Design for Biosecurity

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Lecture 33

Insulin Controversy

So welcome back to this class while continuing the story of insulin. As previously discussed, four key figures played pivotal roles in connecting the dots between the pancreas, insulin, diabetes, and glucose. These individuals were Frederick Banting, Charles Best, John McLeod, and James Collip. While we have already covered Banting, Best, and McLeod, today we will focus on James Collip and how he came into the picture.

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In our last session, we concluded with the experiments where duct ligation was used as a method to isolate the acid-producing cells, leaving only the islets of Langerhans. This led to the realization that pancreatectomy could be used to induce diabetes. Following numerous setbacks over the summer, the team finally reported in the fall that they were able to keep a severely diabetic dog alive by injecting it with an extract made from the duct-ligated pancreas. This extract was prepared according to McLeod's instructions in Selene and, remarkably, it significantly lowered the blood sugar levels in the diabetic dog. This was a landmark experiment conducted in 1921, over a century ago.

Now, today’s class will dive into the aftermath of these findings and the human drama that ensued. It’s important to remember that discoveries often come with intense emotions and controversies, and this story is no exception.

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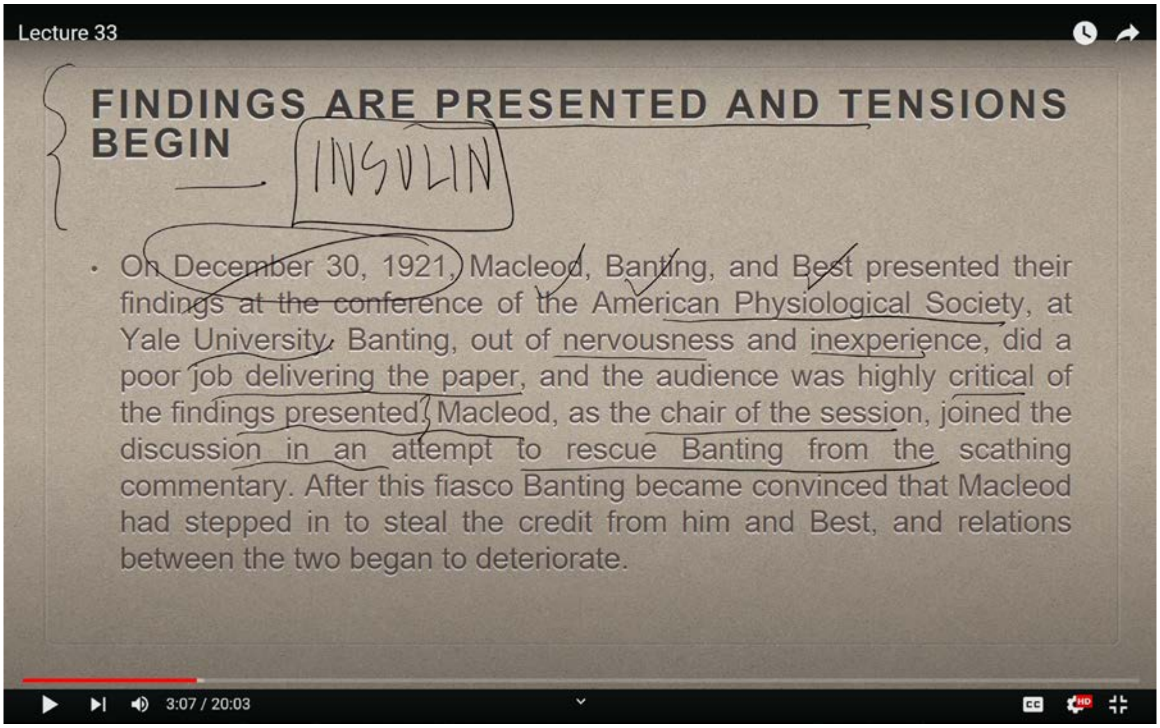

On December 30th, 1921, McLeod, Banting, and Best presented their groundbreaking findings at the American Physiological Society conference held at Yale University in Connecticut. However, the presentation did not go as smoothly as hoped. Banting, due to his nervousness and lack of experience, struggled to deliver the paper effectively, leading to harsh criticism from the audience.

McLeod, who was chairing the session, stepped in to defend Banting and the team's work from the intense scrutiny. The situation was quite tense. As Banting, McLeod, and Best presented their work, describing how they extracted secretions from the duct-ligated dogs and injected them into another dog that had its pancreas removed, they were met with skepticism. The audience, comprised of other scientists, was quick to highlight the perceived flaws and limitations of their experiments.

This incident underscores the challenges faced when presenting pioneering work, especially when the findings challenge established norms or when the experiments themselves have variables that are difficult to control. Despite the criticism, this moment marked a critical turning point in the history of insulin, setting the stage for future developments.

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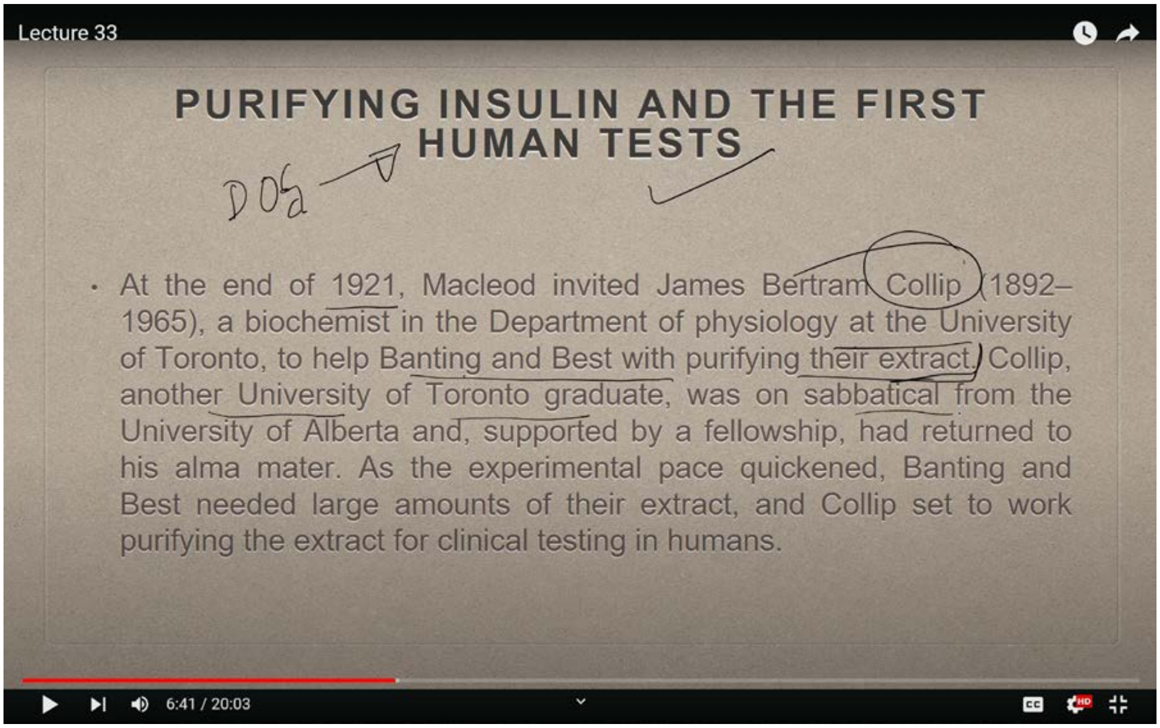

At that time, this situation was a significant issue. McLeod stepped in to defend Banting, but this intervention led to a serious misunderstanding. Banting became convinced that McLeod's actions were not to help but to steal the credit for the discovery. This suspicion caused a deep rift between the two. For Banting, it felt as if McLeod had used the fiasco as a pretext to overshadow him and take all the credit for himself.

Such conflicts over recognition are not uncommon in the scientific community, especially when groundbreaking discoveries are at stake. During that era, receiving credit for a discovery meant reaching the pinnacle of the scientific world. Unfortunately, this situation left a lasting negative impact on both Banting and McLeod, marking the beginning of a deteriorating relationship that would eventually break apart.

Next, we move on to the purification of insulin and the first human trials. Up to this point, all experiments had been conducted on dogs, but now they were transitioning to human testing. This is where James Collip, the fourth key figure in the insulin story, enters the scene. I mentioned earlier that we hadn't yet discussed Collip, but now, at the end of 1921, his role becomes crucial.

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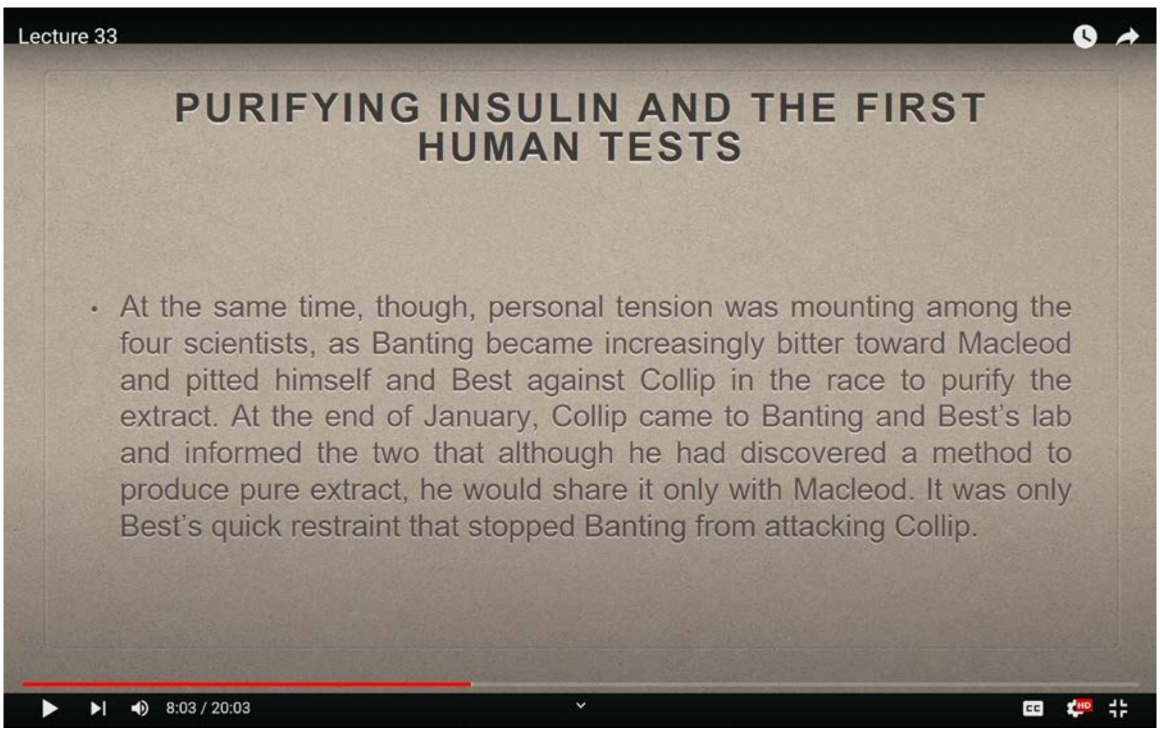

James Bertram Collip, a biochemist in the Department of Physiology at the University of Toronto, joined Banting and Best to help purify the insulin extract. Remember, at that time, they were working only with crude extracts, they had no idea which chemicals were present. This was long before the advent of mass spectrometry or high-performance chromatography. Collip, who was on sabbatical from the University of Alberta and supported by a fellowship, returned to his alma mater at the University of Toronto. As the pace of experiments accelerated, Banting and Best needed a larger supply of purified extract, so Collip set to work on refining the substance for clinical testing in humans.

As they say, timing is everything. The first clinical trial on a human patient, a severely diabetic 14-year-old boy, took place soon after. Although the initial injection of the extract did not produce a significantly beneficial effect, the Toronto team persevered. Shortly afterward, Collip made a breakthrough in the purification process by using alcohol at a concentration slightly over 90% to precipitate the active ingredient, insulin. This was Collip's method of isolating insulin from a complex mixture that emerged from the pancreatic duct.

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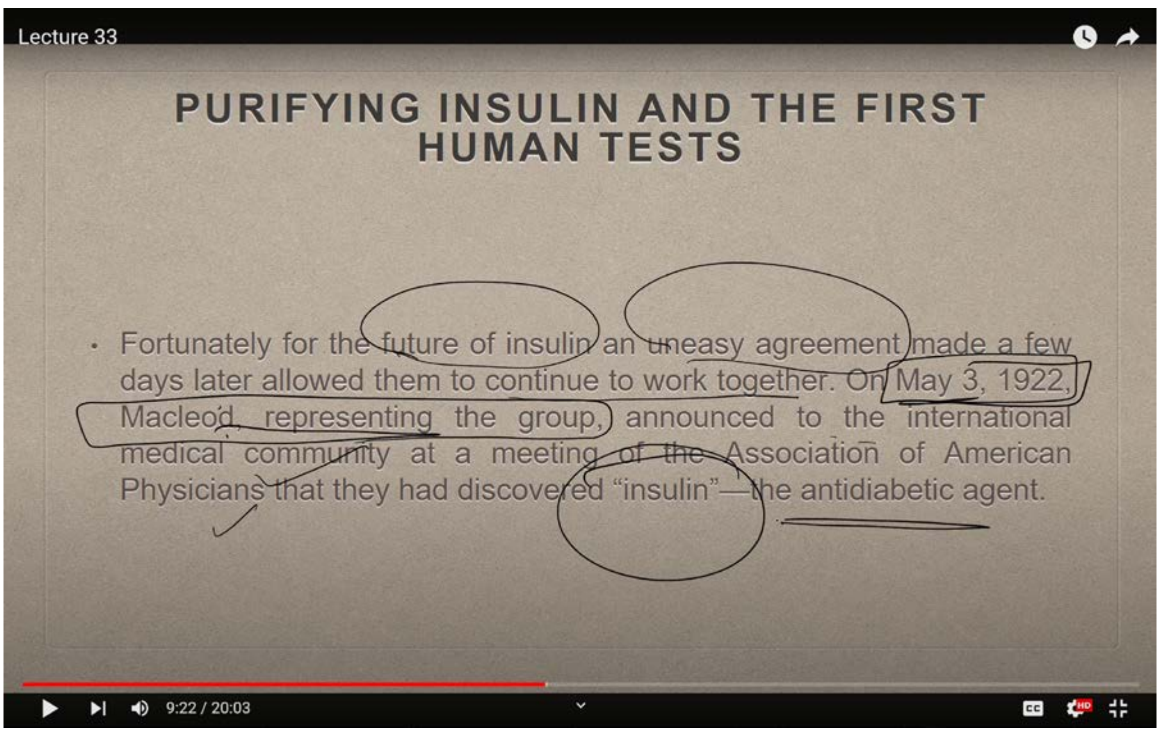

However, as scientific progress was made, personal tensions among the four scientists escalated. Banting, increasingly bitter towards McLeod, began to see himself and Best as rivals to Collip in the race to purify the extract. By the end of January 1922, Collip informed Banting and Best that although he had discovered a method to produce pure insulin, he would only share it with McLeod.

It was only Best's quick intervention that prevented Banting from physically attacking Collip. This was an extremely tense and ugly moment, highlighting the turmoil that the story of insulin went through. As we delve deeper into this narrative, we'll uncover even darker aspects of the insulin story. Fortunately for the future of insulin, an uneasy agreement was reached just days later, allowing the team to continue their collaboration.

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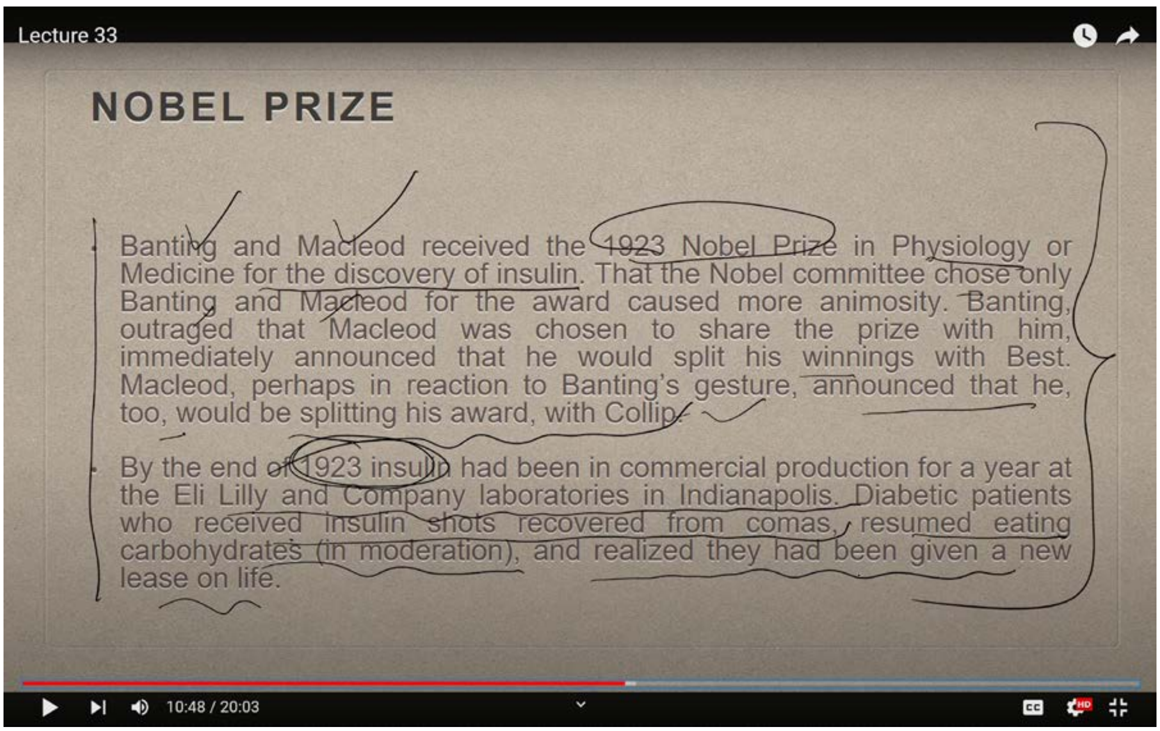

On May 3rd, 1922, McLeod, representing the entire group, made a groundbreaking announcement to the international medical community at a meeting of the Association of American Physicians. He declared that they had discovered insulin, the anti-diabetic agent that would soon revolutionize medicine. Just one year later, in 1923, Banting and McLeod were awarded the Nobel Prize in Physiology or Medicine for this monumental discovery. The significance of this achievement is profound, as it quickly earned them one of the highest honors in science.

However, the Nobel Committee's decision to award the prize only to Banting and McLeod stirred up further animosity. Banting, furious that McLeod was chosen to share the prize with him, immediately announced that he would split his winnings with Charles Best, who was a graduate student at the time. In a likely response to Banting's gesture, McLeod decided to share his portion of the prize with James Collip.

So, while the Nobel Prize officially went to Banting and McLeod, Best and Collip received a share of the recognition through the prize money. However, the fact remains that only Banting and McLeod were honored with the Nobel Prize itself. By the end of 1923, insulin had already been in commercial production for a year at Eli Lilly and Company laboratories in Indianapolis. Diabetic patients who received insulin injections recovered from comas, resumed eating carbohydrates in moderation, and essentially received a new lease on life.

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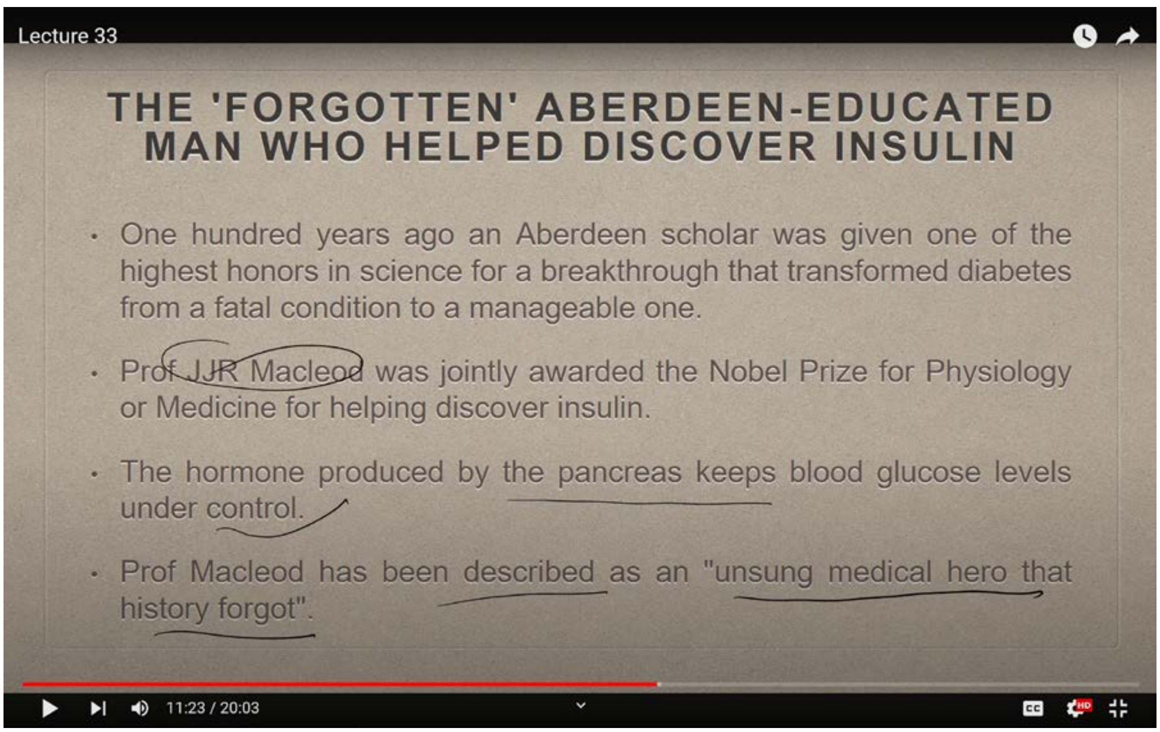

This is the story of the Nobel Prize associated with the discovery of insulin. Yet, in this tale, some contributors have been largely forgotten, one of them being J.J.R. McLeod. A century ago, this Aberdeen scholar was awarded one of the highest honors for his role in a discovery that has saved countless lives. The hormone produced by the pancreas, which keeps blood glucose levels under control, was central to McLeod's work. Yet, history has often overlooked his contributions, labeling him as an unsung medical hero.

It’s quite sad, really. While the controversies surrounding insulin are well-known, McLeod’s pivotal role is often underappreciated. Born in 1876, McLeod moved to Aberdeen at the age of seven. He was educated at Aberdeen Grammar School and later studied medicine at the University of Aberdeen. After becoming a lecturer at the University of Toronto, he collaborated with the young surgeon Frederick Banting. McLeod's earlier work, including his research on glycosyluria, was crucial in establishing the connections between the pancreas, diabetes, glucose, and insulin.

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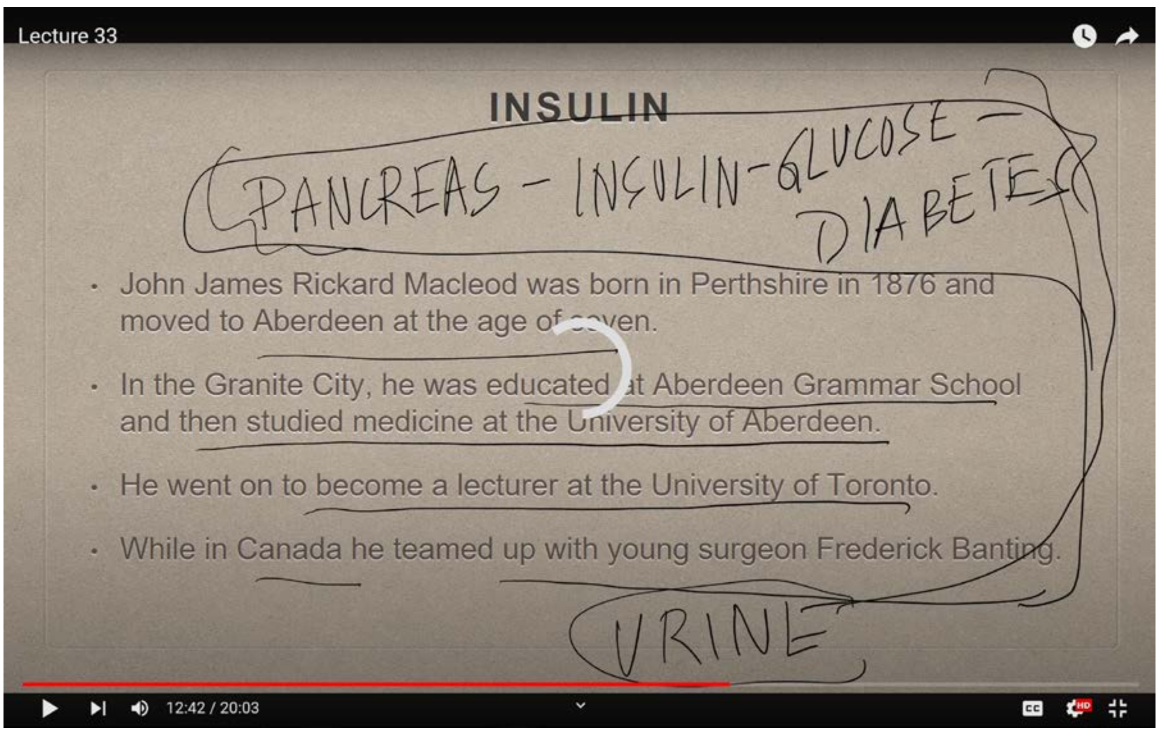

These connections, between the pancreas, insulin, glucose, and diabetes, were fundamental to setting the stage for what we now know as insulin therapy. Banting was the one who successfully isolated the internal secretion of the pancreas and managed to reduce blood sugar levels. Together, Banting and McLeod conducted trials and published their findings in 1922, marking a breakthrough that would eventually ease and prolong the lives of those with diabetes.

The following year, the two men were honored with the Nobel Prize. Here, you can see a picture of John James Rickard McLeod, along with Frederick Banting and Charles Best. The photo also captures the dogs on the rooftop of the University of Toronto's Frederick Banting and Charles Best Medical Building in 1922. These dogs played a crucial role as experimental subjects in the groundbreaking research on insulin.

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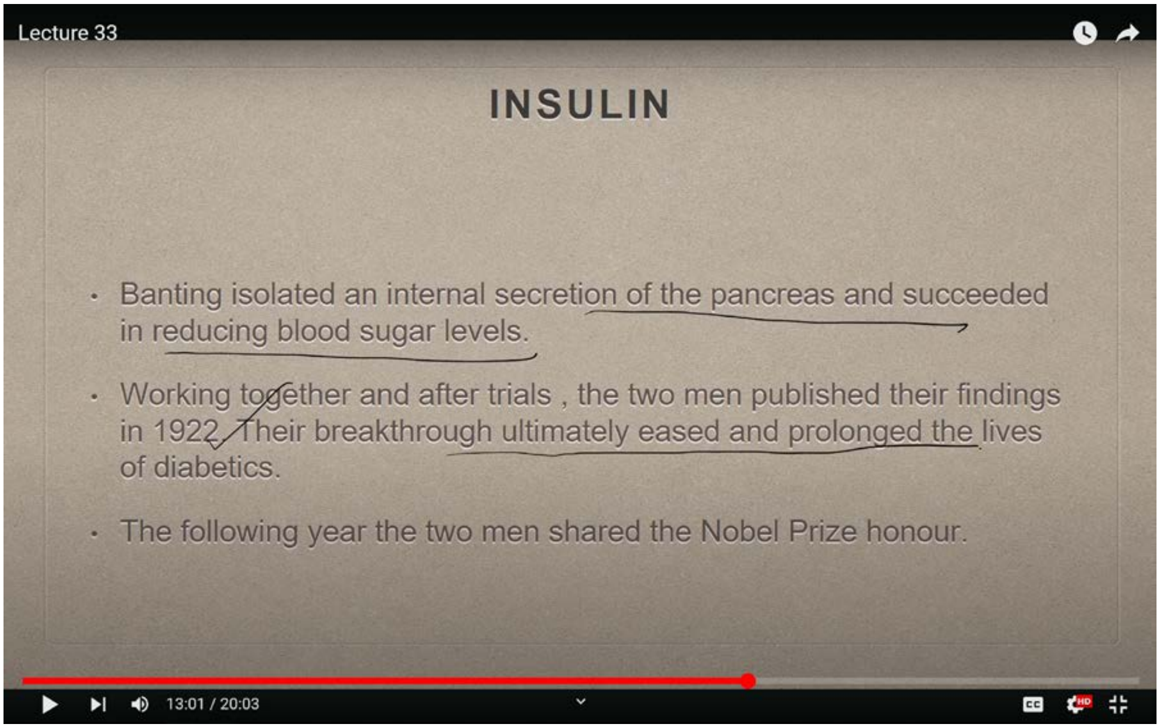

The story of insulin is a testament to the extraordinary efforts of these individuals. It's a narrative filled with good fortune, bad luck, successful and unsuccessful experiments, criticism from colleagues, personal conflicts, egos, and disagreements. Yet, despite all these challenges, science prevailed. Humanity will forever remember these classic experiments, especially the seminal one where, after a summer of numerous setbacks and failures, the team reported in the fall that they were able to keep a severely diabetic dog alive. This was achieved by injecting the dog with an extract made from the duct-ligated pancreas, prepared according to McLeod's instructions in saline. Remarkably, this extract dramatically reduced the blood sugar levels of the diabetic dogs used in the experiments.

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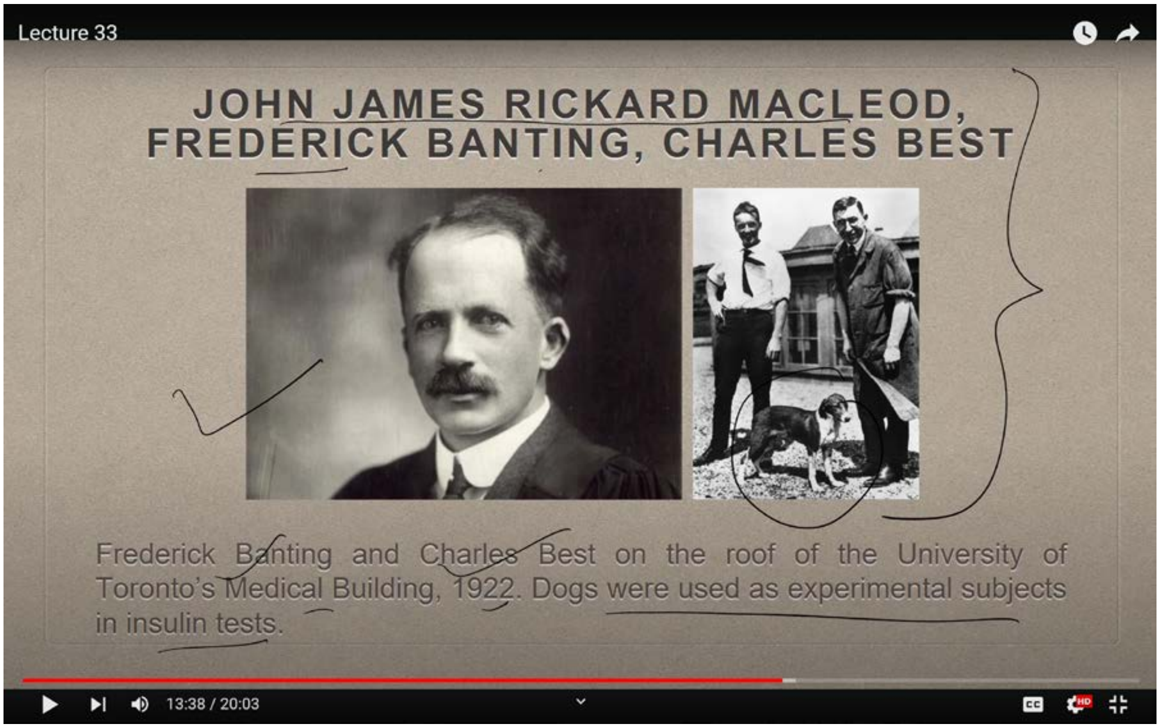

This crucial experiment was followed by another groundbreaking discovery, this time by James Bertram Collip. At the end of January, Collip approached Banting and Best in their lab and informed them that he had discovered a method to produce a pure extract of insulin. Collip's breakthrough involved purifying the extract by using alcohol at a concentration of just over 90%, which precipitated the active ingredient, insulin. This was a monumental discovery that significantly advanced our understanding of how to extract insulin, as well as how to purify similar compounds for therapeutic use. With the active ingredient in hand, it could be re-injected to test its efficacy as a treatment.

This brings us to an essential point, the next major goal was how the pharmaceutical industry could develop and synthesize these compounds outside of the body. This challenge laid the groundwork for future advancements, including the synthesis of insulin through organic chemistry or genetic engineering techniques. It's important to remember that at that time, DNA had not yet been discovered. The understanding of genes and DNA was just beginning to emerge, and it wasn't until the 1950s that Watson and Crick proposed their model of DNA structure, based on crystallographic images.

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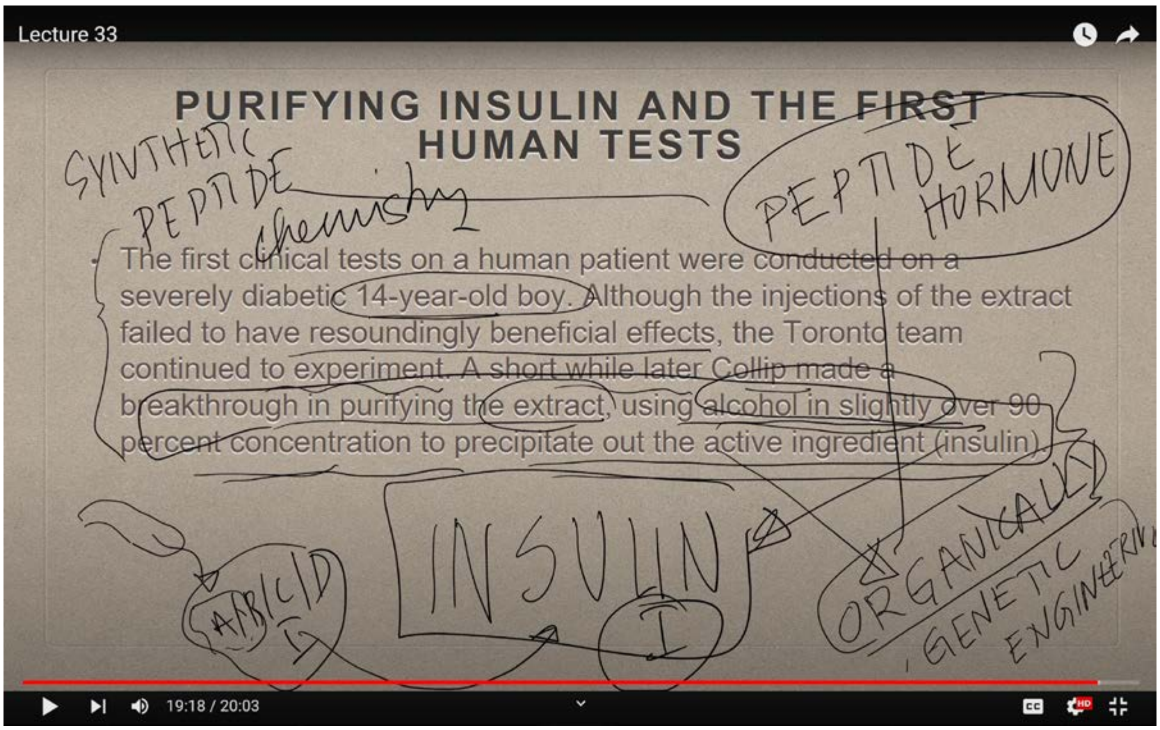

Reflecting on the last 103 years of insulin's history, we see how various other scientific discoveries, such as those in structural chemistry and biology, have evolved and influenced our current knowledge. In the next class, we'll explore the structure of insulin, the methods used to perform binding assays for insulin, and how these assays contribute to the development of various sensors for insulin detection. We'll also discuss the role of radioimmunoassay and ELISA (enzyme-linked immunosorbent assay) in quantifying insulin, and how insulin can be produced through organic synthesis.

When we talk about the organic route, we're referring to the synthetic production of insulin as a small peptide hormone. We'll delve into the methods of synthesizing it using synthetic peptide chemistry, followed by the revolutionary use of genetic engineering tools to produce insulin in large quantities. Despite the advancements, the production of insulin still presents significant challenges, especially as diabetes becomes more prevalent in society. We'll examine the ongoing efforts to reduce the cost of insulin production and how these efforts are shaping future research. So, with this, I will close this class and I will move on to the next class. Thank you.