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Diabetes: A History

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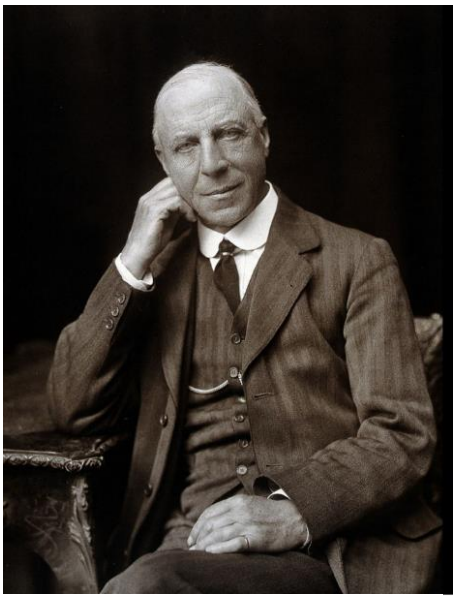
Edward Albert Sharpey-Schafer is frantically pacing within his office at the University of Edinburgh. His scuffling feet are kicking up dust, filling the room with a musty and stale air. Open books lie scattered about the room, their titles ranging from *Resection of the Pancreas* to *Malattie delle glandule salivary e del pancreas*. Perhaps the most fascinating book, however, lies open on Schafer's desk. His pen, uncapped upon the book's pages, drips black ink and blots the words.



Sir Edward Albert Sharpey-Schafer in his office, c. 1928

The year is 1910, and the scrawled handwriting in his journal shows--for the first time--that the pancreas is producing a previously unidentified substance. Schafer has identified a protein called insulin. The scientific sketches in his book are poised to transform the medical community for centuries to come. He will be knighted in only three years' time by King George V.

The discovery of the insulin protein would prove to be a crucial advancement in the treatment of diabetes mellitus, a condition often characterized by high levels of glucose in the blood stream and a slow deterioration of organ function – including vision, kidney function, and sense of touch at the extremities. Insulin's function in the body, and its role in treating patients with diabetes, would be uncovered, a few years after Shafer identified the hormone, by two men and a pack of dogs.

The year is 1922, and the dust from World War I has barely settled. In Toronto, Dr. Frederick Banting and his student, Dr. Charles Best, don white coats--at least cpats that used to be white. Years of laboratory research have stained the once pristine attire. Their pockets are overflowing with filled syringes. Dogs are running amok and food lies scattered about the ground. A persistent barking can be heard down the hall, much to the annoyance of scientific colleagues. Banting and Best have issues besides peeved academics on their minds, however. Just last week, they extracted insulin from the pancreas of the

dogs. Then, they removed the pancreas from a few of the canines and watched their blood sugar levels skyrocket. Today, they are going to test their hypothesis.

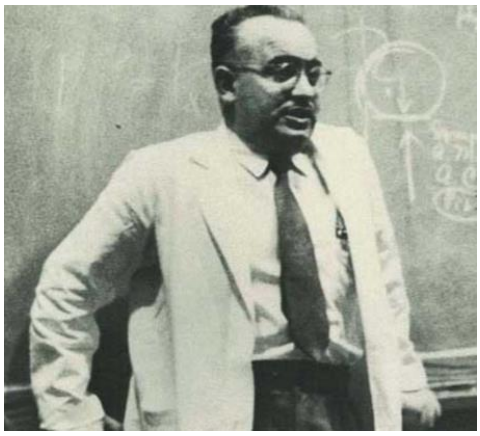
Frederick Banting and Charles Best on the roof of the University of Toronto's Medical Building, c. 1922.

Banting and Best inject insulin into five of the dogs without a pancreas. Then, with a careful eye on their pocket watches, they take blood from the dogs after fifteen, thirty, and sixty minutes. After performing careful tests on the collected blood, they determine that the animals' blood sugar levels dropped after receiving injections of insulin. Banting and Best conclude that insulin can be used as a treatment for diabetic patients with hyperglycemia, or high concentrations of blood sugar. Based on these experiments, they determine that the pancreas secretes insulin, and thus must be the physiological regulator of blood glucose levels, as only the dogs with their pancreas removed had hyperglycemia. After further experiments and validation, Banting and Best's paper is quickly written up and published in *The Journal of Laboratory and Clinical Medicine*. Banting goes on to win the Nobel Prize in Medicine only a year later, at the age of 32. He remains the youngest Nobel laureate in the area of Physiology or Medicine to this day.

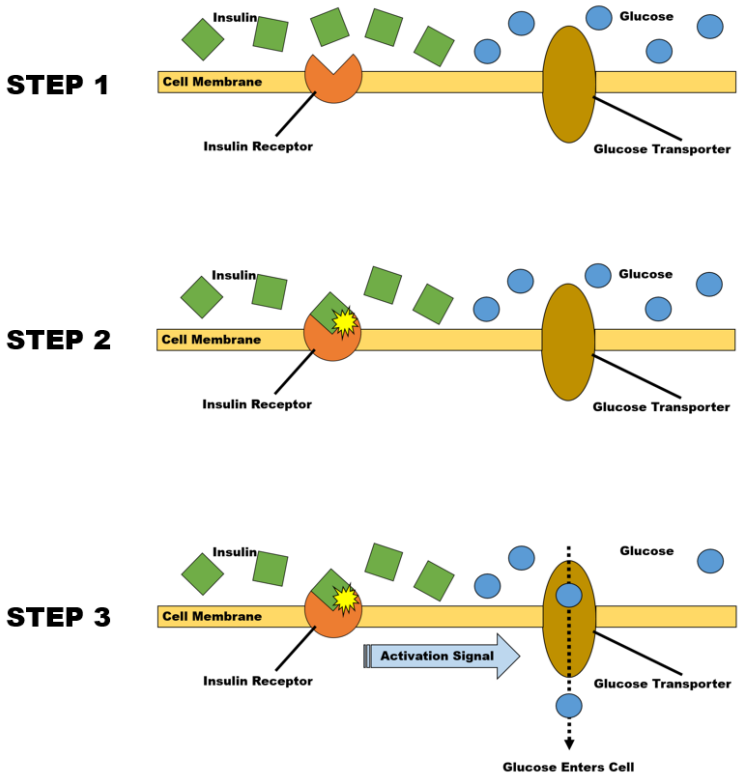
A few years after the publication of Banting and Best's groundbreaking manuscript, clinicians in academic hospitals around the world begin extracting insulin from healthy animals and humans and injecting it into people afflicted with hyperglycemia. In 1923, Eli Lilly and Company begin producing insulin on a commercial level.

The year is 1949. Dr. Rachmiel Levine's brow is furrowed, his feet incessantly tapping on the cement floor. The latest edition of *Nature* lies open on his desk. Inside is an article that states "insulin must enter the cell before sugar can pass through the cell membrane." The authors of the article argue that insulin is **absorbed** by cells, whereupon it activates the signaling pathway responsible for lowering blood glucose levels.

Levine, in his experiments at the Michael Reese Hospital in Chicago, has seen otherwise. Levine fed dogs sugar and then calculated the dilution level of the sugar, observing that it was concentrated only **outside** of cells. Once he injected insulin into the canines, however, the sugar entered the cells while the insulin remained outside, thus demonstrating that insulin "opens" the cell membrane to allow sugar entry. Contrary to the scientific belief held by many of his colleagues, insulin was not absorbed by the cell at all--it merely served as a 'key' to lower blood sugar levels. As a tribute to Levine's findings, the standard explanation of the sugar transport mechanism in cells is called the "Levine effect."



Dr. Rachmiel Levine lecturing to medical students, c. 1954



Model of the 'Levine effect', which demonstrates the manner in which insulin allows for glucose to enter the cell. The green squares are insulin molecules and the blue circles are glucose molecules. When insulin binds to the Insulin Receptor (orange), an activation signal notifies the glucose transporter (brown) to take in glucose.

Further research in the fields of metabolism and endocrinology has demonstrated that insulin is a small protein that binds to cellular receptors, thus initiating a "signaling cascade" that brings glucose transporters to the membrane to begin taking in sugars. Figure 1 shows this process. The green squares represent insulin and the blue circles represent glucose. Insulin "sticks" to a receptor on the surface of cells (aptly named the Insulin Receptor) and triggers an activation signal that allows a protein known as the Glucose

Transporter to begin "absorbing" glucose from outside of the cell. This "sticking" of insulin and subsequent uptake of sugar is crucial to a healthy body because our cells use glucose to create energy. Unfortunately, diabetic patients either do not produce enough insulin or cannot adequately absorb glucose into their cells.

This theory, put forth by Levine, places diabetes research on a trajectory of mechanistic work, allowing scientists to ask more detailed questions and solve them using rigorous observation and validation. Instead of merely noting different diabetes symptoms, researchers begin to explore how diabetes impacts cells at the level of specific proteins, receptors and signaling pathways – that is, how diabetes works at the molecular level. In this way, they develop highly targeted and effective treatments.

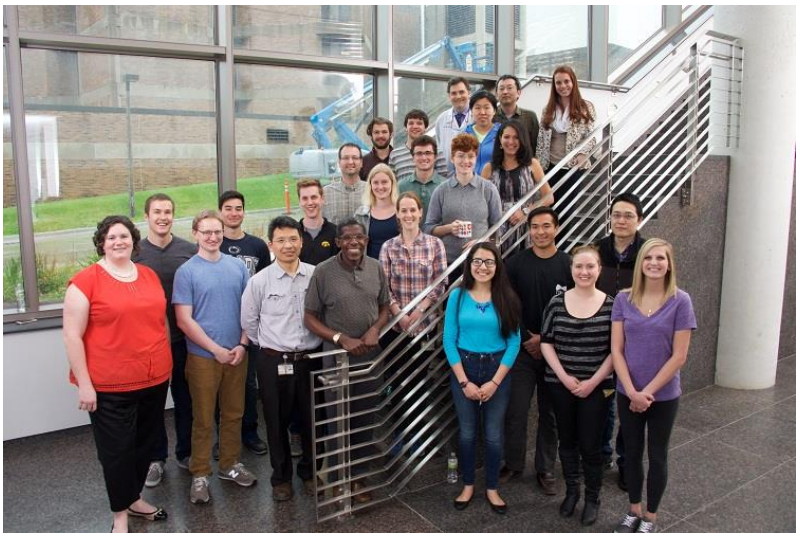
The year is 1959. Dr. Solomon Berson and Dr. Rosalyn Yalow are hard at work in the Bronx Veteran Affairs Hospital. Yalow had earned a PhD in Physics in 1945 from the University of Illinois at Urbana-Champaign, where she was the only woman among the department's 400 members. Now, Drs. Berson and Yalow are on the verge of creating a new tool to allow scientists to study insulin and glucose in living cells. Both scientists are founding members of the Radioisotope Service in the hospital, a state-of-the-art center that uses radioactivity to study how compounds are manipulated in the human body.

Dr. Solomon Berson and Dr. Rosalyn Yalow in the laboratory, c. 1959. Dr. Yalow would go on to win a Nobel Prize in Medicine in 1977, the only woman VA doctor to be awarded the honor.

Berson and Yalow have worked tirelessly in the lab to develop the radioimmunoassay, a technique that measures the concentration of proteins, such as insulin, in the blood through the use of antibodies and radioactive compounds. The assay paves the way for *in vivo* (in living organisms) measurements of insulin levels, and provides clinicians with a powerful tool to diagnose diabetic patients. In 1978, Dr. Yalow will become the first female President of the Endocrine Society.

Today, the Abel laboratory at the University of Iowa is combining scientific research from the last century to improve the way that diabetic patients are treated. We use mice with specific genetic

deletions to study the role of different genes and proteins in the development and treatment of diabetes. After deleting a certain gene, we track the health of the mice over time to study the role of that gene in the cell. Innovative new machines and experimental techniques have drastically accelerated the rate of scientific progress, allowing us to answer questions at the molecular level in just a few days. The Fraternal Order of Eagles Diabetes Research Center was dedicated in April 2011 after a gift of $25 million from the Fraternal Order of Eagles. Today, the Center houses more than 90 scientific investigators in different disciplines working on questions related to diabetes, insulin signaling, metabolism and cardiovascular function.



The Abel Laboratory at the Fraternal Order of Eagles Diabetes Research Center, University of Iowa. Picture taken in May of 2015.

A recent study from the Diabetes Research Center showed that removal of the Insulin Receptor in cells leads to early-onset heart failure, demonstrating a clear link between insulin signaling and heart function. Insulin is, in effect, a "glue" that holds the heart together. According to a 2014 Statistics Report by the Centers for Disease Control and Prevention, over 30 million Americans have been diagnosed with diabetes. Furthermore, about two-thirds of all diabetes-related deaths come about as a result of heart attacks and strokes.

The tale of diabetes throughout time has shown that a "happily ever after" ending is not yet possible, but scientists have much to learn from their predecessors. By looking at the past, researchers can continue moving forward. What will the next decade hold?