https://www.medanta.org/patient-education-blog/types-of-insulin-for-diabetes-treatment

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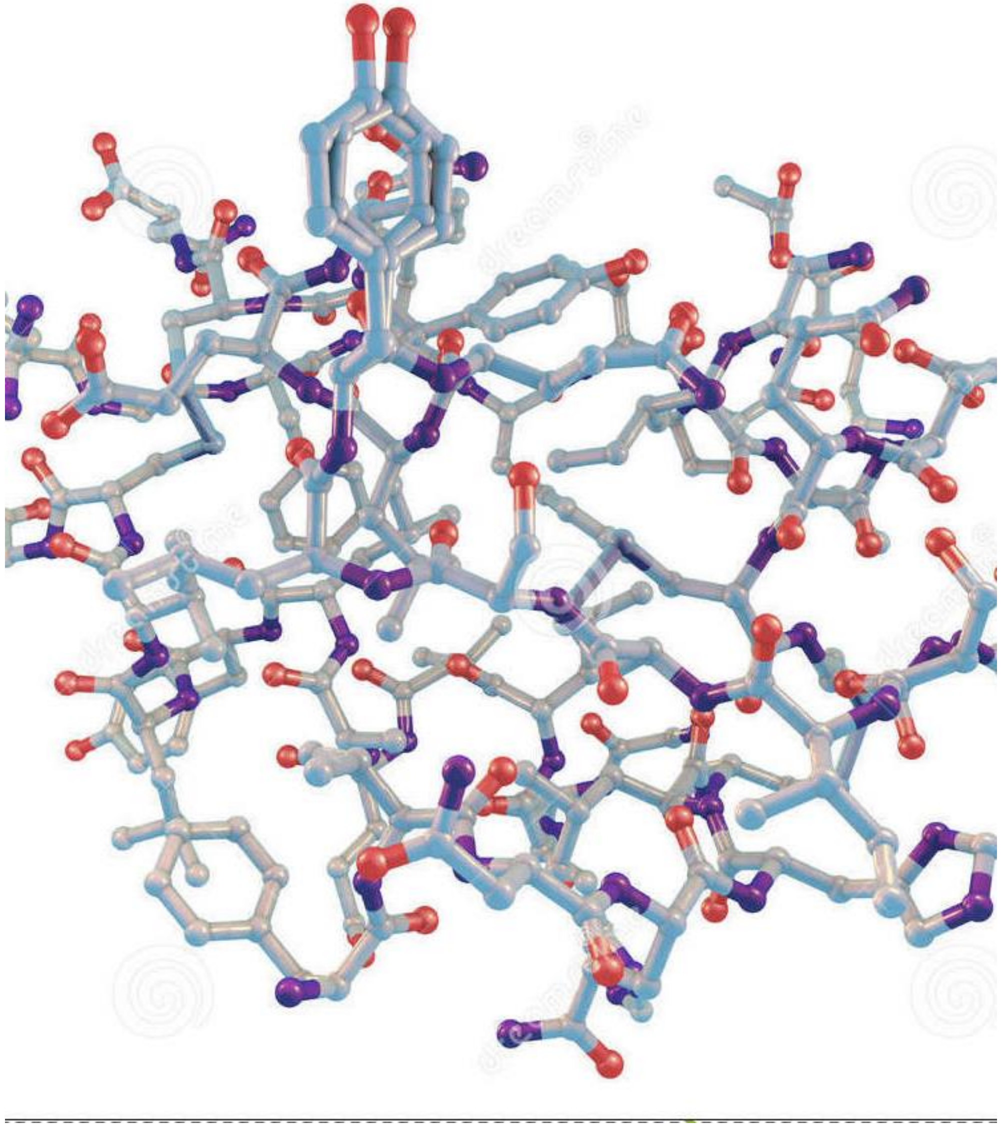
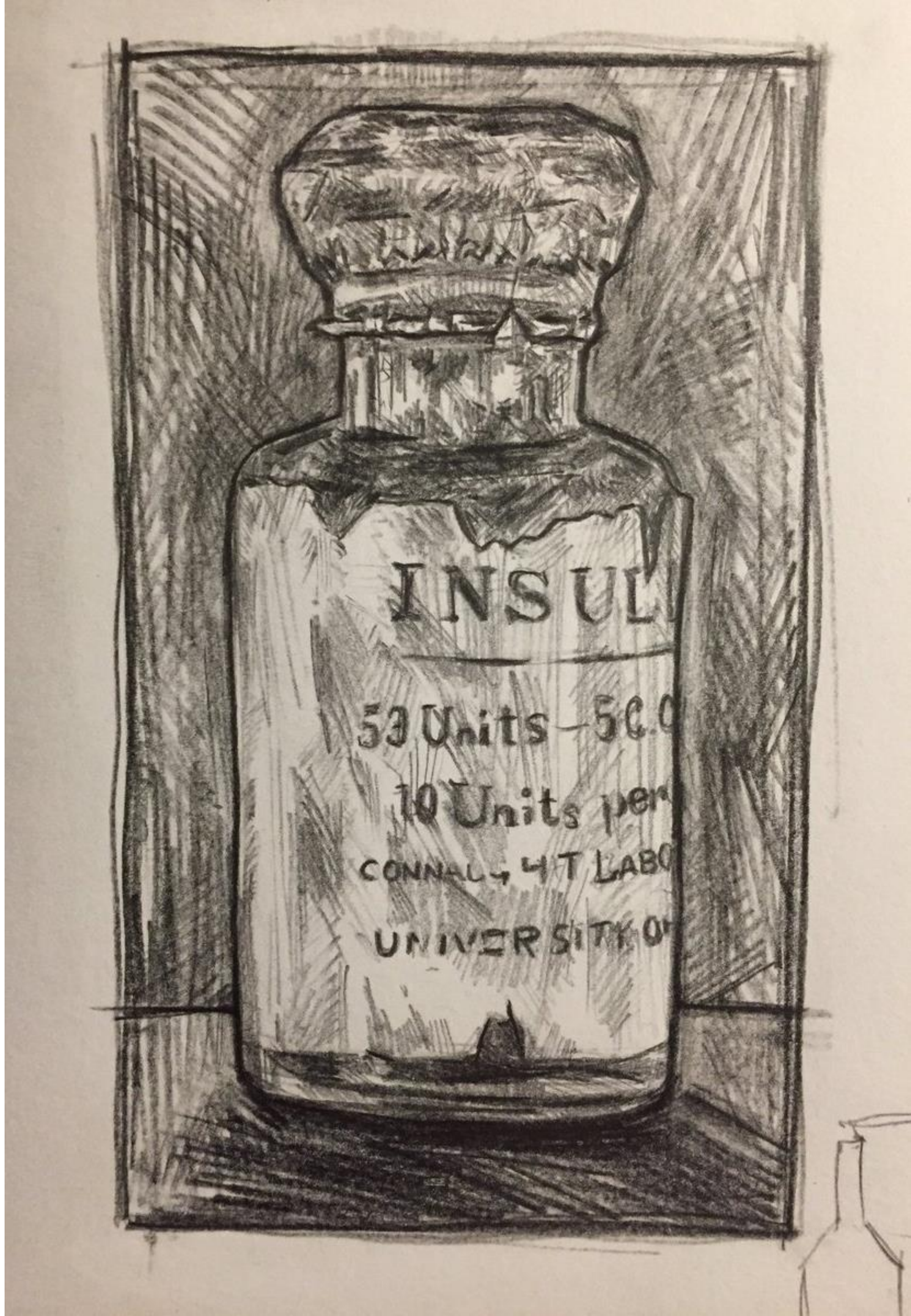
images: https://www.diabetes.org/
https://www.canadianinsulin.com/articles/insulin-discovery
https://www.diabetes.co.uk/insulin/history-of-insulin.html



INSULIN

Insulin is a hormone produced by the pancreas that has a number of important functions in the human body, particularly in the control of blood glucose levels and preventing hyperglycemia. It also has an effect on several other areas of the body, including the synthesis of lipids and regulation of enzymatic activity.

HISTORY



1869

- Paul Langerhans, a medical student in Berli, discovers a distinct collection of cells within the pancreas. These cells would later be called the Islets of Langerhans.

Oskar Minkowski (left) Joseph von Menring (right)

1889

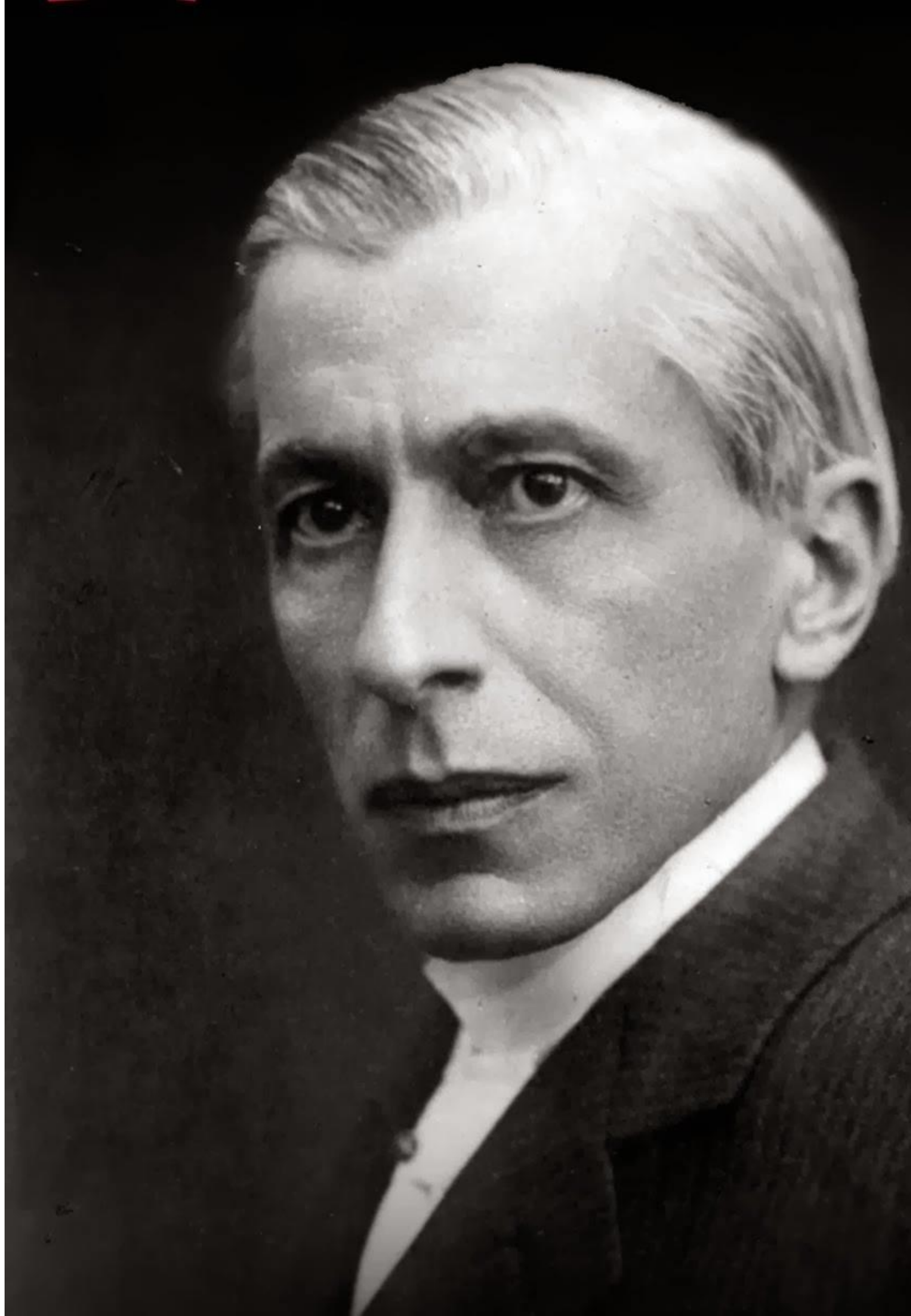
- Oscar Minkowski and Joseph von Mering remove a dog's pancreas to study the effects on digestion. Flies are found to be feeding off the dog's urine, which is shown to contain sugar.

1901

- Eugene Opie discovers that the Islets of Langerhans produce insulin and that the destruction of these cells resulted in diabetes.

1916

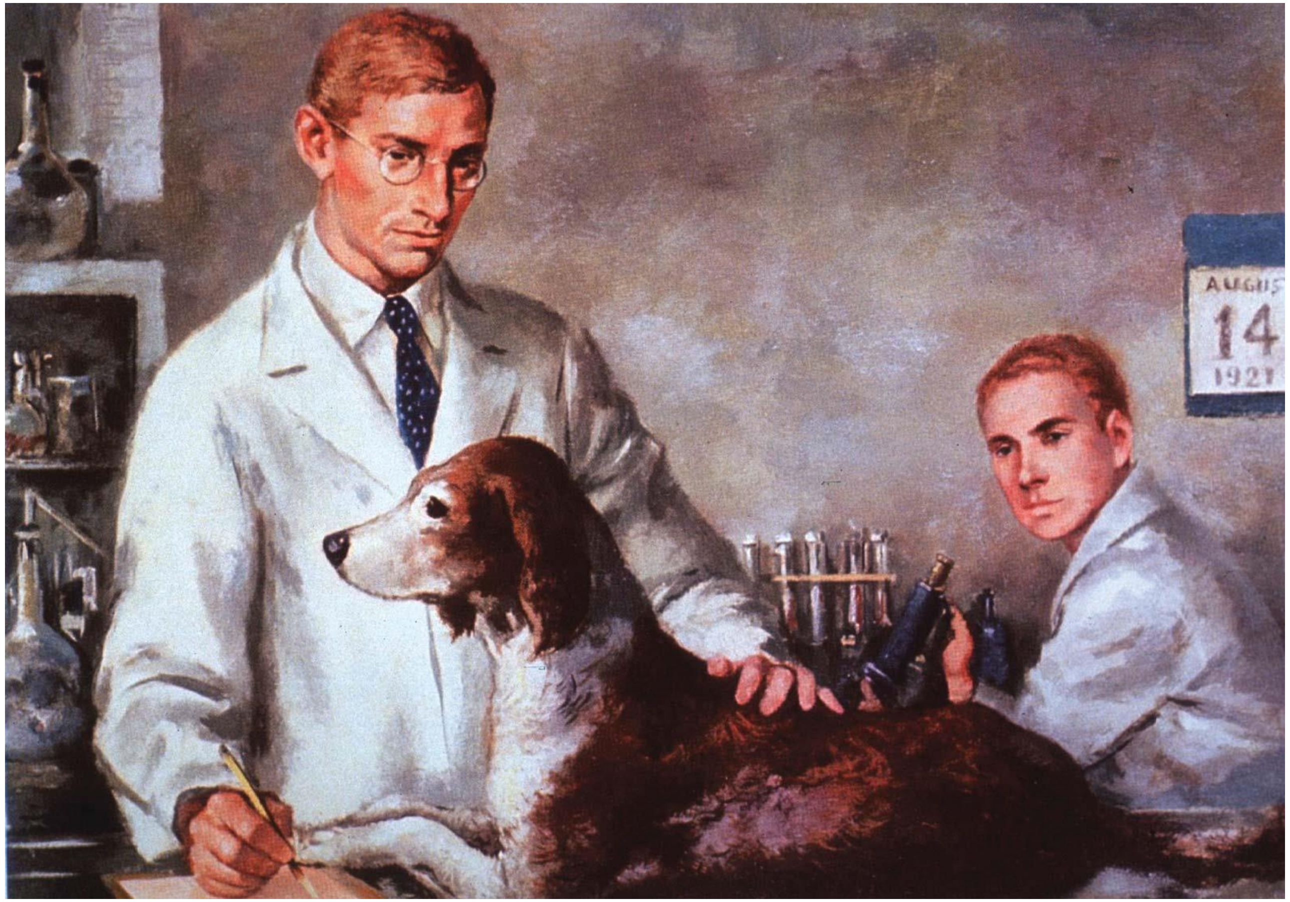
- Romanian professor Nicolae Paulescu develops an extract of the pancreas and shows that it lowers blood sugar in diabetic dogs. World War I prevents the experiments from continuing and it is not until 1921 that Paulescu publishes evidence of the experiments.



1921

- Dr Frederick Banting and medical student Charles Best perform experiments on the pancreases of dogs in Toronto, Canada.

- Professor John James Rickard Macleod provides Banting and Best with a laboratory to carry out the experiments.
- John James Rickard Macleod was a Scottish physiologist



- When the pancreases are removed the dogs showed symptoms of diabetes. The pancreas was then sliced and ground up into an injectable extract. This is injected a few times a day which helped the dogs to regain health.
- Given the early success, Macleod wants to see more evidence that the procedure worked and provides pancreases from cows to make the extract which is named ‘insulin’.

1922

- A 14-year-old boy with type 1 diabetes called Leonard Thompson is given the first medical administration of insulin. A second dose purified by James B. Collip is successful. Leonard lives for another 13 years.
- Previously patients with **Type 1 Diabetes** would be put onto starvation diets and would have only months to live. Leonard lives another 13 years before succumbing to pneumonia.

1922

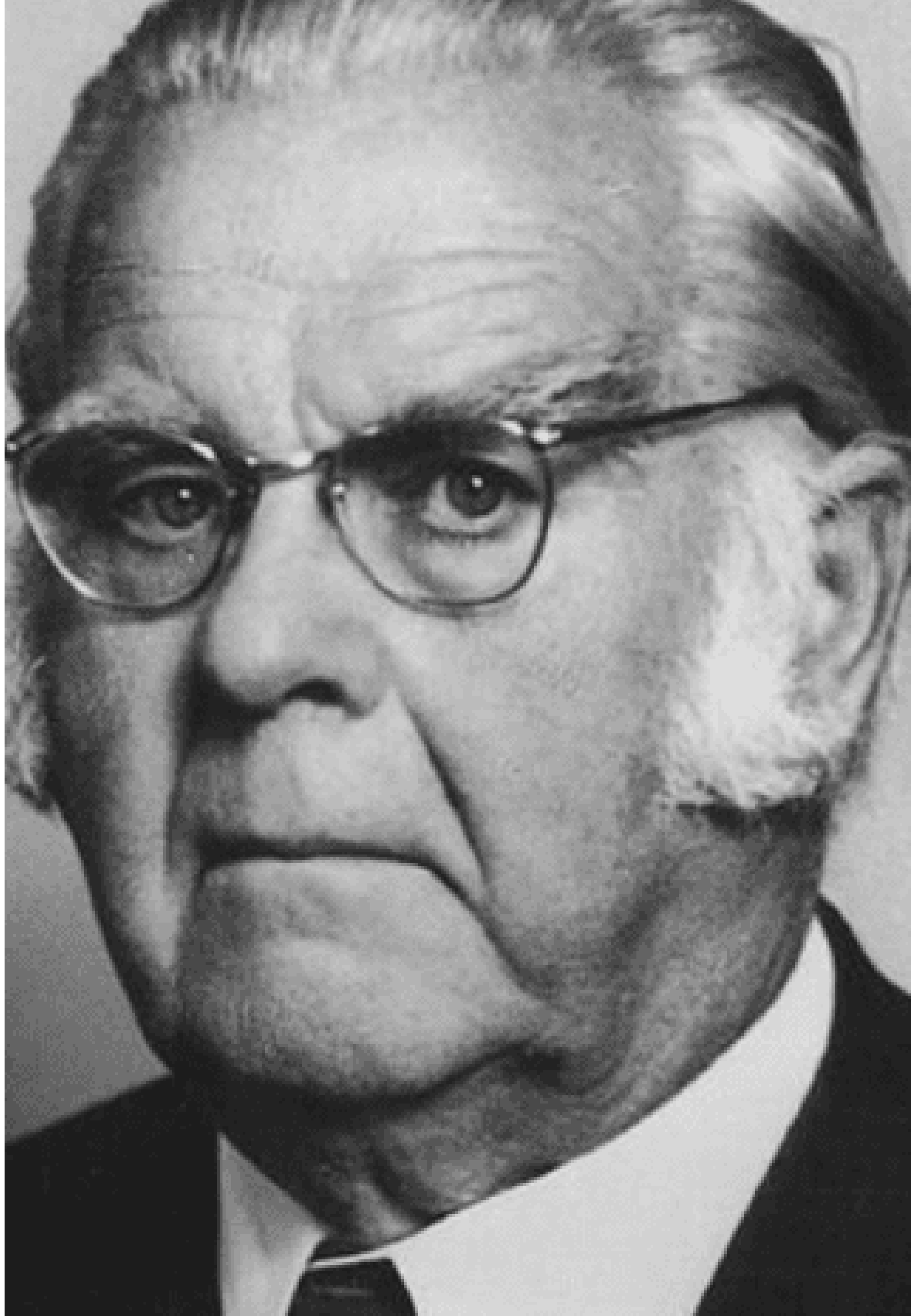
- As news of insulin’s success spread, Banting and Best begin receiving letters asking for help for others with type 1 diabetes. Banting and Best improve their techniques for the production of insulin and **Elli Lilly** becomes the first insulin manufacturer.

1923

- Banting and Macleod are awarded the Nobel Prize in Physiology or Medicine. Banting and Macleod, however, feel Best and Collip were equally eligible and shared their prize money with their two colleagues

1936

Danish physician Hans Christian Hagedorn discovers the action of insulin can be prolonged with the addition of protamine

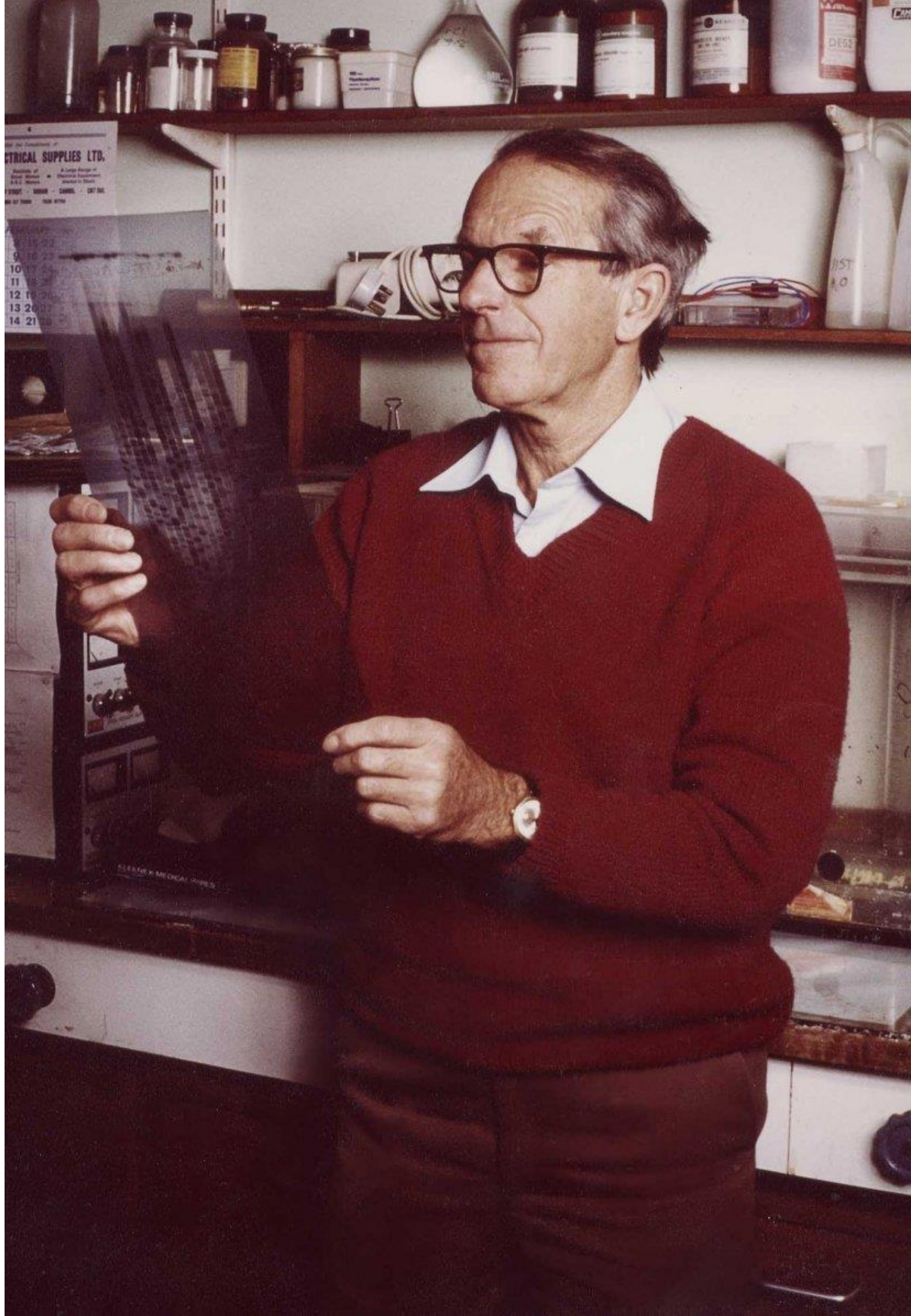


1950

NPH, an **intermediate acting insulin**,
is marketed by Danish pharmaceutical company Novo Nordisk.

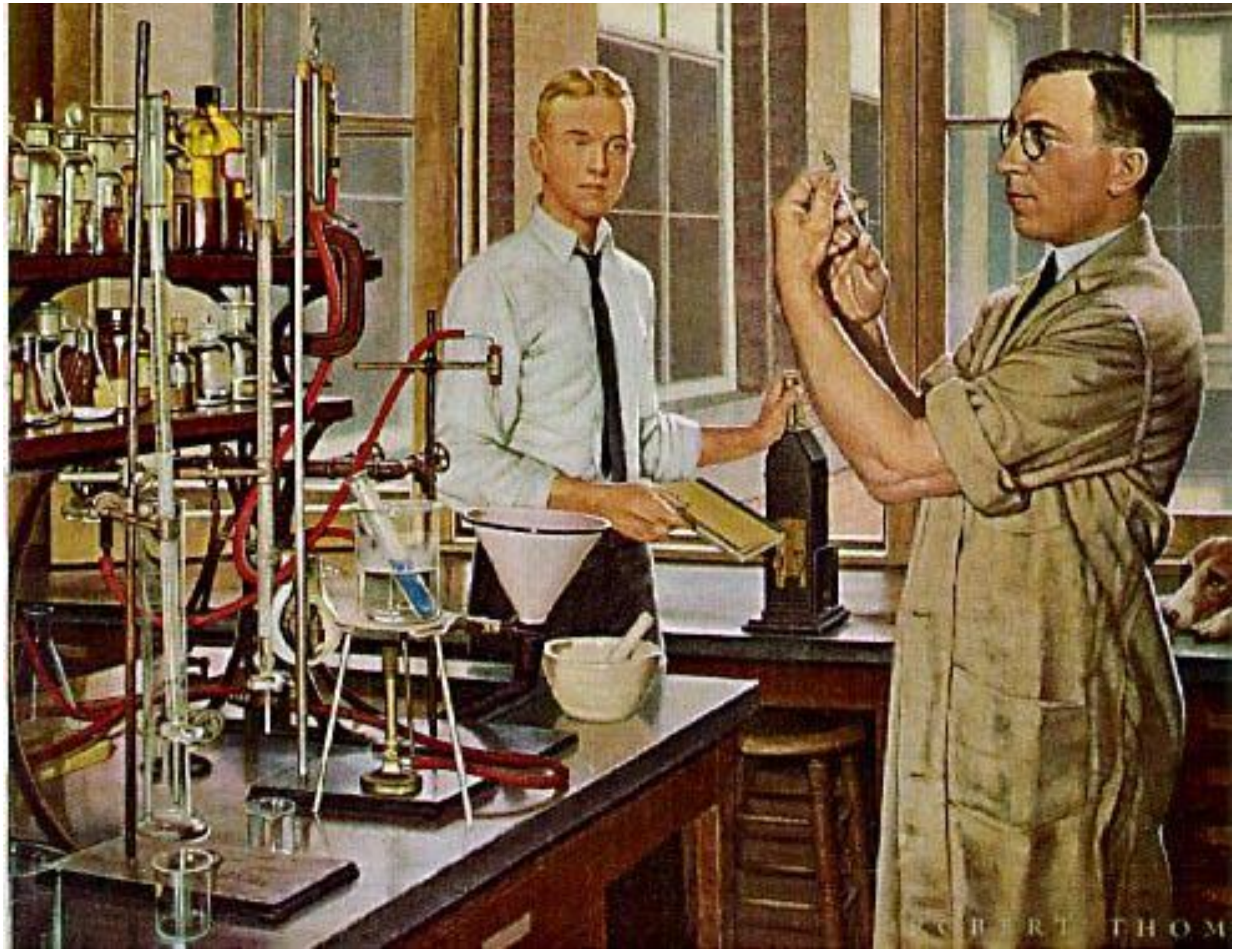
1955

- Insulin is sequenced by British biochemist Frederick Sanger, and is the first protein to be fully sequenced.
- In 1958 Sanger receives the Nobel Prize in Chemistry for his research.



1963

Insulin becomes the first human protein to be chemically synthesized.



1978

- Biotechnology firm Genentech uses recombinant DNA techniques to produce synthetic “human” insulin. Insulin is the first human protein by to be manufactured through biotechnology.

1982

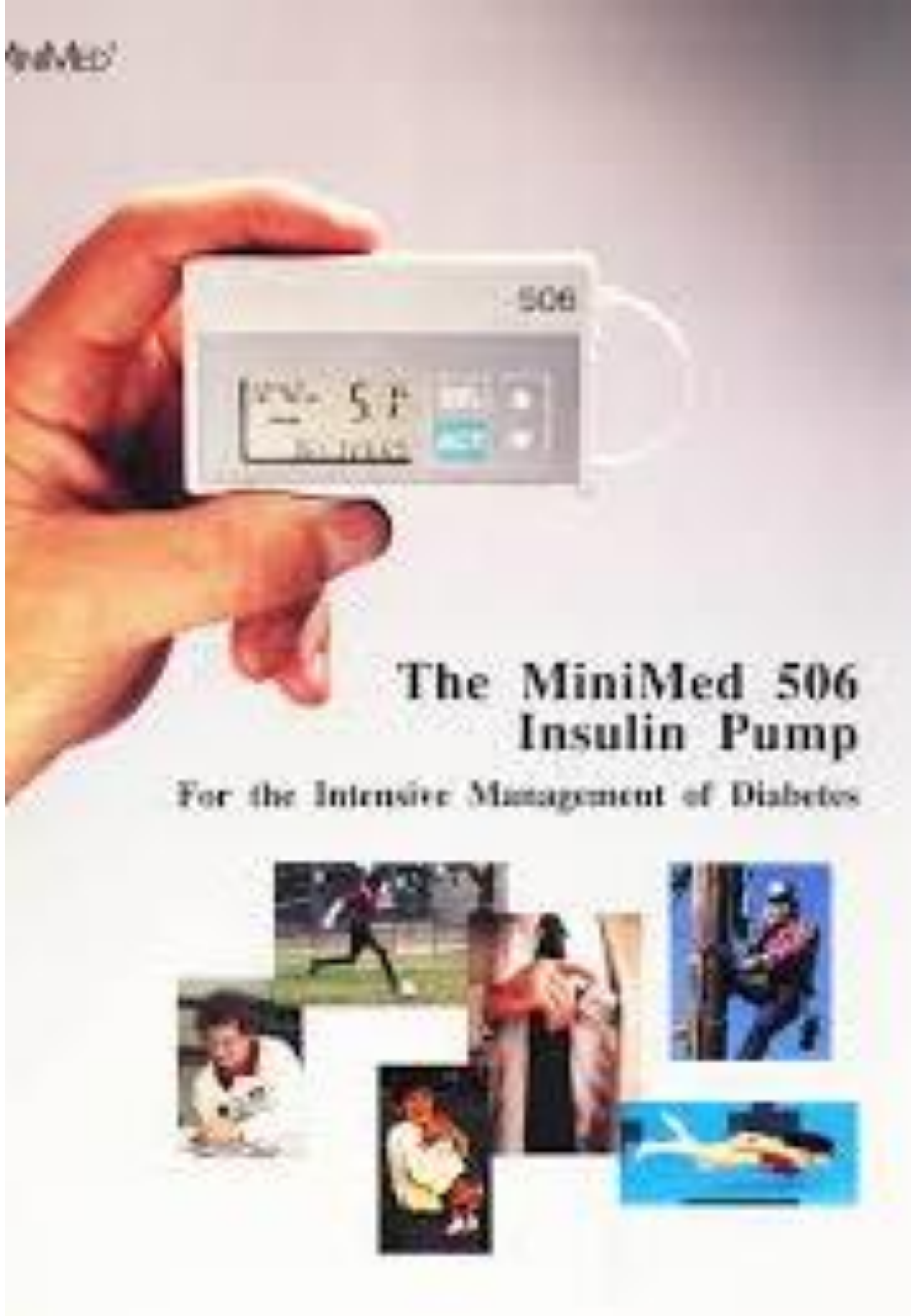
- Synthetic insulin is renamed 'human insulin' marking it as distinct from **insulin derivate from animals**. Human insulin has the advantage of being less likely to allergic reactions than animal insulin. Humuli, manufactured by Eli Lilly, becomes widely available through the 1980s.

1985

Novo Nordisk introduces the Insulin Pen delivery system.

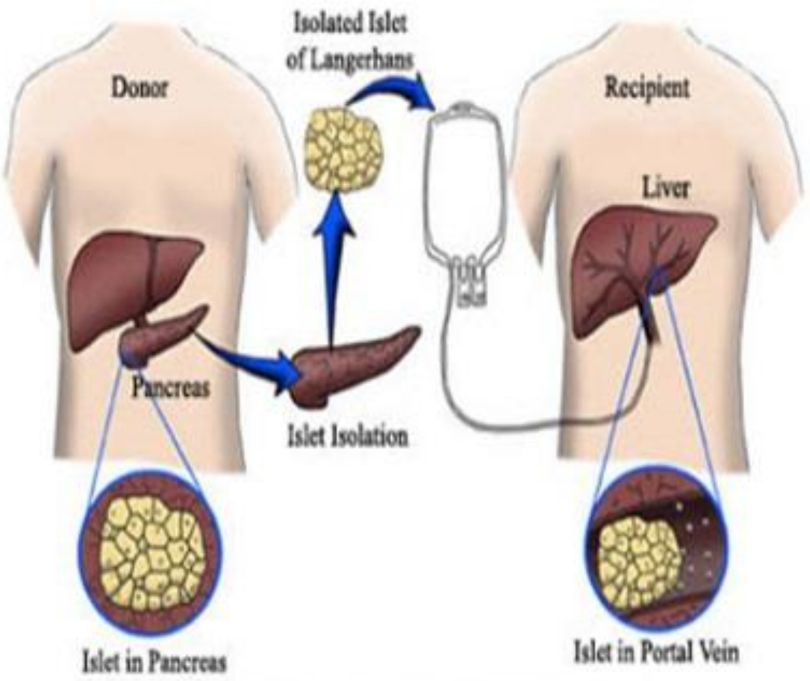
1992

- Medtronic releases the MiniMed 506 insulin pump, which delivers meal bolus memory and daily insulin totals.



1996

- Eli Lilly markets the analogue insulin lispro under the trade name Humalog. Analogue insulin is a genetically modified form of insulin whereby the amino acid sequence is altered to change how the insulin is absorbed, distributed, metabolised and excreted



Courtesy of the University of Alberta

2000

- More than 470 patients with type 1 diabetes receive islet cell transplantation during the next five years. The procedures help diabetes patients become free from insulin providing they take immunosuppressant drugs.

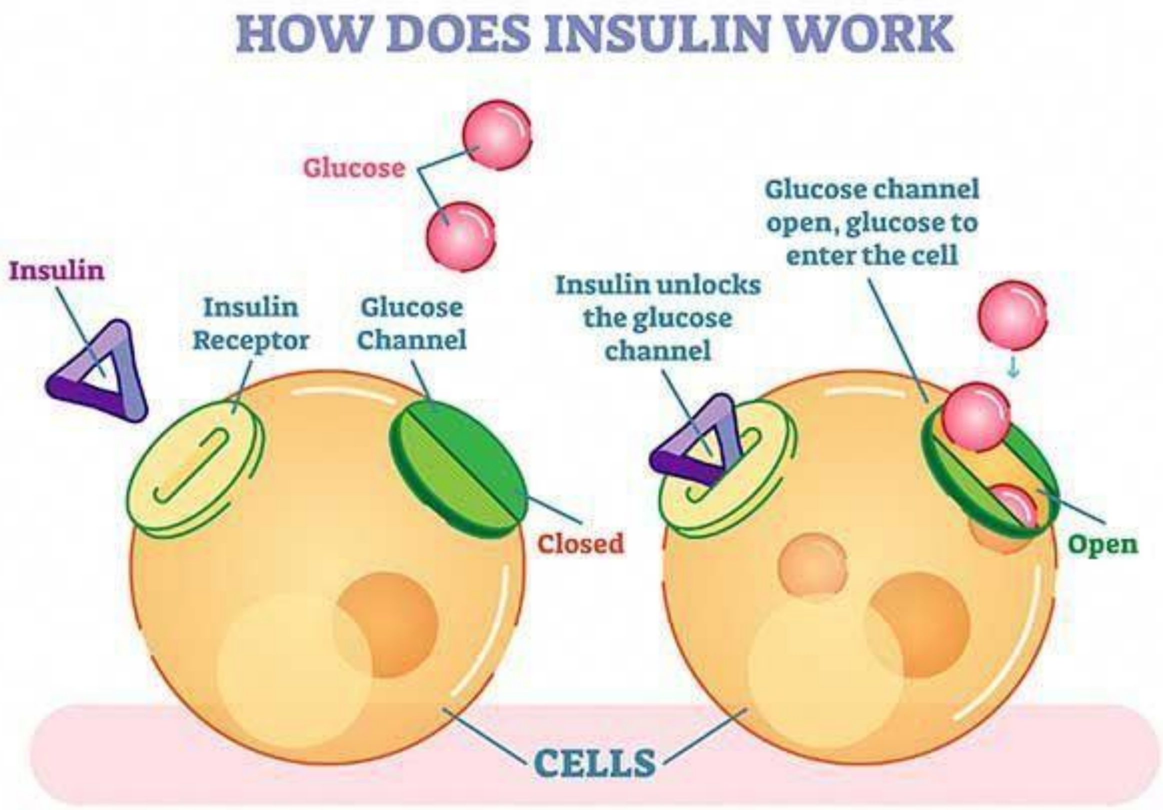
2013

- The University of Cambridge develops an artificial pancreas that pairs the technology of an insulin pump with a continuous glucose monitor

2015

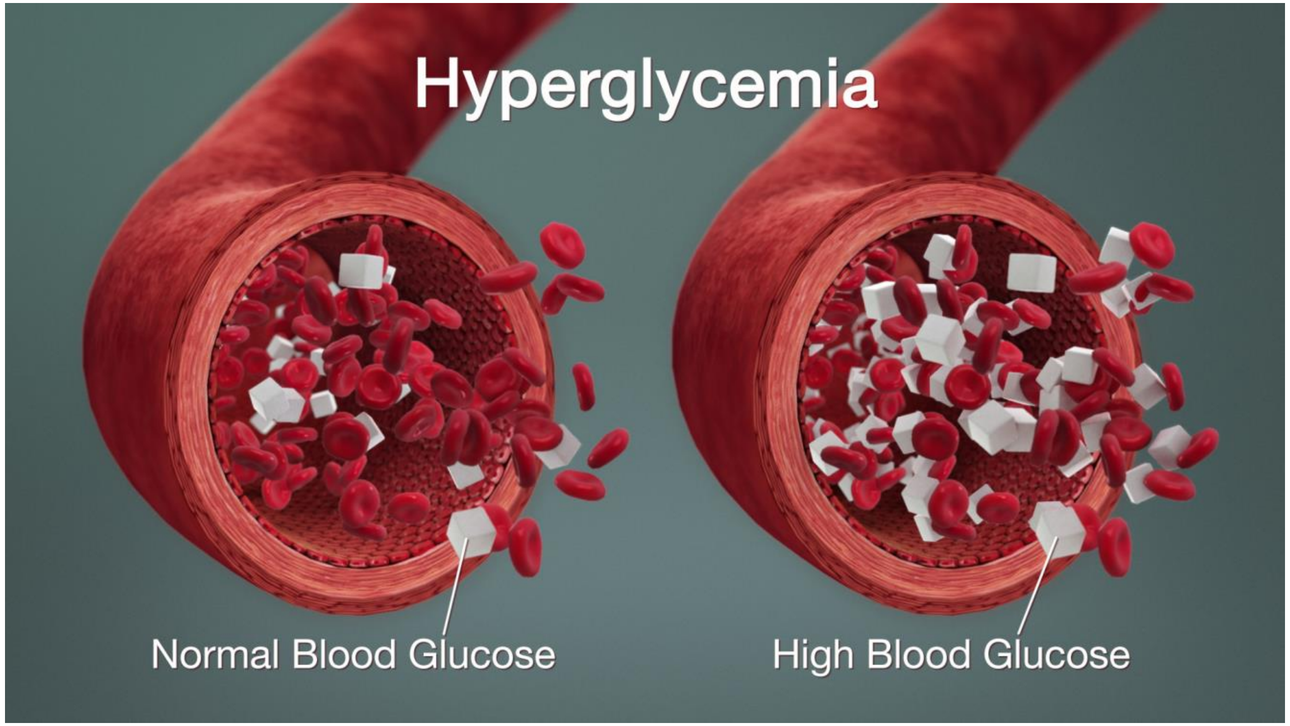
- Dr Edward Damiano introduces the iLet, which he calls "a bridge to a cure". The device is a bionic pancreas that delivers both insulin and glucagon every five minutes as required

HOW DOES IT WORK?



INSULIN AND METABOLIC PROCESSES

The most important role of insulin in the human body is its interaction with glucose to allow the cells of the body to use glucose as energy. The pancreas usually produces more insulin in response to a spike in blood sugar level, for example after eating a meal high in energy. This is because the insulin acts as a “key” to open up the cells in the body and allows the glucose to be used as an energy source.

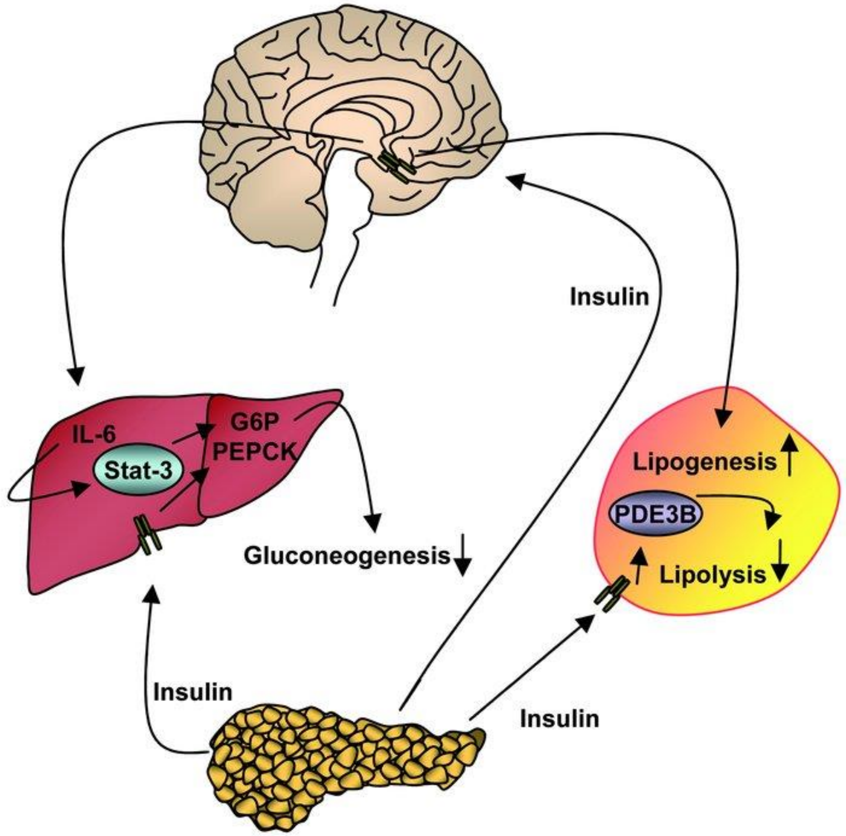


INSULIN AND METABOLIC PROCESSES

Additionally, when there is excess glucose in the bloodstream, known as hyperglycemia, insulin encourages the storage of glucose as glycogen in the liver, muscle and fat cells. These stores can then be used at a later date when energy requirements are higher. As a result of this, there is less insulin in the bloodstream, and normal blood glucose levels are restored.

INSULIN AND METABOLIC PROCESSES

- Insulin stimulates the synthesis of glycogen in the liver, but when the liver is saturated with glycogen, an alternative pathway takes over. This involves the uptake of additional glucose into adipose tissue, leading to the synthesis of lipoproteins.

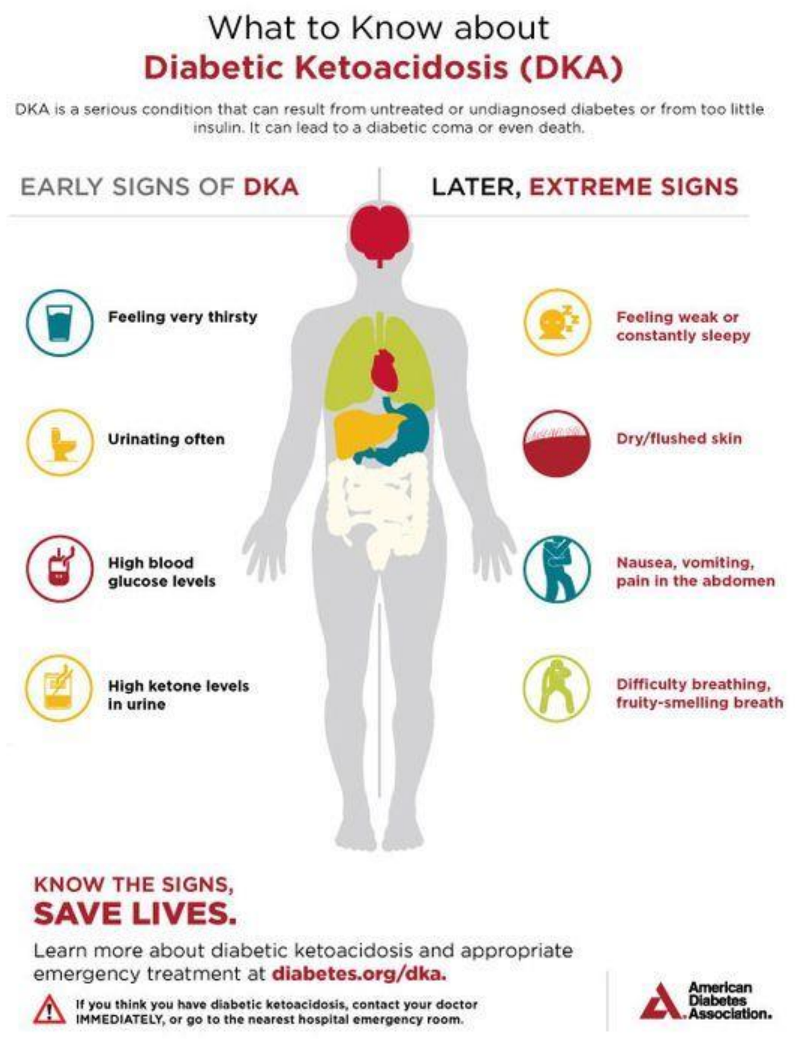


RESULTS WITHOUT INSULIN

- In the absence of insulin, the body is not able to utilize the glucose as energy in the cells. As a result, the glucose remains in the bloodstream and can lead to high blood sugar, known as **hyperglycemia**. Chronic hyperglycemia is characteristic of diabetes mellitus and, if untreated, is associated with severe complications, such as damage to the nervous system, eyes, kidneys and extremities.

RESULTS WITHOUT INSULIN

- In severe cases, lack of insulin and reduced ability to use glucose as a source of energy can lead to a reliance of fat stores as the sole source of energy. The breakdown of these fats can release ketones into the bloodstream, which can lead to a serious condition called ketoacidosis.



OTHER FUNCTIONS OF INSULIN

In addition to the regulation of glucose, insulin also plays a role in other areas of the body. It may be involved in all of the following functions to:

- **Modify the activity of enzymes** and the resulting reactions in the body.
- **Build muscle following sickness or injury** via the transportation of amino acids to the muscle tissue, which is required to repair muscular damage and increase size and strength. It helps to regulate the uptake of amino acids, DNA replication and the synthesis of proteins.
- **Manage synthesis of lipids** by uptake into fat cells, which are converted to triglycerides.
- **Manage breakdown or protein and lipids** due to changes in fat cells.
- **Uptake of amino acids and potassium** into the cells that cannot take place in the absence of insulin.
- **Manage excretion of sodium** and fluid volume in the urine.
- **Enhance learning and memory** of the brain functions.

TYPES OF INSULIN

- Human Insulin and Insulin Analogs are available for insulin replacement therapy. Insulins also are classified by the timing of their action in the body – specifically, how **quickly** they start to act, when they have a **maximal** effect and how **long** they act.
- Insulin analogs have been developed because human insulins have limitations when injected under the skin. In high concentrations, such as in a vial or cartridge, human (and also animal insulin) clumps together.
- This clumping causes **slow and unpredictable** absorption from the subcutaneous tissue and a dose-dependent duration of action (i.e. the larger dose, the longer the effect or duration). In contrast, **insulin analogs** have a more predictable duration of action. The rapid acting insulin analogs work more quickly, and the long acting insulin analogs last longer and have a more even, "peakless" effect.

CHARACTERISTICS OF INSULIN

- **Insulins are categorized by differences in:**
- Onset (how quickly they act)
- Peak (how long it takes to achieve maximum impact)
- Duration (how long they last before they wear off)
- Concentration (Insulins sold in the U.S. have a concentration of 100 units per ml or U100. In other countries, additional concentrations are available. Note: If you purchase insulin abroad, be sure it is U100.)
- Route of delivery (whether they are injected under the skin or given intravenously)

TYPES OF INSULIN

There are ***three*** *main groups of insulins:* ***Fast-acting, Intermediate-acting*** *and* ***Long-acting insulin.***

FAST-ACTING INSULIN:

- Is absorbed quickly from your fat tissue (subcutaneous) into the bloodstream.
- Is used to control the blood sugar during meals and snacks and to correct high blood sugars

INCLUDES:

- **1. Rapid Acting Insulin Analogs** (Insulin Aspart, insulin Lyspro, Insulin Glulisine) which have an onset of action of 5 to 15 minutes, peak effect in 1 to 2 hours and duration of action that lasts 4-6 hours. With all doses, large and small, the onset of action and the time to peak effect is similar, The duration of insulin action is, however, affected by the dose – so a few units may last 4 hours or less, while 25 or 30 units may last 5 to 6 hours. As a general rule, assume that these insulins have duration of action of 4 hours.

INCLUDES:

- **2. Regular human insulin** which has an onset of action of 1/2 hour to 1 hour, peak effect in 2 to 4 hours, and duration of action of 6 to 8 hours. The larger the dose of regular the faster the onset of action, but the longer the time to peak effect and the longer the duration of the effect.

INTERMEDIATE-ACTING INSULIN

- Is absorbed more slowly, and lasts longer
- Is used to control the blood sugar overnight, while fasting and between meals

INCLUDES:

NPH Human Insulin which has an onset of insulin effect of 1 to 2 hours, a peak effect of 4 to 6 hours, and duration of action of more than 12 hours. Very small doses will have an earlier peak effect and shorter duration of action, while higher doses will have a longer time to peak effect and prolonged duration.

INCLUDES:

- **Pre-Mixed Insulin** which is NPH pre-mixed with either regular human insulin or a rapid- acting insulin analog. The insulin action profile is a combination of the short and intermediate acting insulins.

LONG-ACTING INSULIN:

- Is absorbed slowly, has a minimal peak effect, and a stable plateau effect that lasts most of the day.
- Is used to control the blood sugar overnight, while fasting and between meals

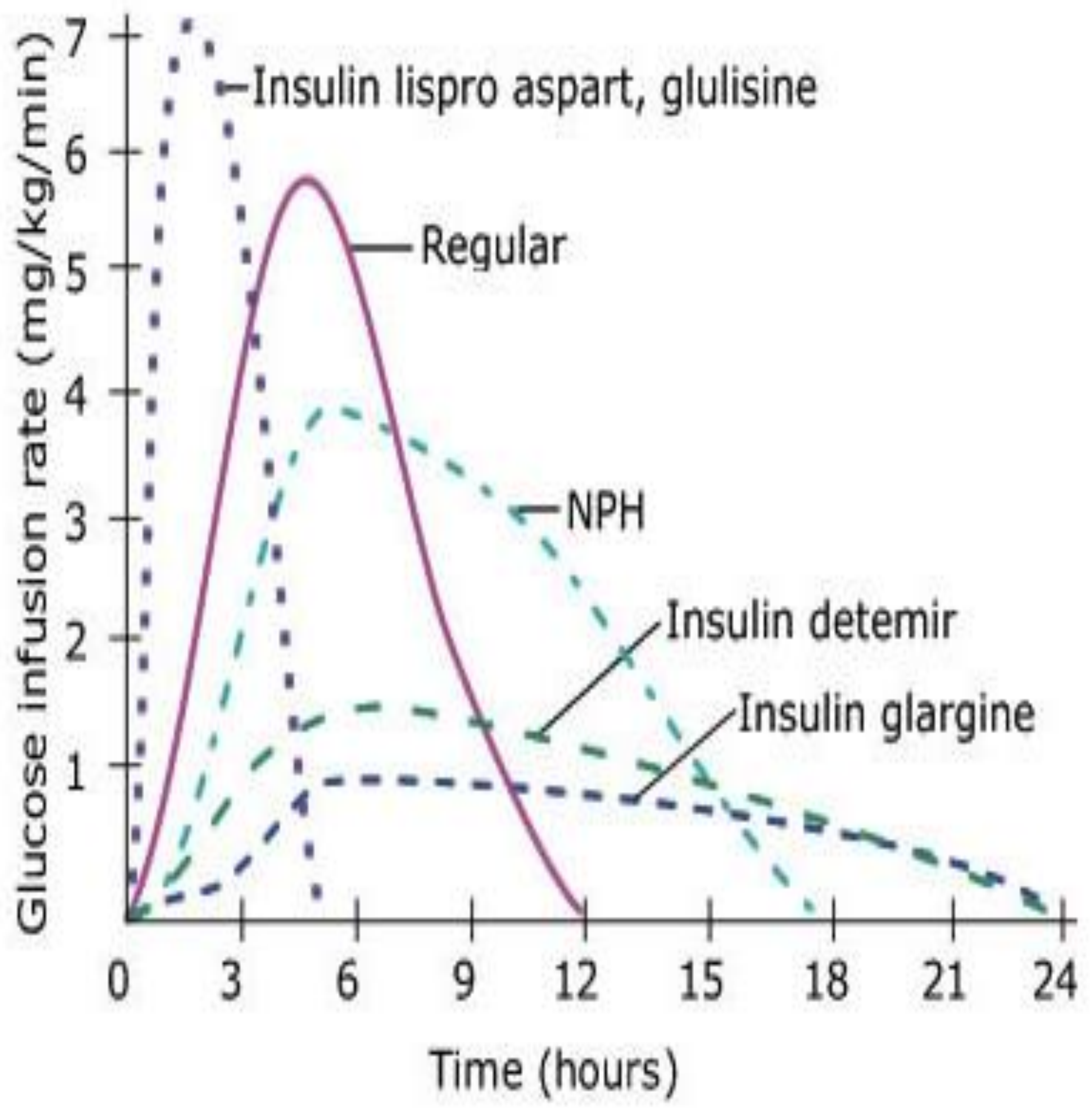
INCLUDES:

- **Long acting insulin analogs** (Insulin Glargine, Insulin Detemir) which have an onset of insulin effect in 1 1/2-2 hours. The insulin effect plateaus over the next few hours and is followed by a relatively flat duration of action that lasts 12-24 hours for insulin detemir and 24 hours for insulin glargine.

TABLE OF INSULIN ACTION

Type of Insulin	Onset	Peak	Duration	Appearance
Fast-acting				
Regular	½-1 hr.	2-4 hr.	6-8 hr.	clear
Lyspro/ Aspart/ Glulisine	<15 min.	1-2 hr.	4-6 hr.	clear
Intermediate-acting				
NPH	1-2 hr.	6-10 hr.	12+ hr.	cloudy
Long-acting				
Detemir	1 hr.	Flat, Max effect in 5 hrs.	12-24 hr.	clear
Glargine	1.5 hr.	Flat, Max effect in 5 hrs.	24 hr.	clear

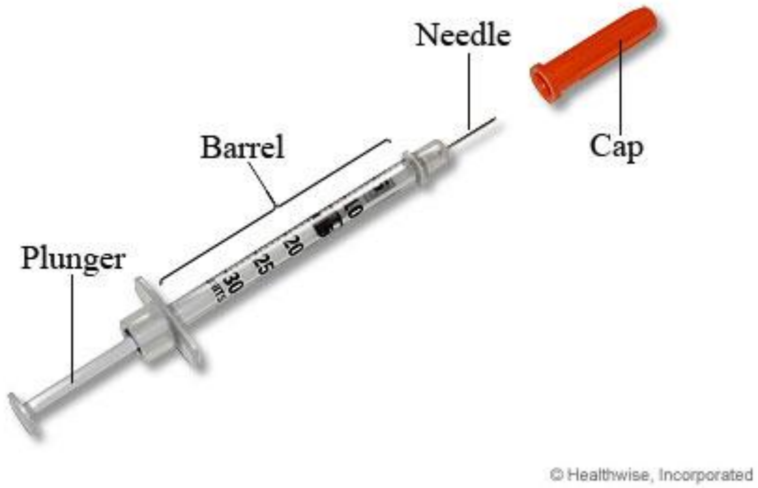
GRAPH ILLUSTRATING THE TIME ACTION CURVES OF DIFFERENT INSULINS



INSULIN ADMINISTRATION

Insulin is administered by two routes of delivery:

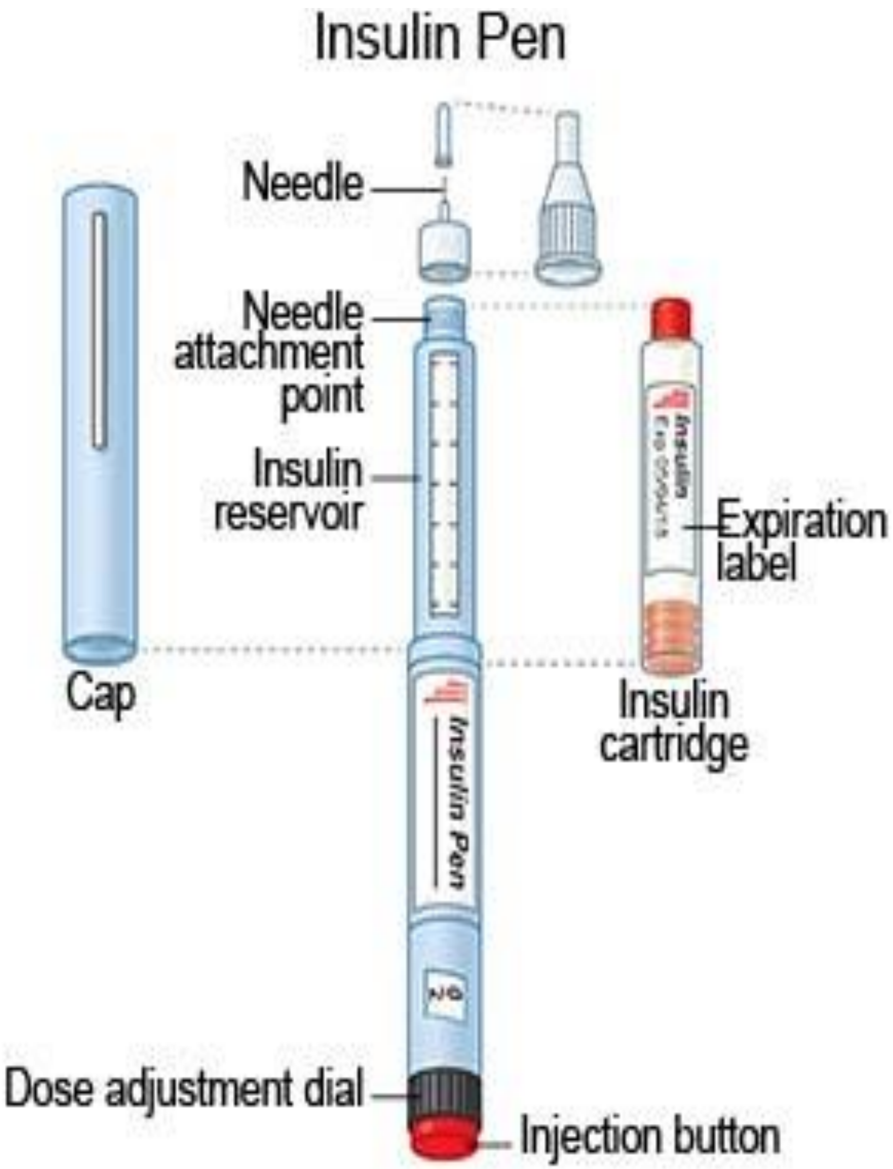
- **Injection**
- **Infusion**



INJECTION

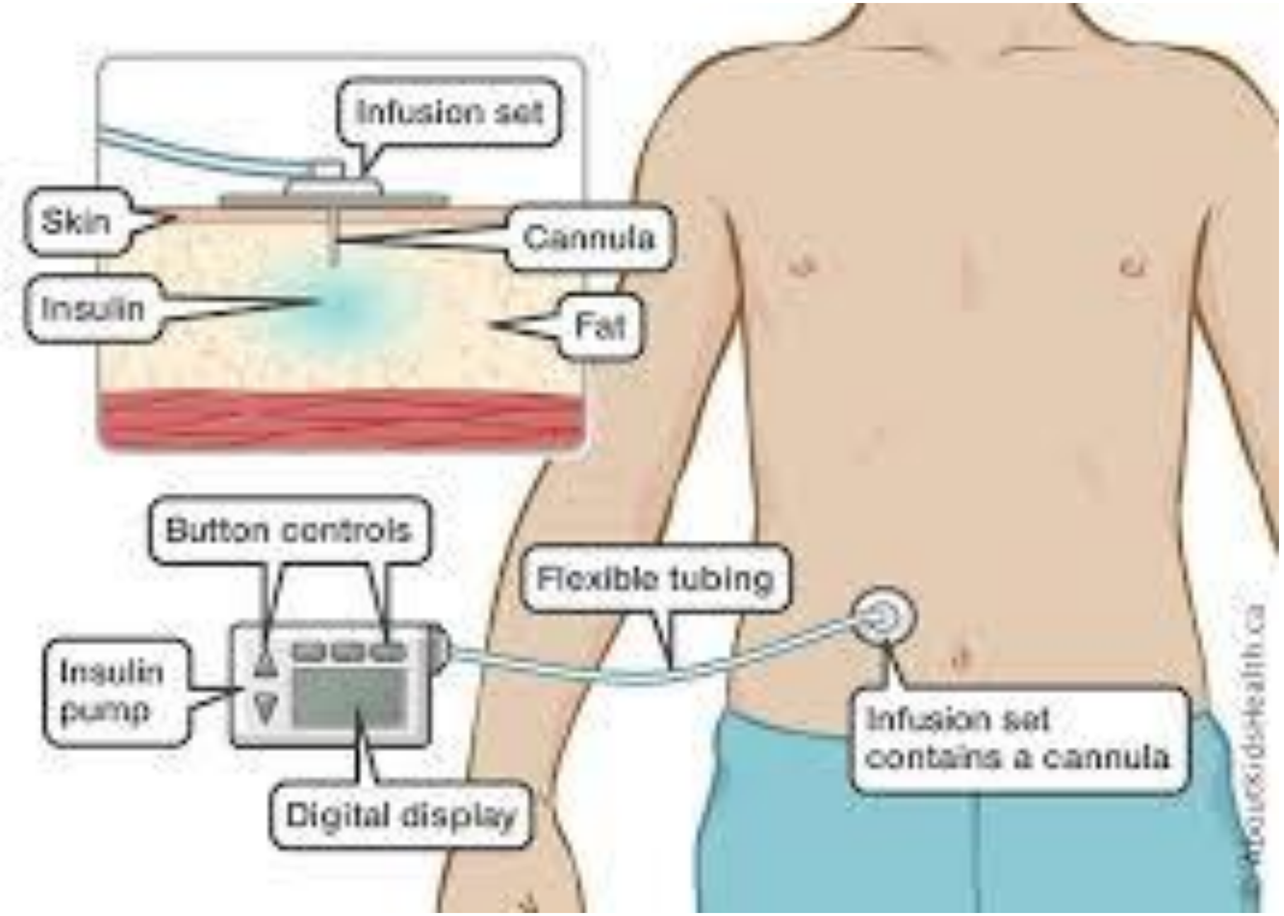
Insulin syringe:

- This is the most common insulin delivery method. The classic injection device is an insulin syringe. The plastic, disposable syringes currently are available in three sizes, and hold up to 30, 50 or 100 units of insulin. The needles are fine (up to 31 gauge) with lengths ranging from 3/16th of an inch for infants, to ½ inch or more for adults. The insulin is injected into the layer of fat (subcutaneous tissue) just under the skin.
- (Rarely, insulin may be injected into a muscle. This should happen only under a medical supervision in a hospital or medical care setting.)



INSULIN PEN:

- A popular alternative to the insulin syringe is an **insulin pen**. An insulin pen has a replaceable reservoir of insulin called a cartridge, a replaceable needle to puncture the skin and to deliver insulin to the subcutaneous tissue, a dial to choose the insulin dose, and a mechanical pumping or insulin release mechanism. These may be disposable devices or re-useable devices with disposable insulin cartridges. They are very convenient for active individuals taking multiple injections, as well as those who are visually or dexterity-challenged.



CONTINUOUS SUBCUTANEOUS INSULIN INFUSION DEVICE:

- **Continuous subcutaneous insulin infusion (CSII) devices** (also known as insulin pumps) are the most sophisticated form of insulin delivery. These are small, computerized devices that are programmed to deliver insulin under the skin. The insulin pump is durable and lasts for years, but the insulin supply and certain pump components (insulin reservoir, tubing and infusion set) are changed every few days.

INFUSION

- Human regular insulin may be injected directly into the vein in a hospital setting under close medical supervision only. Insulin is added to intravenous fluids, and the insulin dose and blood sugar are strictly monitored. The intravenous route of delivery is ONLY given under a doctor's orders in a hospital to facilitate the management of diabetes during surgery or an intensive care stay.

DESIGNING AN INSULIN REGIMEN

The main goal in designing an insulin regimen is to mimic how the body normally releases insulin. In type 2 diabetes, there are two main ways to replace insulin.

Intensive Insulin Therapy closely mimics the natural insulin production.

The second, referred to as Conventional or Sliding Scale Insulin Therapy, more loosely approximates insulin needs.

FOR INTENSIVE REGIMENS

general principles

A BASAL OR BACKGROUND INSULIN DOSE

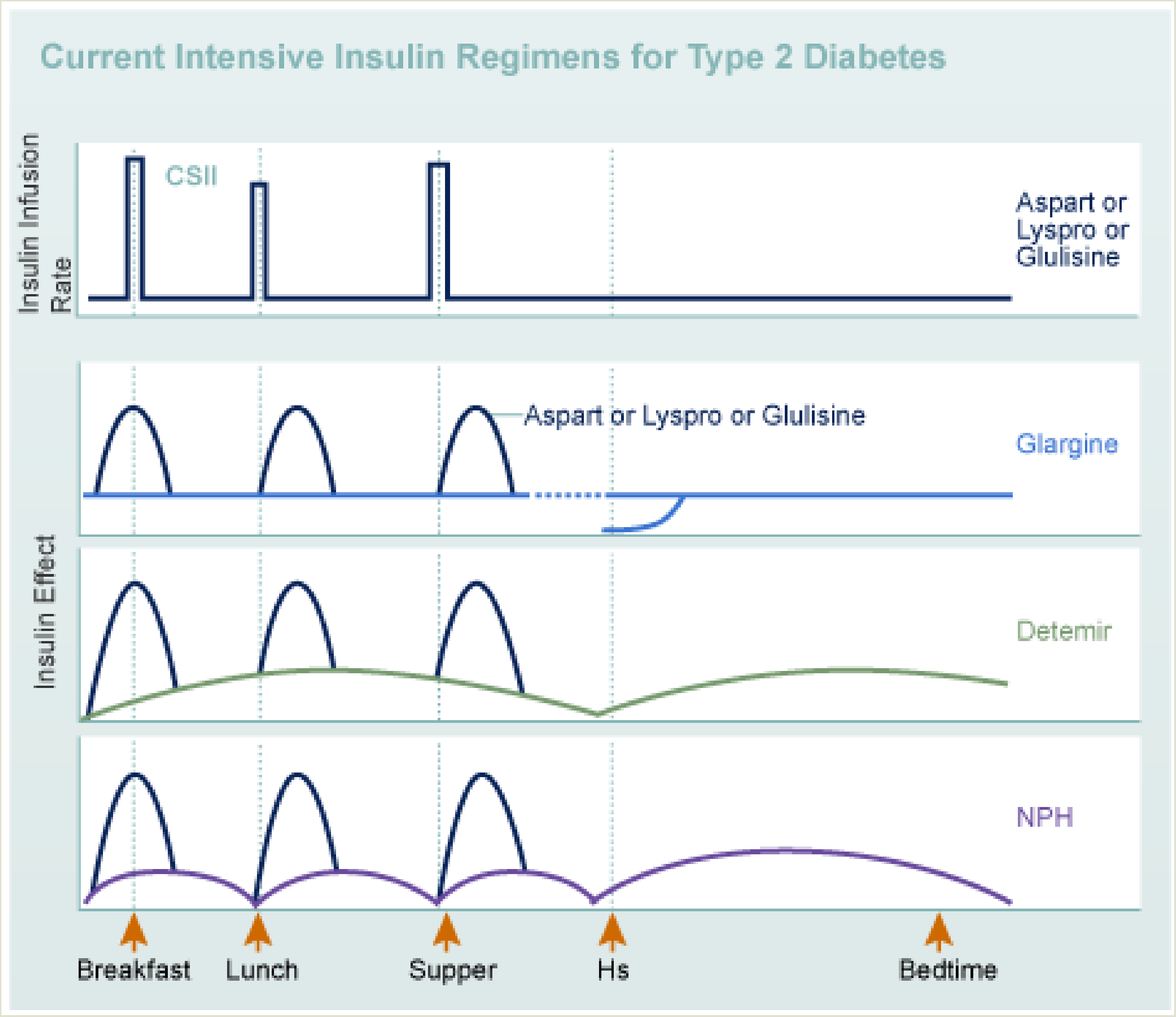
- This will be prescribed as one or two injections of long acting insulin, or, if your patient is using an insulin pump, a daily infusion rate of continuous, small amounts of rapid acting insulin.
- The background/basal insulin dose is usually the same day to day. With an insulin pump patient have the option of temporarily changing the background rate for a few hours – up or down as needed.

A BOLUS INSULIN DOSE TO COVER THE SUGAR OR CARBOHYDRATE IN PATIENTS FOOD

- This will be presented as an insulin to carbohydrate ratio(I:CHO).
- The I:CHO ratio tells you how many grams of carbohydrate can be covered by one unit of rapid acting insulin.
- Patient will need to calculate how much carbohydrate he will eat, and take a dose of insulin that matches the food.

A BOLUS INSULIN DOSE TO BRING BLOOD SUGAR BACK TO THE NORMAL RANGE

- A high blood sugar correction bolus insulin dose to bring patients blood sugar back into the target range.
- This will be presented as a correction factor. This correction factor refers to how much patients blood sugar will drop after 1 unit of insulin rapid acting insulin.
- When blood sugar is too high, patient will need to calculate how much his blood sugar is over the target, and, based on the correction factor, then the dose of insulin that will bring him down into the desired range.



COMMON INTENSIVE REGIMENS FOR TYPE 2 DIABETES:

- Long-acting insulin (glargine/detemir) once or twice a day with rapid acting insulin (Aspart, glulisine, lispro) before meals and as need to correct high blood sugars.
- Rapid acting insulin (Aspart, glulisine, lispro) delivered via an insulin pump.
- Three small doses of NPH before meals, and a larger dose of NPH at night , with rapid acting insulin (aspart, glulisine, lispro) before meals and, as needed, for snacks and to correct high blood sugars

SLIDING SCALE THERAPY

- The term “sliding scale” refers to the progressive increase in the pre-meal or nighttime insulin dose, based on pre-defined blood glucose ranges. Sliding scale insulin regimens approximate daily insulin requirements.

COMMON SLIDING SCALE REGIMENS:

- Long-acting insulin (glargine/detemir or NPH), once or twice a day with short acting insulin (aspart, glulisine, lispro, Regular) before meals and at bedtime
- Long-acting insulin (glargine/detemir or NPH), given once a day
- Regular and NPH, given twice a day
- Pre-mixed, or short-acting insulin analogs or Regular and NPH, given twice a day

THE GENERAL PRINCIPLES OF SLIDING SCALE THERAPY ARE:

- The amount of carbohydrate to be eaten at each meal is pre-set.
- The basal (background) insulin dose doesn't change. Patient takes the same long-acting insulin dose no matter what the blood glucose level.
- The bolus insulin is based on the blood sugar level before the meal or at bedtime
- Pre-mixed insulin doses are based on the blood sugar level before the meal

DISADVANTAGES OF THE SLIDING SCALE REGIMEN:

- The sliding scale method does not accommodate changes in insulin needs related to snacks or to stress and activity.
- You still need to count carbohydrates.
- Sliding scales are less effective in covering a pre-meal high blood sugar, because the high blood glucose correction and food bolus cannot be split.

CALCULATING INSULIN DOSE

FIRST, SOME BASIC THINGS TO KNOW ABOUT INSULIN:

- **Approximately 40-50% of the total daily insulin dose is to replace insulin overnight, when you are fasting and between meals.** This is called background or basal insulin replacement. The basal or background insulin dose usually is constant from day to day.
- **The other 50-60% of the total daily insulin dose is for carbohydrate coverage (food) and high blood sugar correction**. This is called the bolus insulin replacement.

BOLUS – CARBOHYDRATE COVERAGE

- **The bolus dose for food coverage is prescribed as an insulin to carbohydrate ratio.The insulin to carbohydrate ratio represents how many grams of carbohydrate are covered or disposed of by 1 unit of insulin.**
- Generally, one unit of rapid-acting insulin will dispose of 12-15 grams of carbohydrate. This range can vary from 4-30 grams or more of carbohydrate depending on an individual's sensitivity to insulin. Insulin sensitivity can vary according to the time of day, from person to person, and is affected by physical activity and stress.

BOLUS – HIGH BLOOD SUGAR CORRECTION (ALSO KNOWN AS INSULIN SENSITIVITY FACTOR)

- **The bolus dose for high blood sugar correction is defined as how much one unit of rapid-acting insulin will drop the blood sugar.**
- Generally, to correct a high blood sugar, one unit of insulin is needed to drop the blood glucose by 50 mg/dl. This drop in blood sugar can range from 15-100 mg/dl or more, depending on individual insulin sensitivities, and other circumstances.

EXAMPLES

Here is some examples and therapeutic principles on how to calculate the carbohydrate coverage dose, high blood sugar correction dose and the total mealtime insulin dose.

EXAMPLE #1: CARBOHYDRATE COVERAGE AT A MEAL

- First, you have to calculate the carbohydrate coverage insulin dose using this formula:

CHO insulin dose =Total grams of CHO in the meal÷ grams of CHO disposed by 1 unit of insulin
(the grams of CHO disposed of by 1 unit of insulin is the bottom number or denominator of the Insulin: CHO ratio).

FOR EXAMPLE #1, ASSUME:

- Patient is going to eat 60 grams of carbohydrate for lunch
- Patients Insulin: CHO ratio is 1:10
- To get the CHO insulin dose, plug the numbers into the formula:

CHO insulin dose =Total grams of CHO in the meal (60 g)
÷ grams of CHO disposed by 1 unit of insulin (10) = 6 units

- **You will need 6 units of rapid acting insulin to cover the carbohydrate.**

EXAMPLE #2: HIGH BLOOD SUGAR CORRECTION DOSE

- Next, you have to calculate the high blood sugar correction dose.

High blood sugar correction dose = Difference between actual blood sugar and target blood sugar*÷ correction factor.

*Actual blood sugar minus target blood sugar

FOR EXAMPLE #2, ASSUME:

- 1 unit will drop blood sugar 50 points (mg/dl) and the high blood sugar correction factor is 50.
- Pre-meal blood sugar target is 120 mg/dl.
- actual blood sugar before lunch is 220 mg/dl.
- Now, calculate the difference between actual blood sugar and target blood sugar:
- **220 minus 120 mg/dl = 100 mg/dl**
- To get the high blood sugar correction insulin dose, plug the numbers into this formula:
- **Correction dose =**
  Difference between actual and target blood glucose (100mg/dl)
  ÷ correction factor (50) = 2 units of rapid acting insulin
- **So, you will need an additional 2 units of rapid acting insulin to "correct" the blood sugar down to a target of 120 mg/dl.**

EXAMPLE #3: TOTAL MEALTIME DOSE

- Finally, to get the total mealtime insulin dose, add the CHO insulin dose together with the high blood sugar correction insulin dose:

CHO Insulin Dose+ High Blood Sugar Correction Dose = Total Meal Insulin Dose

FOR EXAMPLE #3, ASSUME:

- The carbohydrate coverage dose is 6 units of rapid acting insulin.
- The high blood sugar correction dose is 2 units of rapid acting insulin.

Now, add the two doses together to calculate total meal dose.

Carbohydrate coverage dose (6 units) + high sugar correction dose (2 units) = 8 units total meal dose!

The total lunch insulin dose is 8 units of rapid acting insulin.

EXAMPLE #4: FORMULAS COMMONLY USED TO CREATE INSULIN DOSE RECOMMENDATIONS

This example illustrates a method for calculating of background/basal and bolus doses and estimated daily insulin dose when you need full insulin replacement. Bear in mind, this may be too much insulin if patient is newly diagnosed or still making a lot of insulin on his own. And it may be too little if he is resistant to the action of insulin.

THE INITIAL CALCULATION OF THE BASAL/BACKGROUND AND BOLUS DOSES REQUIRES ESTIMATING TOTAL DAILY INSULIN DOSE:

TOTAL DAILY INSULIN REQUIREMENT

- The general calculation for the body's daily insulin requirement is:

Total Daily Insulin Requirement(in units of insulin)
= Weight in Pounds ÷ 4

- Alternatively, if you measure body weight in kilograms:

Total Daily Insulin Requirement (in units of insulin)
= 0.55 X Total Weight in Kilograms

EXAMPLE

- If you are measuring body weight in kilograms:

Assume weight is 80Kg

- **In this example:**

TOTAL DAILY INSULIN DOSE
= 0.55 x 80 Kg = 44 units of insulin/day

BASAL/BACKGROUND AND BOLUS INSULIN DOSES

Next, you need to establish the basal/background dose, carbohydrate coverage dose (insulin to carbohydrate ratio) and high blood sugar correction dose (correction factor).

Basal/background insulin dose:

Basal/background Insulin Dose = 40-50% of Total Daily Insulin Dose

EXAMPLE

- Assume weigh 80 Kg

total daily insulin dose **= 0.55 x 80 Kg = 44 units of insulin/day**

In this example:

- **Basal/background insulin dose = 50% of TDI (44 units) = 22 units**
  of either long acting insulin,(such as glargine or detemir) or rapid acting insulin if you are using an insulin pump (continuous subcutaneous insulin infusion device).

THE CARBOHYDATE COVERAGE RATIO:

- **500 ÷ Total Daily Insulin Dose = 1 unit insulin covers so many grams of carbohydrate**

This can be calculated using the Rule of "500": Carbohydrate Bolus Calculation

EXAMPLE:

Assume total daily insulin dose (TDI)
= 80 kg*0,55= 44 units

- **In this example:**
- **Carbohydrate coverage ratio**
  = 500 ÷ TDI (44 units)
  = 1unit insulin/ 11 g CHO

THIS EXAMPLE

above assumes that patient have a constant response to insulin throughout the day. In reality, individual insulin sensitivity varies.

Someone who is resistant in the morning, but sensitive at mid-day, will need to adjust the insulin-to-carbohydrate ratio at different meal times. In such a case, the background insulin dose would still be approximately 22 units; however, the breakfast insulin-to-carbohydrate ratio might be breakfast 1:8 grams, lunch 1:14 grams and dinner 1:11 grams.

THE HIGH BLOOD SUGAR CORRECTION FACTOR:

Correction Factor = 1800 ÷Total Daily Insulin Dose = 1 unit of insulin will reduce the blood sugar so many mg/dl

This can be calculated using the Rule of "1800".

EXAMPLE:

- Assume total daily insulin dose (TDI) = 80 kg*0,55= 44 units
- **In this example:**

Correction Factor
= 1800 ÷ TDI(44 units)
= 1 unit insulin will drop reduce the blood sugar level by 40,9 mg/dl

While the calculation is 1 unit will drop the blood sugar 40,9 mg/dl, to make it easier most people will round up or round down the number so the suggested correction factor may be 1 unit of rapid acting insulin will drop the blood sugar 40-50 mg/dl.

ASK ME


THANK YOU
FOR YOUR
ATTENTION