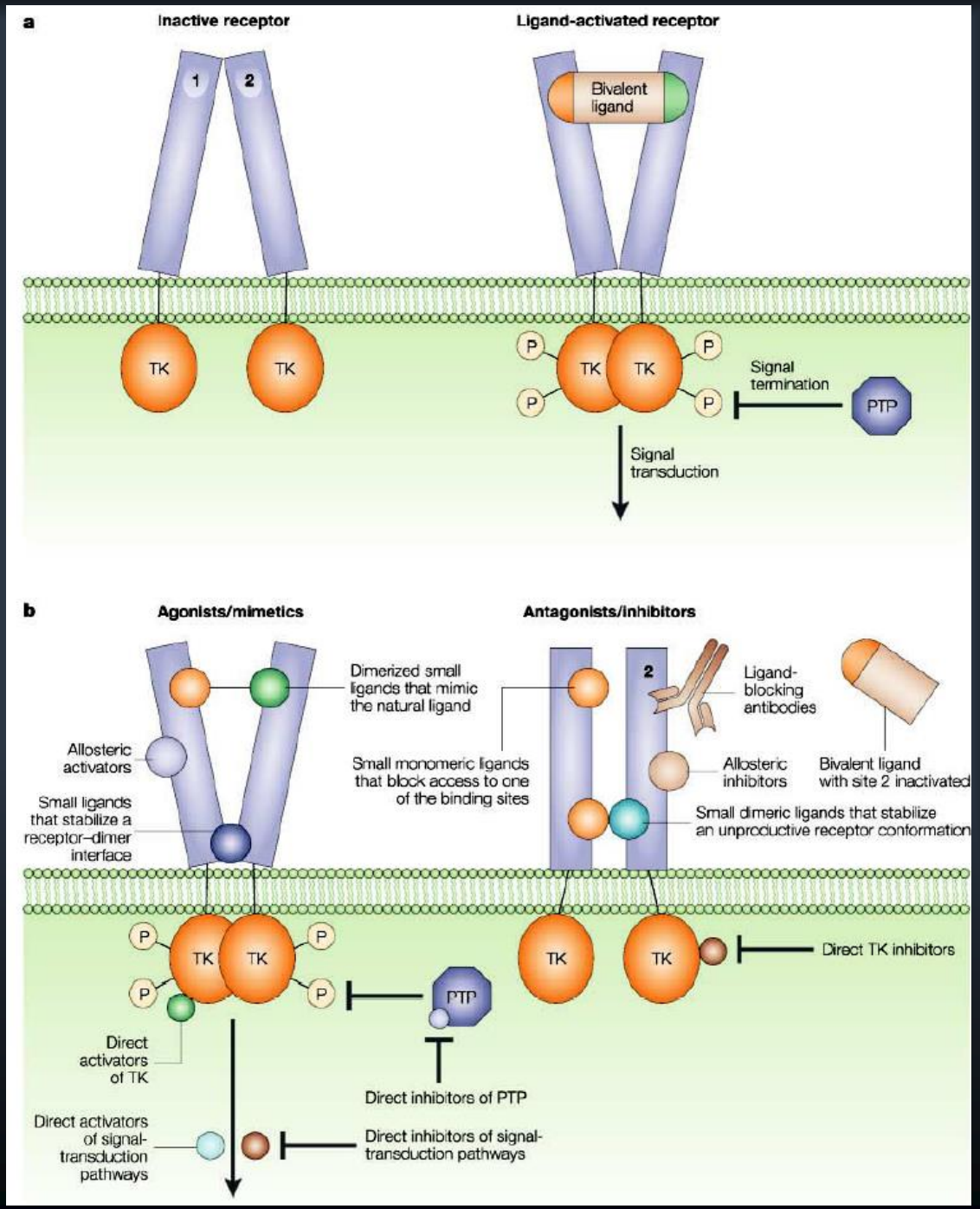
In each case, insulin triggers these effects by binding to the insulin receptor.



The insulin receptor (IR) is a transmembrane glycoprotein, composed of 2α and 2β domains.

Its intracellular tyrosine kinase domain is activated by binding of insulin, leading to a cascade of signaling events.

This is better-depicted by the following two video clips



Two video clips:

1. Insulin production
2. Insulin docking


wehi.edu.au
Insulin Production
and
Type 1 Diabetes

# Part 2
# Insulin Receptor + Type 2 Diabetes

# Insulin drug evolution

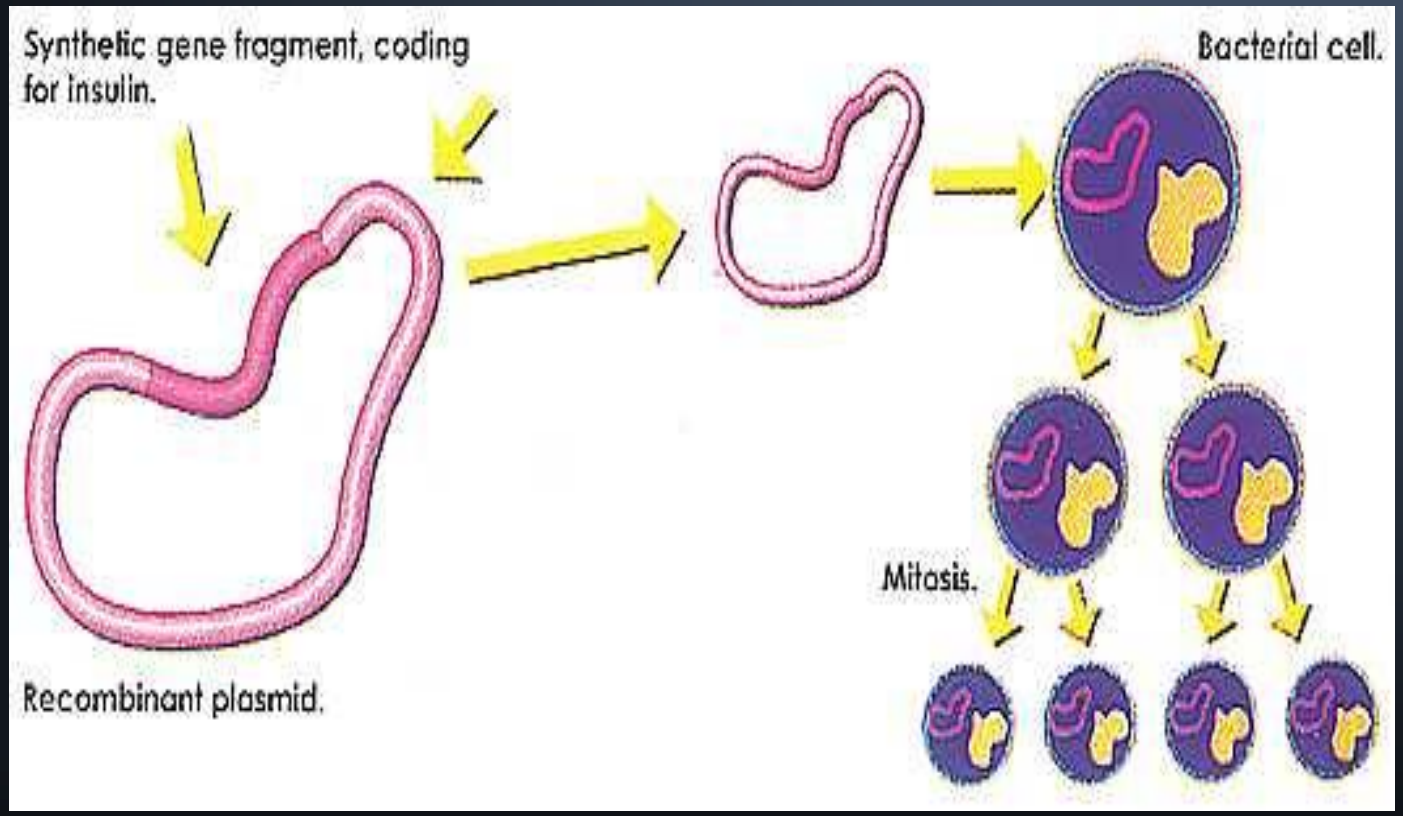
**Stage 1** Insulin was extracted from the glands of cows and pigs. (1920s)

| | Amino Acid Substitutions | | | | | | |
|---|---|---|---|---|---|---|---|
| | A-Chain Position | | | B-Chain Position | | | |
| Source/Types | A8 | A10 | A21 | B28 | B29 | B30 | B31 and B32 |
| Beef | Ala | Val | Asn | Pro | Lys | Ala | |
| Pork | Thr | Ile | Asn | Pro | Lys | Ala | |
| Human | Thr | Ile | Asn | Pro | Lys | Thr | |

**Stage 2** Convert pig insulin into human insulin by removing the one amino acid that distinguishes them and replacing it with the human version.

**Stage 3 - Recombinant DNA technology (late 1970's)**

Insert the human insulin gene into E. coli and culture the recombinant E.coli to produce insulin (trade name = Humulin®). Yeast is also used to produce insulin under trade name = Novolin® 1987.



# Management of Diabetes Mellitus

# Nutritional Management for Type I Diabetes

- Consistency and timing of meals
- Timing of insulin
- Monitor blood glucose regularly

# Nutritional Management for Type II Diabetes

- Weight loss
- Smaller meals and snacks
- Physical activity
- Monitor blood glucose and medications

# Nutrition Recommendations

- Carbohydrate
  - 60-70% calories from carbohydrates and mono-unsaturated fats
- Protein
  - 10-20% total calories

# Nutrition Recommendations

- Fat
  - <10% calories from saturated fat
  - 10% calories from PUFA
  - <300 mg cholesterol
- Fiber
  - 20-35 grams/day
- Alcohol
  - Type I – limit to 2 drinks/day, with meals
  - Type II – substitute for fat calories

# Diabetic Exchange Lists

Refer to the Diabetes exchange lists meal planning guide