Design for Biosecurity

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Lecture 32

Setting the Stage for the Discovery of Insulin

Welcome back to the next lecture. Today, we will delve into the events that set the stage for one of the most significant medical discoveries: insulin. As I previously mentioned, four key individuals played pivotal roles in this journey, leading to the 1923 Nobel Prize in Medicine. Now, here we are in 2024, 101 years later, and during this time, diabetes has escalated to epidemic proportions. But to truly understand the significance of this discovery, we must journey back to the 1800s, where the first clues linking insulin, pancreatic secretion, and diabetes began to emerge.

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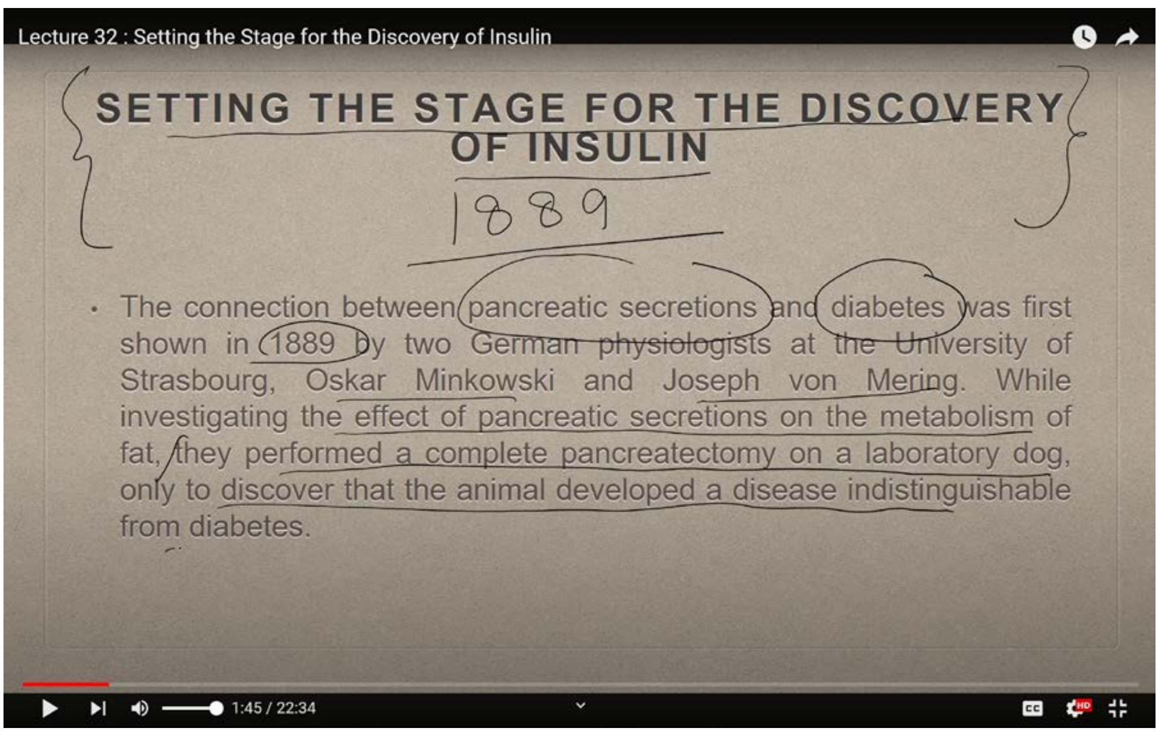

The critical connection between pancreatic secretion and diabetes was first identified in

1889 by two German physiologists, Oskar Minkowski and Josef von Mering, at the University of Strasbourg. While investigating the role of pancreatic secretion in fat metabolism, they performed a complete pancreatectomy on laboratory dogs. To their surprise, the animals developed a condition indistinguishable from diabetes. This was a time when animal ethics were not as stringent as today, and dogs, pigs, cats, and other relatively large animals were commonly used in scientific research.

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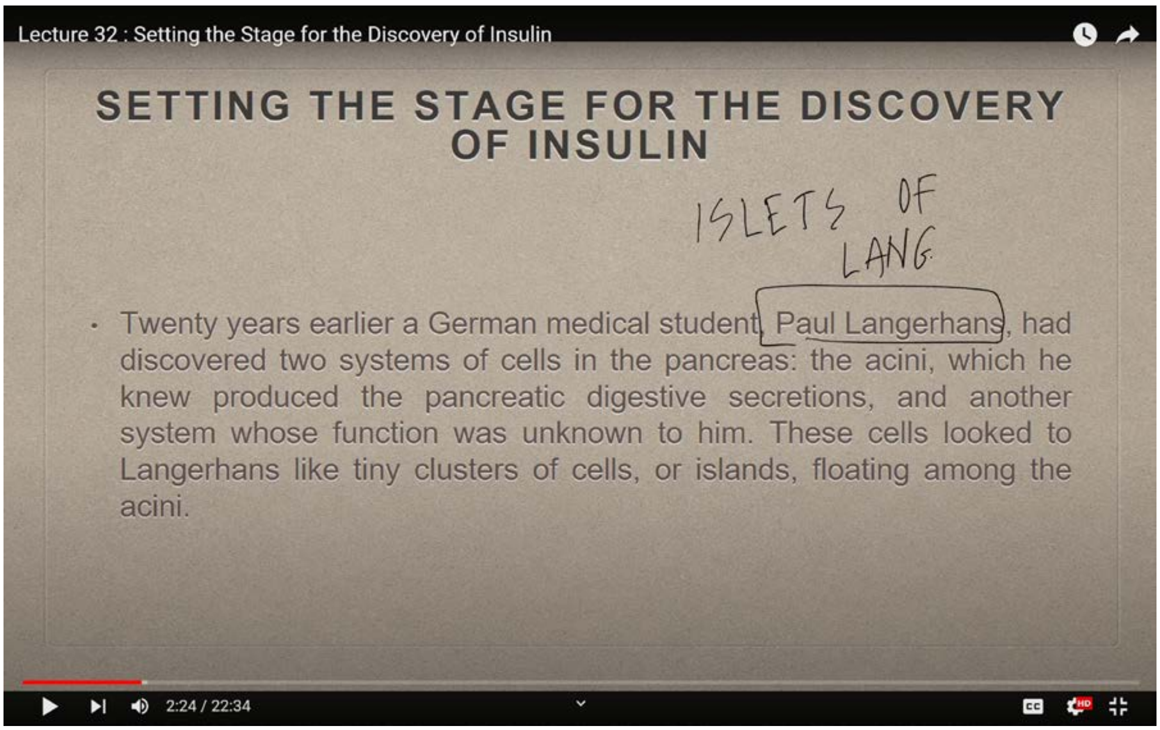

Now, let's rewind 20 years earlier. In 1869, a German medical student named Paul Langerhans, who would later lend his name to the cells we now know as the islets of Langerhans, discovered two distinct types of cells in the pancreas. The first type, known as acini, was already understood to produce pancreatic digestive secretions. The second type, however, remained a mystery to Langerhans. These cells appeared as tiny clusters, almost like islands floating among the acini, but their function was unknown to him at the time.

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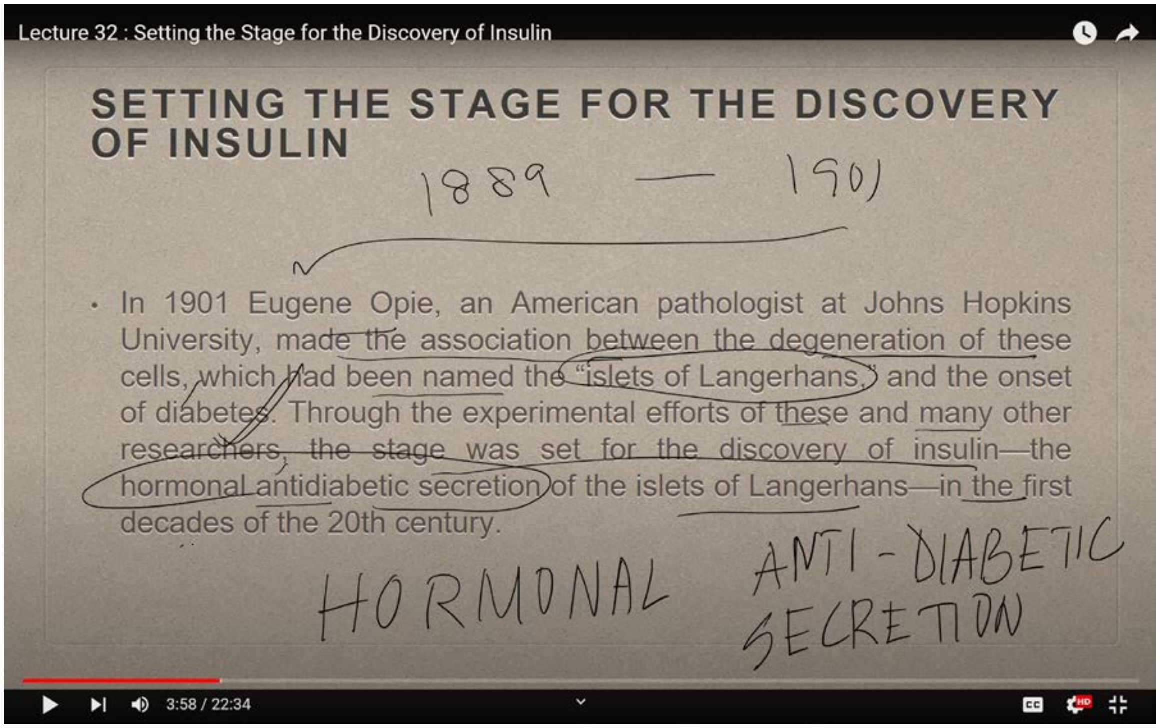

Fast forward to 1901, when Eugene Opie, an American pathologist at Johns Hopkins University, made a significant leap forward. He associated the degeneration of these mysterious cells, now named the islets of Langerhans, with the onset of diabetes. Through the tireless experimental efforts of these and many other researchers, the stage was set for the discovery of insulin, a hormonal anti-diabetic secretion produced by the islets of Langerhans. This terminology, "hormonal anti-diabetic secretion," is crucial as it underscores the biological significance of insulin in combating diabetes.

As with any groundbreaking discovery, certain prerequisites had to be met. The foundational work by Oskar Minkowski and Josef von Mering, followed by Paul Langerhans' identification of these enigmatic cells, and further advanced by Eugene Opie's insights, all set the stage for what was to come.

By 1920, the pieces were falling into place. Frederick Grant Banting, a struggling surgeon in London, Ontario, Canada, emerged as a key figure. The youngest son of a Methodist farmer in Alliston, Ontario, Banting almost pursued a career in the Methodist ministry.

However, he ultimately felt a stronger calling toward medicine. It was during World War I that Banting’s medical education was accelerated, reducing his five-year course at the University of Toronto.

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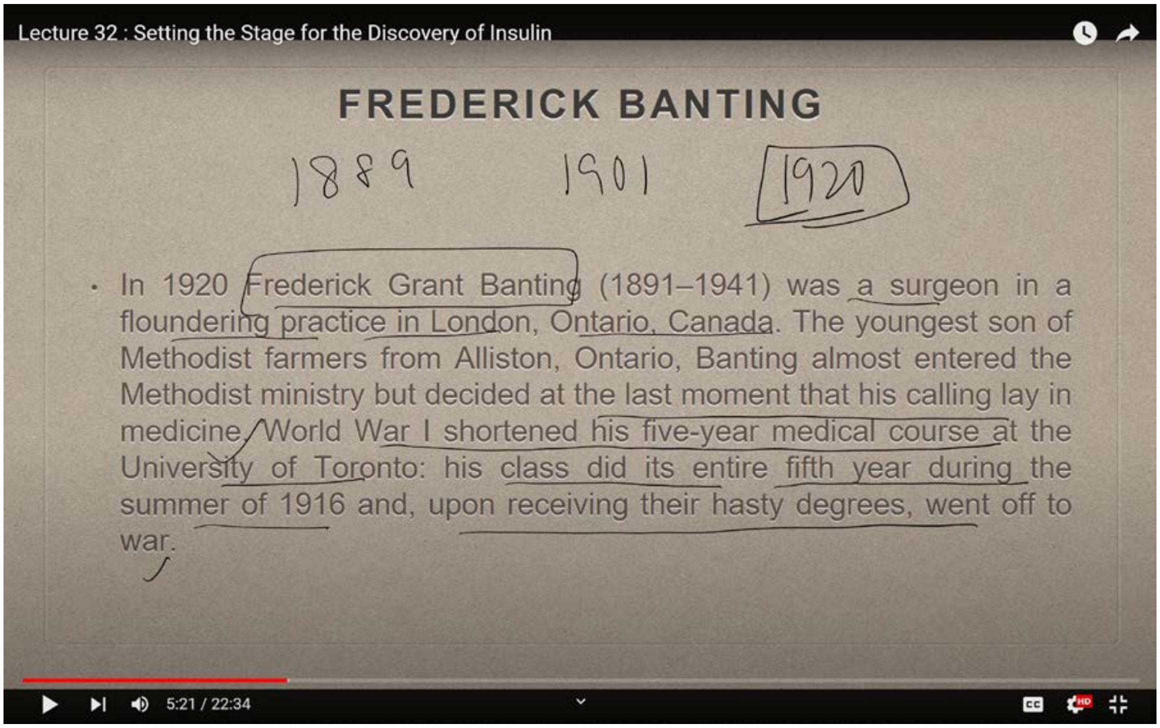

During the summer of 1916, Banting's entire class completed their fifth year of medical training in a rush, receiving their degrees hastily before heading off to war. It’s easy to assume that the lives of scientists are linear, as if they always knew their path from day one, but in reality, their journeys are often filled with challenges and setbacks. Banting was no exception.

Banting served as a medical officer in the Canadian Army Medical Corps during World War I. In 1919, after being wounded by shrapnel in his arm, he returned to Toronto. He then trained as a surgeon at the Hospital for Sick Children, but eventually decided to open a small surgical practice in London, Ontario. Unfortunately, his practice didn’t generate enough income, forcing him to accept a position as a demonstrator at the local medical school. It was in this role, on October 30, 1920, while preparing a lecture on the function of the pancreas, that Banting had a fateful moment.

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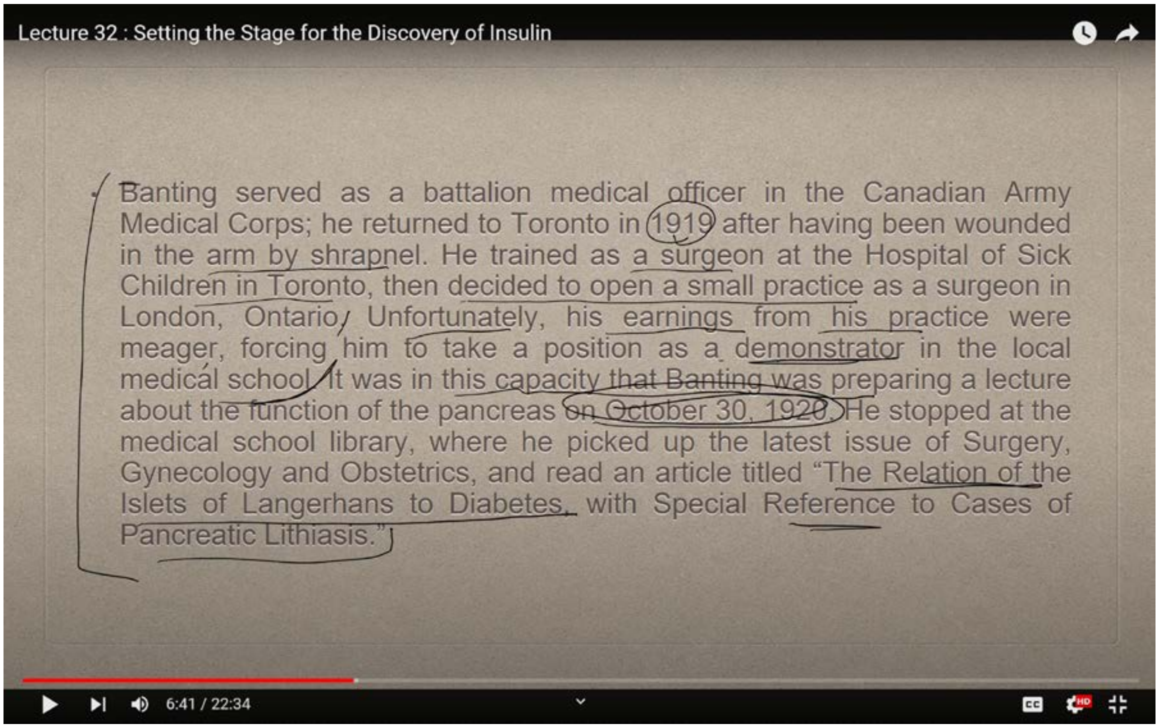

While in the medical school library, Banting came across the latest issue of Surgery, Gynecology, and Obstetrics. Inside, he read an article titled The Relation of the Islets of Langerhans to Diabetes, with Special Reference to the Cases of Pancreatic Lithiasis. This moment sparked his imagination. Despite a life that had veered from nearly becoming a missionary to experiencing the horrors of war, followed by a less-than-successful private practice, Banting now found himself inspired by this article. His interest in the pancreas reignited, and he began formulating an idea for an experiment to further explore the relationship between pancreatic secretions and diabetes.

On November 7, Banting, encouraged by a colleague, approached John James Richard Macleod, a prominent Scottish physiologist and an expert in carbohydrate metabolism at the University of Toronto. Macleod had published numerous papers on glycosuria (the presence of sugar in urine), a key symptom of diabetes. When Banting presented his idea, however, Macleod was unimpressed. Banting's knowledge on the topic was limited, and

Macleod, being deeply familiar with the literature on diabetes, was highly skeptical of the soundness of Banting's proposal.

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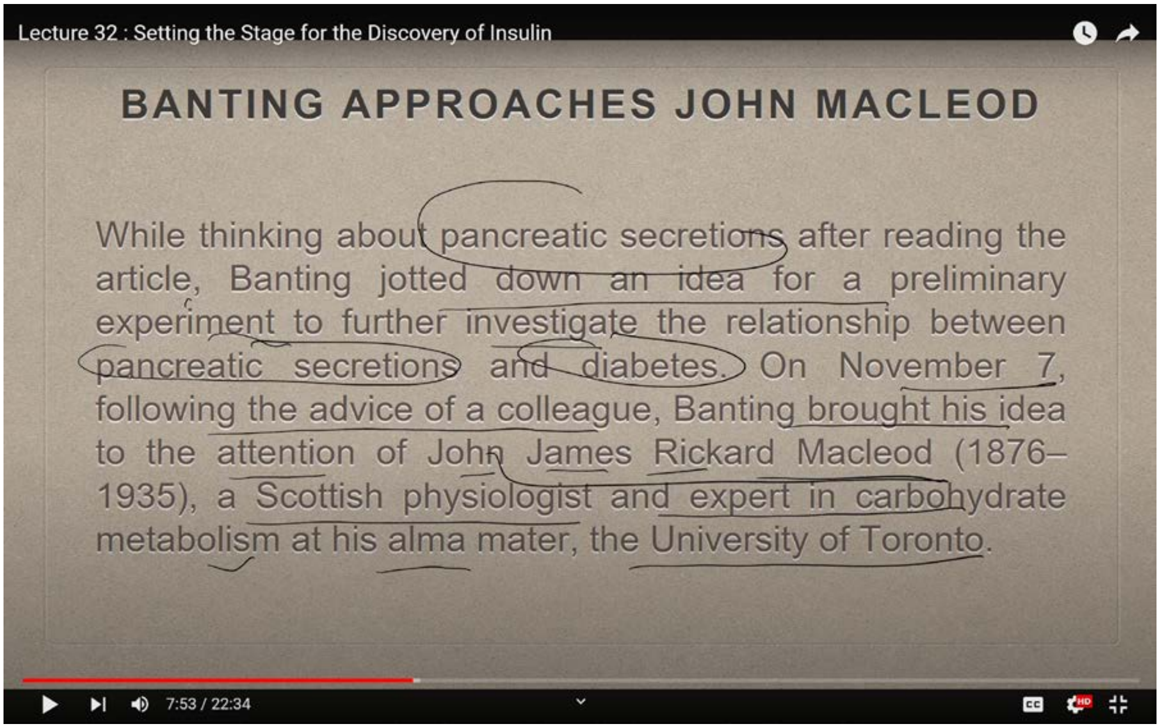

This kind of skepticism is not uncommon in scientific circles. Scientists often have their own strong opinions and can be quick to dismiss ideas that seem underdeveloped or lack solid grounding. But here's the thing: if you truly believe in your idea, you shouldn't be easily discouraged. Even the most groundbreaking ideas often start out as seemingly foolish notions. Banting himself, despite his lack of expertise, eventually won a Nobel Prize for his work on insulin alongside Macleod, even though Macleod had initially been doubtful of his idea.

Banting's theory may have seemed far-fetched, but he had a clear vision about the connection between the pancreas and diabetes that he was determined to explore. Against

all odds, Macleod ultimately decided to give Banting a chance. Despite his initial skepticism, Macleod provided Banting with a laboratory space, an assistant, and access to laboratory dogs for his experiments, allowing him two months at the end of the academic year to pursue his idea.

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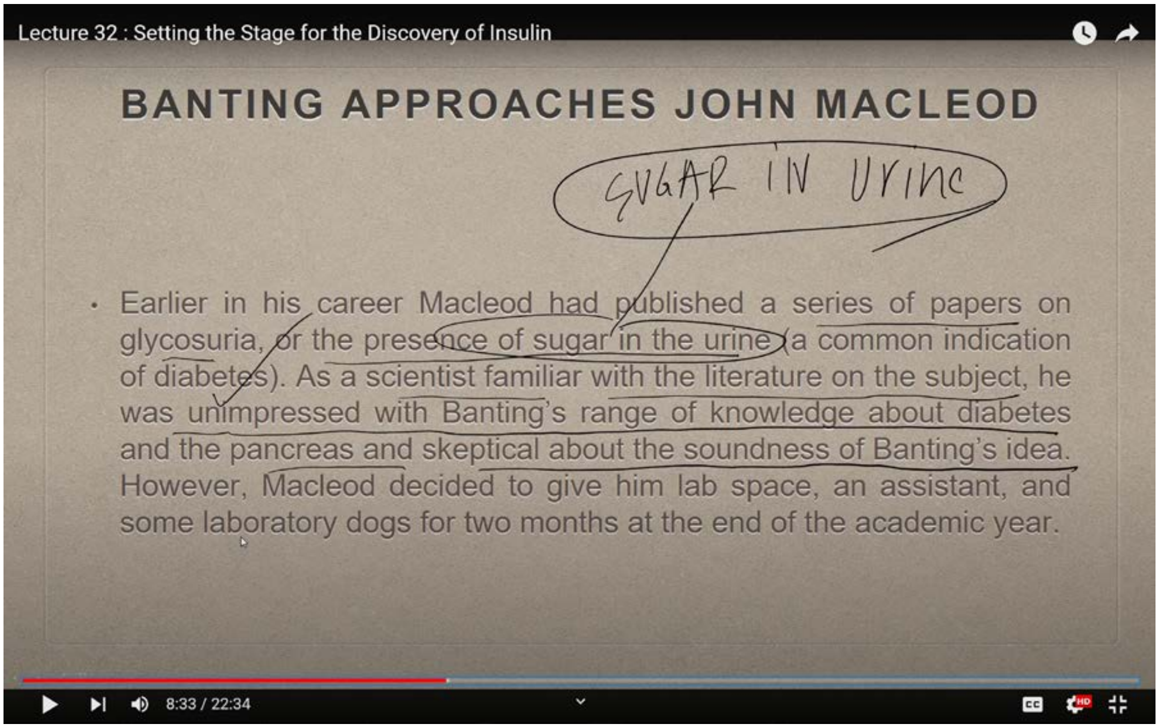

Banting now had the essentials: experimental animals, a modest laboratory space, a trained assistant, and perhaps even some funding. Despite his skepticism, Macleod supported Banting's efforts, although he remained unconvinced by Banting's proposed experimental approach. It's important to keep that in mind: Macleod, though a supporter, had his doubts.

Let's take a moment to delve into Macleod's background. He was the son of a minister and received his medical education at the University of Aberdeen in Scotland. Later, he pursued biochemical training at the University of Leipzig in Germany. In 1903, Macleod emigrated to the United States, where he took a position as a professor of physiology at Western Reserve University, what is known today as Case Western Reserve University in Cleveland, Ohio. After spending 15 years there, he moved on to accept a professorship at the University of Toronto, where his research focused on respiration. So, to summarize, Macleod's journey took him from Scotland to Germany, then to the United States, and finally to Canada. He was truly a man on the move, a "rolling stone" in the world of science, constantly exploring new ideas.

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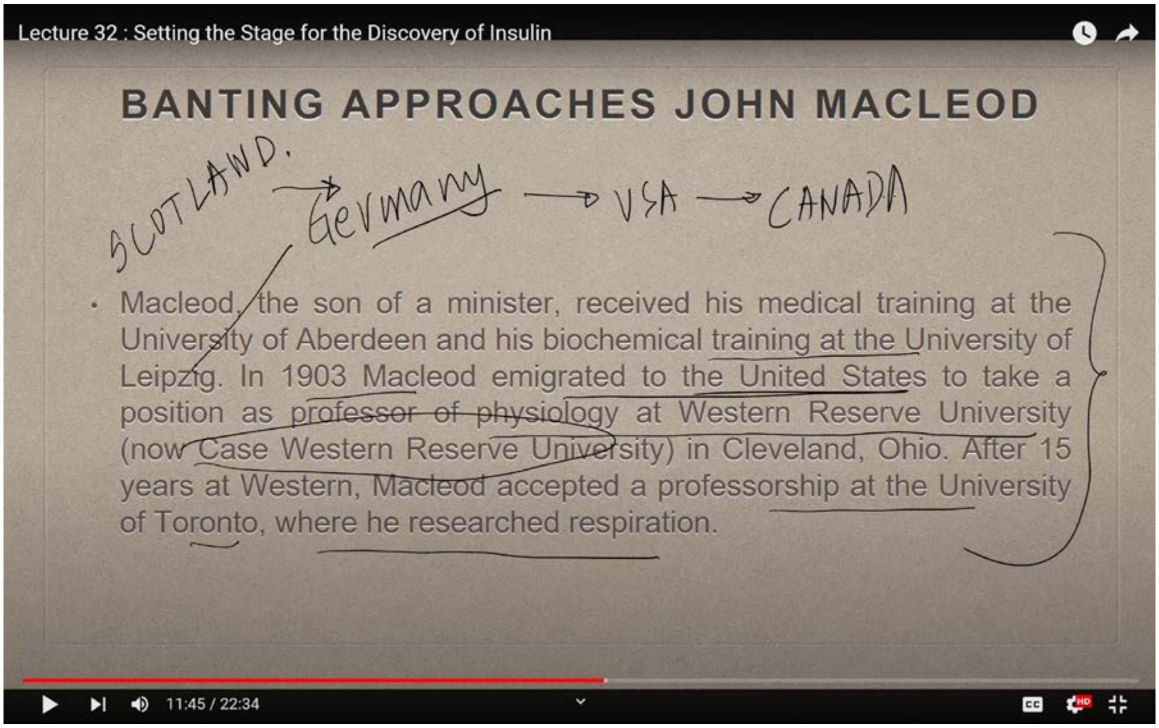

With this background established, Banting’s experiments began. His partner in this endeavor was Charles Herbert Best, and here is where the story broadens to include the other key figures in this discovery. So far, we've discussed Frederick Banting and John Macleod. Now let me introduce the third member of this quartet: Charles Herbert Best. The fourth member, James Collip, will come into play a little later.

Charles Best joined the experiment in May of 1921. Best, born in America to Canadian parents, had just completed his bachelor's degree in physiology and biochemistry at the University of Toronto. He had been hired as a research assistant to Macleod, who was his former professor, and was then assigned to work alongside Banting. Thus, the 29-year-old surgeon and the 22-year-old assistant, Charles Best, began their collaboration. This marked the beginning of one of the most significant medical breakthroughs in history, one that would forever change the trajectory of diabetes treatment in a positive direction.

It’s interesting to note that this success was the result of both timing and a stroke of luck.

While Banting and Best were making their strides in Toronto, scientists in Germany and Hungary had come remarkably close to isolating pure insulin. However, a lack of resources and the devastation brought by World War I had hindered their progress. Consequently, it was the Toronto team that became the first to announce the discovery of insulin, a discovery that would change countless lives.

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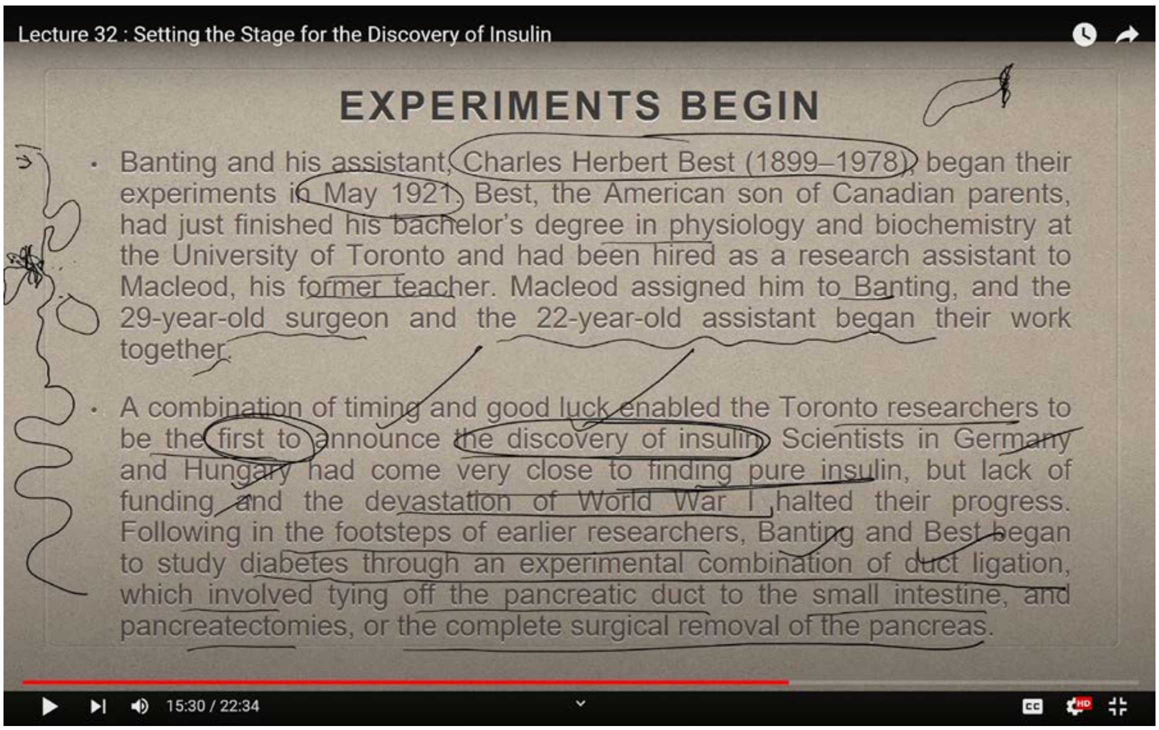

Consider how war can impact scientific research: it can either advance or impede it, depending on whether the research aligns with the priorities of the wartime agenda. During periods of conflict, if your scientific work is deemed a priority, it may receive support and flourish. Conversely, if it does not align with wartime priorities, it may be sidelined. This was precisely the situation in 1919, during the First World War.

At that time, researchers in Germany and Hungary had just begun to make strides in reporting their findings, but their progress was abruptly halted due to the war. In response, Banting and Best continued the work of their predecessors by exploring diabetes through experimental methods that involved duct ligation and pancreatitis.

Duct ligation involved tying off the pancreatic duct, which prevents the digestive secretions from reaching the small intestine. To visualize this, imagine the pancreas as an organ that secretes important enzymes. If you block the duct, you stop the flow of these secretions. Alternatively, pancreatitis or the complete surgical removal of the pancreas was another method used. Removing the pancreas entirely was a more drastic approach, but it allowed researchers to observe the effects of its absence.

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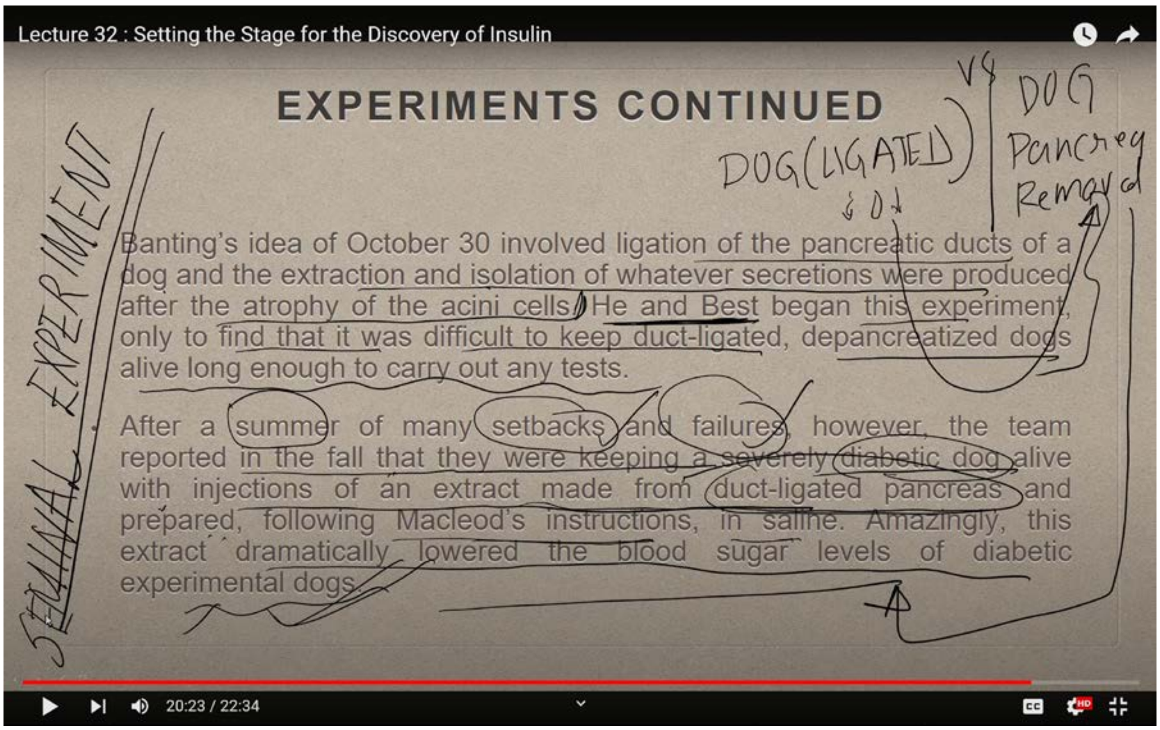

In their experiments, Banting and Best observed that duct ligation led to the atrophy of the acinar cells, those that produce digestive enzymes, leaving only the islet cells behind. Remarkably, dogs with ligated ducts did not develop diabetes, while dogs subjected to pancreatomy (removal of the pancreas) immediately showed signs of glycosuria. Glycosuria, as noted in earlier research by McLeod, is the presence of sugar in the urine, a classic indicator of diabetes.

Thus, their experiments revealed that the absence of pancreatic tissue resulted in diabetes, while the duct ligation, though it restricted the flow, prevented the onset of the disease.

In contrast, completely removing the pancreas means there would be no pancreatic secretion at all. This period, the 1920s, was marked by such groundbreaking experiments, which were conducted on dogs, now a century ago. Banting's idea from October 30th involved ligating the pancreatic duct of a dog and then isolating any secretions produced after the atrophy of the acinar cells. However, Banting and Best encountered significant challenges. They found it difficult to maintain the duct ligation for extended periods, and the surgically altered dogs struggled to survive long enough for thorough testing.

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The challenge of keeping the duct ligated was substantial; each attempt required multiple surgeries to ensure the duct remained sealed and to prevent infections, while also ensuring the dog’s survival. After enduring a summer of numerous setbacks and failures, the team managed to report in the fall that they had successfully kept a severely diabetic dog alive using an extract made from the duct-ligated pancreas, prepared according to McLeod’s instructions and dissolved in saline. Remarkably, this extract dramatically reduced the blood sugar levels of the diabetic dog.

Imagine the scenario: you have a limited number of dogs, large animals, and in some cases, you ligate the pancreatic duct, resulting in minimal secretion. In other cases, you completely remove the pancreas and collect whatever residual secretion remains from the duct-ligated pancreas. This extract was then injected into the diabetic dogs. After a summer of dealing with dead animals and failed results, the team finally achieved a breakthrough. The injective extract from the duct-ligated pancreas successfully lowered the blood sugar levels of the diabetic experimental dogs, demonstrating the potential of their innovative approach.

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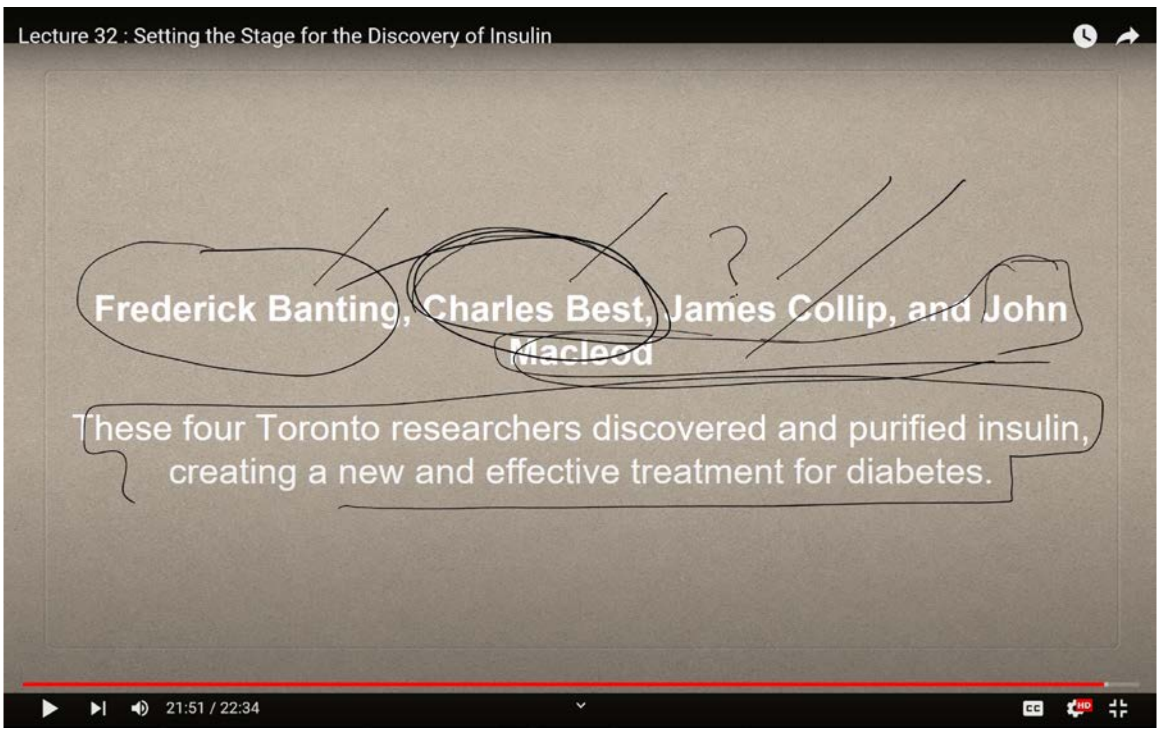

Despite numerous failures, the team made a significant breakthrough in the fall of 1921, from August to December. They succeeded in keeping a severely diabetic dog alive using an extract derived from a duct-ligated pancreas, prepared in saline following McLeod's instructions. This extract astonishingly reduced the blood sugar levels of the diabetic dogs, marking a pivotal moment in medical history.

This experiment from 1921, which was over a century ago, was groundbreaking. It altered the trajectory of diabetes treatment and had a profound impact on human health. It was a testament to the life-saving potential of insulin therapy, a crucial development in the fight against diabetes. As reflected in the tribute to John McLeod, where it states that many owe their lives to insulin, this discovery was truly transformative.

The same molecule that could save lives also had a darker side, demonstrating how insulin could be used both to sustain life and, tragically, to end it. In our next class, we will continue the story of Frederick Banting and Charles Best, and we will also introduce James Collip and John McLeod, exploring their roles in this remarkable journey. So let's move on to the next class and discuss it. Thank you.