Design for Biosecurity

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Lecture 31

Story of Insulin

Welcome back to the lecture series on design for biosecurity. This week, we'll begin with a recap of what we've covered so far, and then dive into our final case study: insulin. But before we explore insulin, let's reflect on how our journey began.

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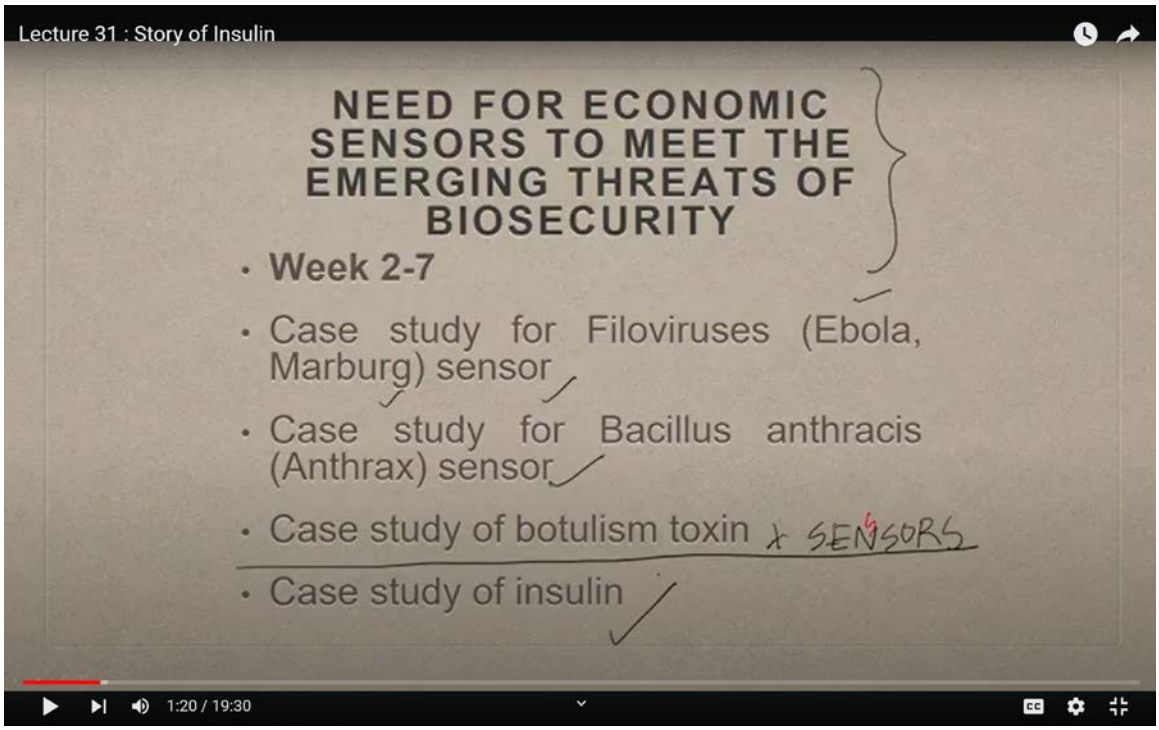

At the outset, I emphasized the urgent need for cost-effective sensors to address the growing threats to biosecurity. This has been a recurring theme since the second week of our discussions. Over the past weeks, we've examined various biosecurity threats and the corresponding detection technologies.

We started by discussing the filoviruses that cause Ebola and Marburg. We explored

sensors for detecting these viruses, moving next to Bacillus anthracis, the bacterium responsible for anthrax. We examined anthrax sensors in detail, and finally, we delved into botulinum toxins and the sensors designed to detect these deadly substances. Our exploration of these sensors culminated last week, which brings us to today's focus, insulin.

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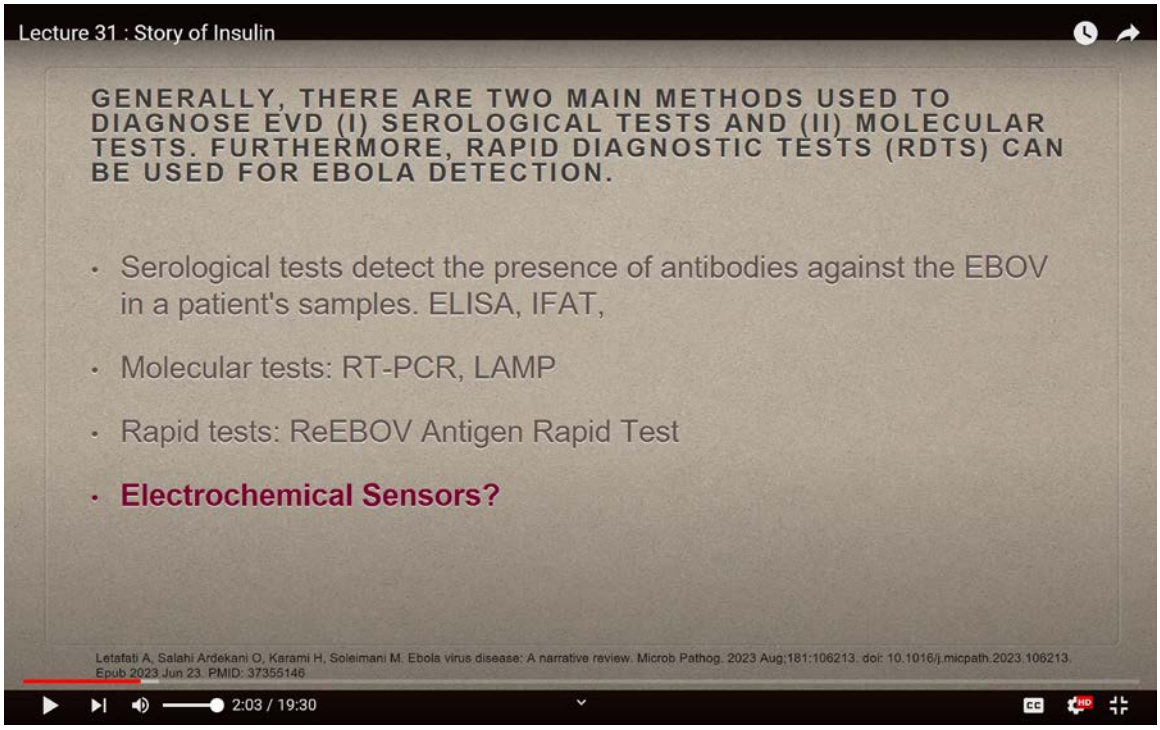

Before I delve into the insulin case study, let me take you through our journey once again, specifically our work on Ebola. I suggested you read Richard Preston's The Hot Zone, which gives a gripping account of the Ebola virus. We examined how the virus was first identified, its epidemic spread, and its zoonotic transmission pathway, from animals to humans. We also studied how the virus enters the human body, its ability to persist in various environments, and its genome structure. We discussed its devastating effects, particularly hemorrhagic fever, along with other severe symptoms. Following this, we reviewed the range of sensors that have been developed to detect the virus. We also mapped out the geographic spread of the epidemic across different countries.

After Ebola, we shifted our focus to anthrax. Our discussion began with the 2001 anthrax

attacks in the United States. We examined how anthrax spores persist in the environment and can be transmitted to humans. We explored the different types of anthrax infections, cutaneous, inhalation, and gastrointestinal, and the symptoms associated with each. We also looked at methods of prevention, particularly in high-risk occupations. Our global and local perspectives on anthrax included an anthrax map spanning three continents. We considered why anthrax is such a potent bioterrorism agent, tracing its use in a bioterror attack that occurred in the last 25 years. This led us to a detailed account of the FBI's involvement in the investigation of that attack.

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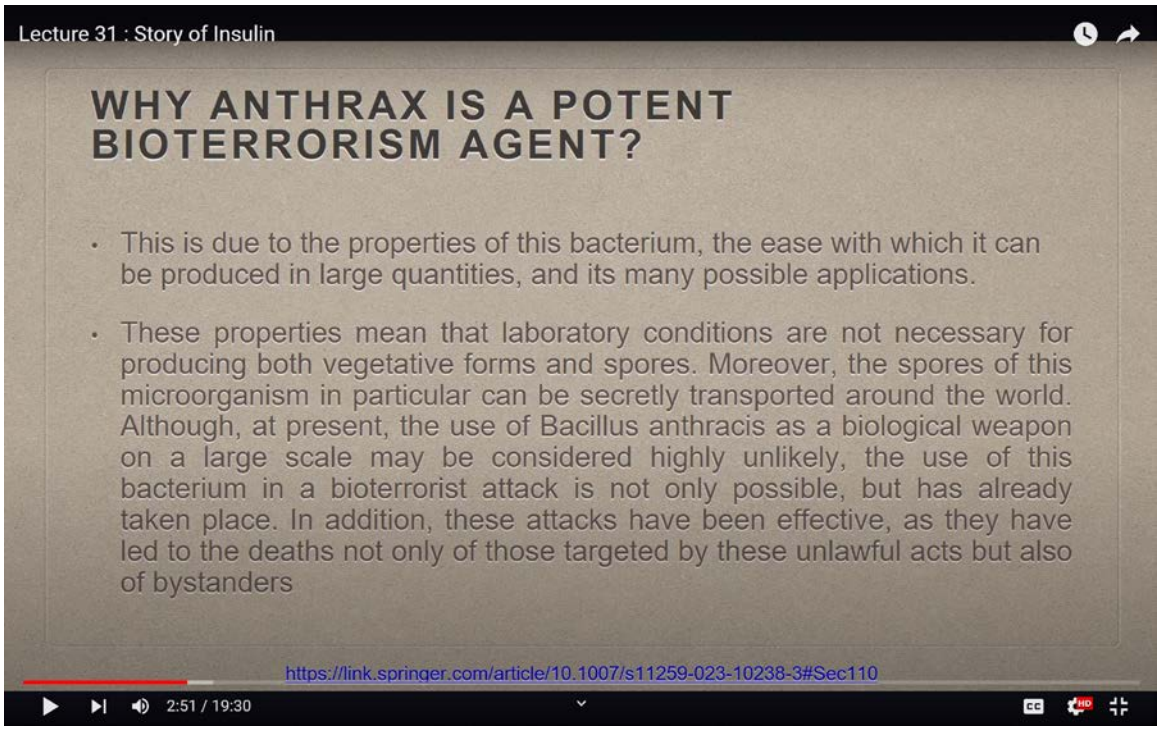

From there, our focus shifted to anthrax detection methods, and we explored the relevant sensor technologies. Specifically, we looked at the Rayleigh equation and quartz crystal microbalance, which are instrumental in detecting anthrax spores.

After that, we explored the different configurations of Quartz Crystal Microbalance (QCM). We then transitioned into the theory behind QCM and examined how QCM can be coupled with electrochemical setups to enhance sensor capabilities. Following this, we

delved into Atomic Force Microscopy (AFM), focusing on its various applications in sensor technology. We covered the distinct modes of AFM: contact mode, non-contact mode, and intermittent mode, providing a detailed analysis of how each operates.

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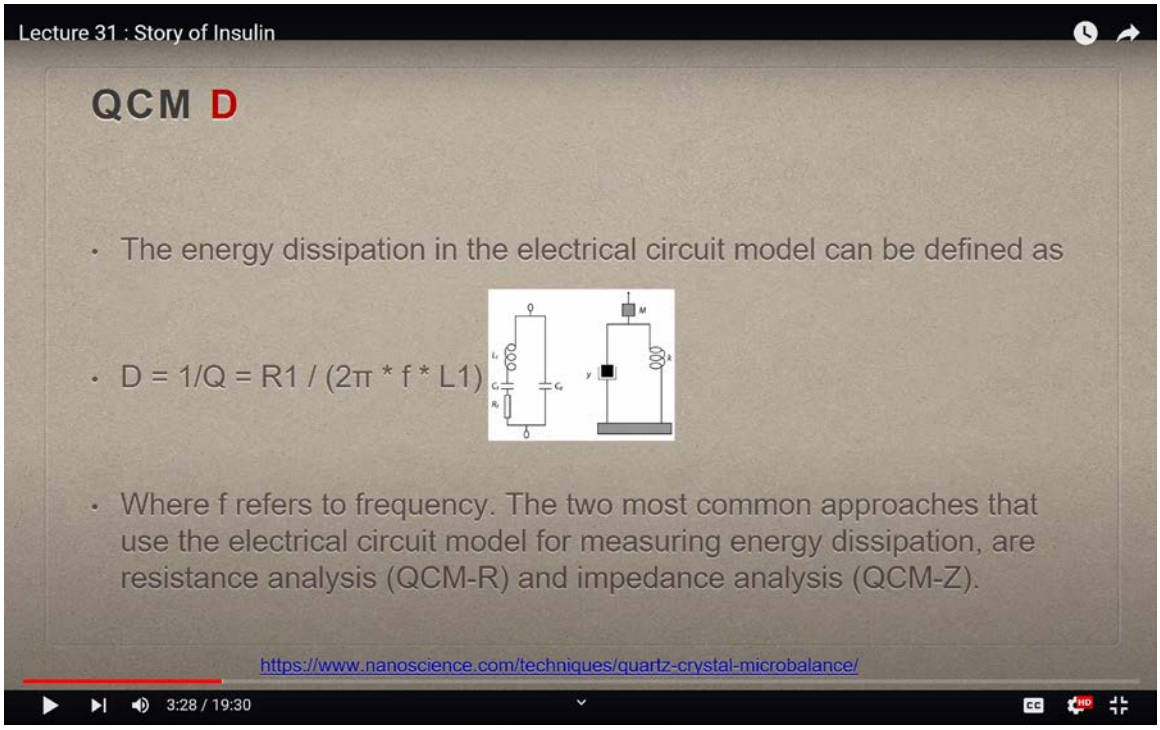

Our discussion then shifted to infrared scattering scanning and near-field optical microscopy, which led us into the world of near-field Raman imaging. We also explored the concept of tapping-mode AFM combined with infrared (IR) technology, followed by a comparison between Raman spectroscopy and IR spectroscopy. I provided a quick recap to solidify these concepts, where we discussed Raman shift and emphasized the key differences between Raman and IR spectroscopy.

One of the charts I presented illustrated the identification of various molecular moieties within this process and highlighted the complementary nature of Raman and IR spectroscopy. We then discussed the applications of Raman imaging, particularly in sensor development, and touched on laser selection for Raman spectroscopy, identifying the specific challenges associated with eliminating fluorescence from Raman spectra.

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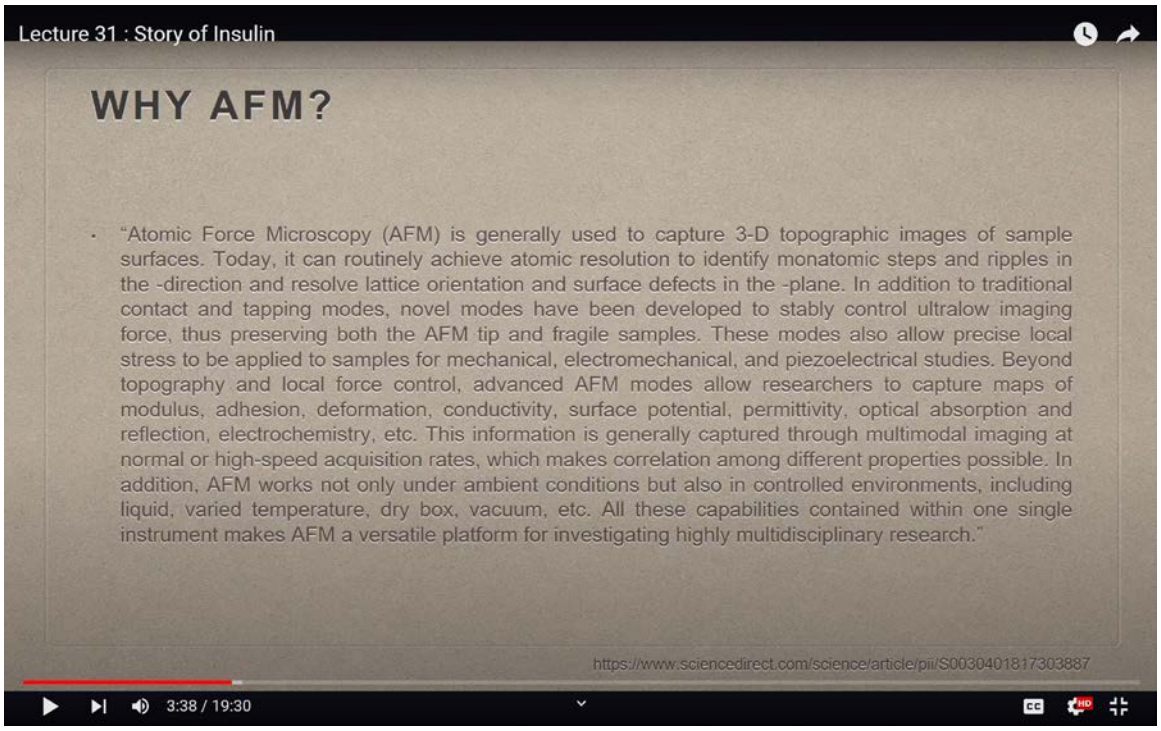

Moving forward, we covered AFM integrated with electrochemical workstations, a technology that is steadily being miniaturized and gaining popularity worldwide. Following this, we discussed the recognition elements used in biosensing: monoclonal antibodies, peptides, aptamers, epitopes, and phage display. We compared monoclonal and polyclonal antibodies, focusing on the production of monoclonal antibodies using two major techniques: the hybridoma technique and the phage display method.

Next, we examined smaller elements of antibodies, such as the single-chain variable domain (scFv). We then returned to aptamers and phage display, moving on to surface plasmon resonance (SPR). SPR, as we discussed, is a label-free detection method that is rapidly becoming more user-friendly and spurring numerous innovations. We also examined how SPR events are measured, specifically the shift observed due to molecular binding on the chip surface.

From there, we discussed the design and fabrication of lateral flow immunoassays (LFIAs). We covered all aspects of microfluidics within LFIAs, explaining how these assays work.

We also addressed the various types of assays, competitive assays, sandwich non-competitive assays, along with positive and negative controls and other essential components.

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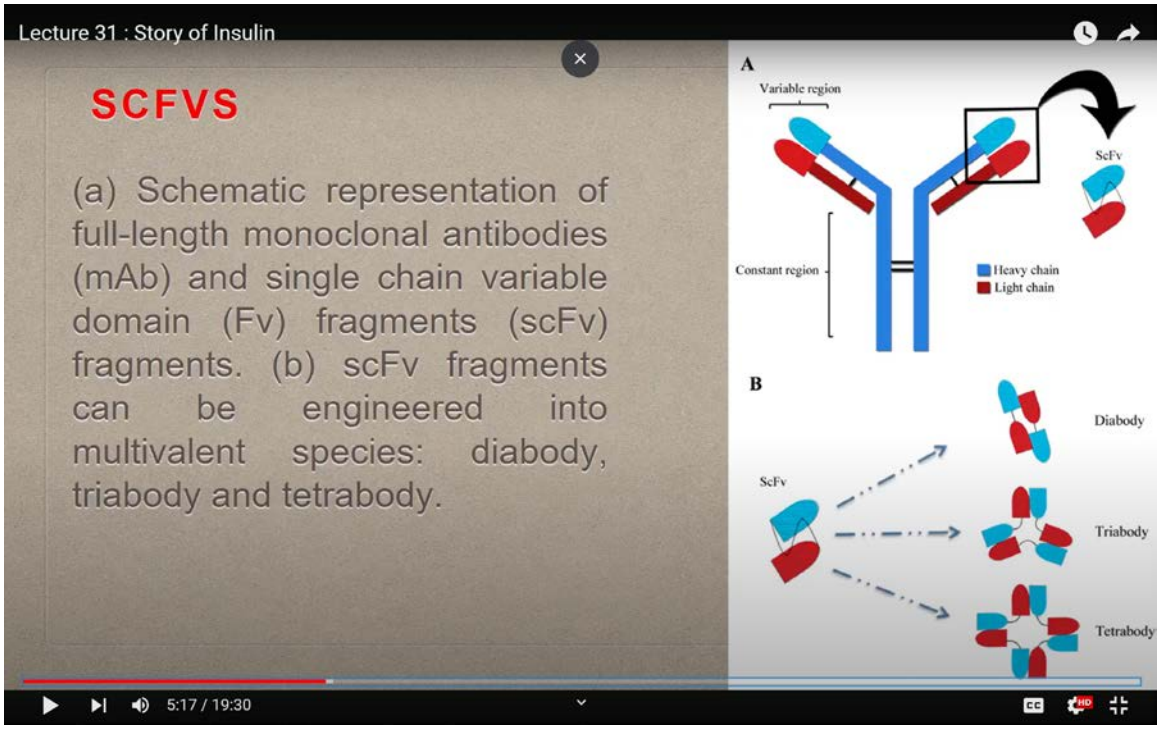

Shifting gears, we focused on botulinum toxin, discussing its transmission, key case studies, and critical points. We provided an overview of botulism, detailing the symptoms of foodborne botulism, as well as other forms of the disease, including infant botulism, wound botulism, and inhalation botulism. Whenever inhalation botulism comes up, it signifies that botulinum toxin is a potent bioterrorist agent. We also explored other types of intoxications and, finally, touched on an interesting application of the toxin: Botox therapy, which has therapeutic uses beyond its notorious reputation.

We began by discussing how botulinum toxin, widely known for its use in Botox therapy, plays a significant role in the fashion and beauty industry. We covered the different types of Botox injections, particularly types A and B, and explored the benefits of Botox therapy. We then moved on to examine the crystal structure of botulinum toxin, diving deeper into

its mechanism of action. Specifically, we looked at how the toxin targets the synaptic zone, enters the neuron, and cleaves the SNAP-25 protein, effectively disabling it. This led us to discuss how the cleaved segments of SNAP-25 are repurposed for developing biosensors, especially electrochemical and SPR-based immunoassays, which enable multi-analyte detection.

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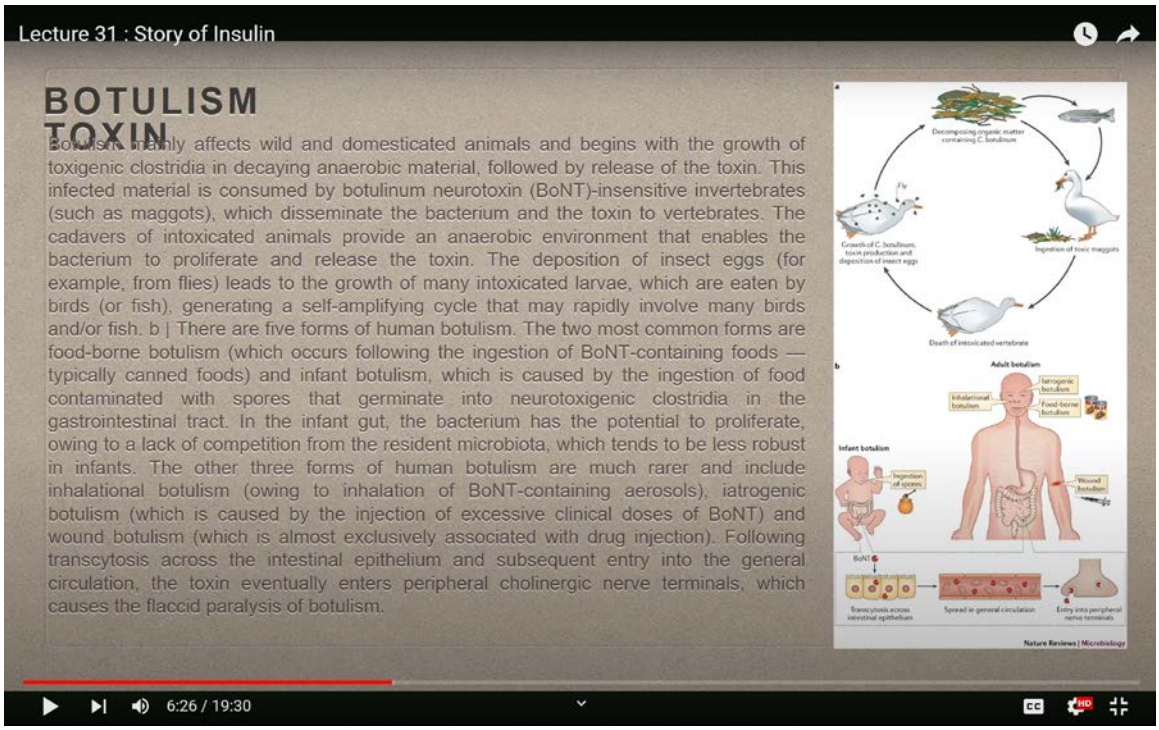

One key example was the electrochemical assay where methylene blue acts as an electroactive agent, and by cleaving the SNAP-25 structure, we observe a corresponding drop in the electrical signal. We then transitioned to a discussion on SPR assays, which are pivotal in the detection of botulinum toxin. We reviewed how the toxin acts specifically on SNAP-25 and detailed the process by which SPR assays detect this interaction and produce a signal.

From there, we moved on to immunoassay chips designed for the simultaneous detection of multiple toxins. For instance, in cases where both botulinum toxin and staphylococcal enterotoxin B are present in food, these assays become crucial for identifying

contaminants. In our previous class, we wrapped up by discussing various food sources that could harbor botulinum toxin and the growing need for multi-analyte detection in the food industry.

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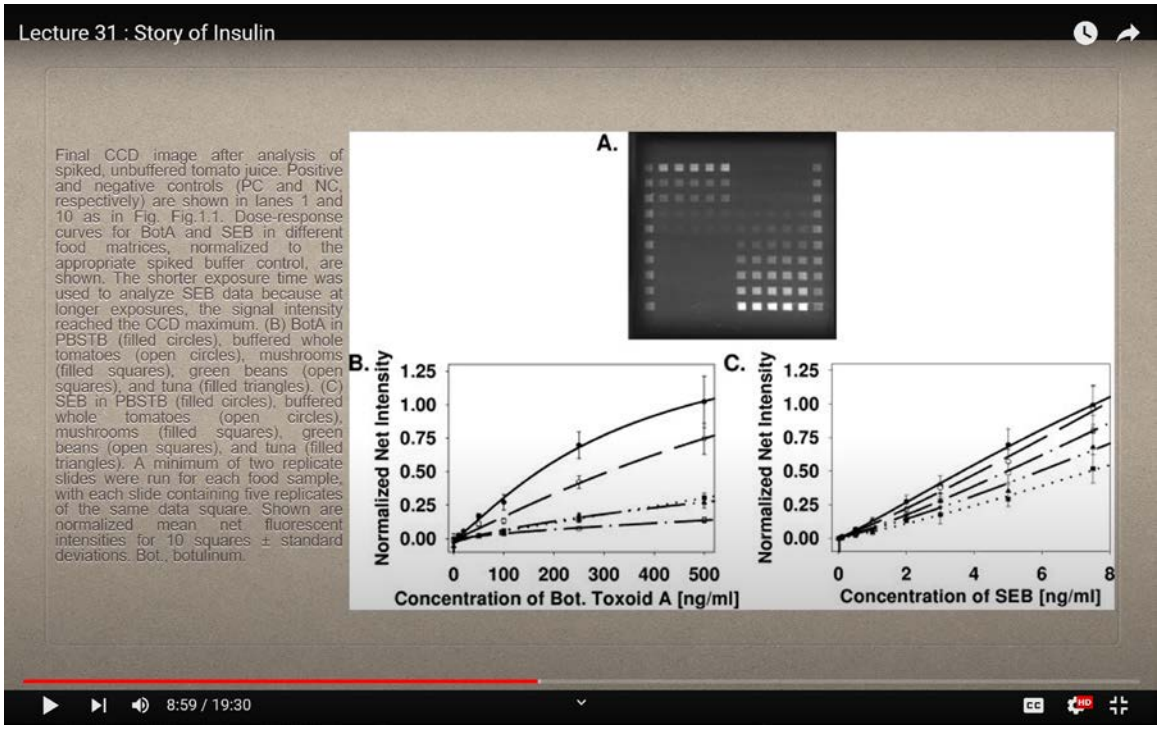

Reflecting on this journey, we've covered a wide range of microbial agents, including viruses, bacteria, and spores, exploring how they function and affect human health. Now, we are shifting our focus to a compound with an entirely different, yet equally significant, role, a molecule that has the potential to save lives, but also, in some cases, take them: insulin.

Insulin, a molecule produced by the human body, is central to managing diabetes, a condition that is alarmingly prevalent in India, which is often called the diabetes capital of the world. Diabetes has reached epidemic proportions, with various theories attributing its rise to factors such as lifestyle changes and dietary habits. Regardless of the causes, the reality is that diabetes poses a significant public health challenge, and when we think of diabetes, one of the first things that comes to mind is insulin therapy.

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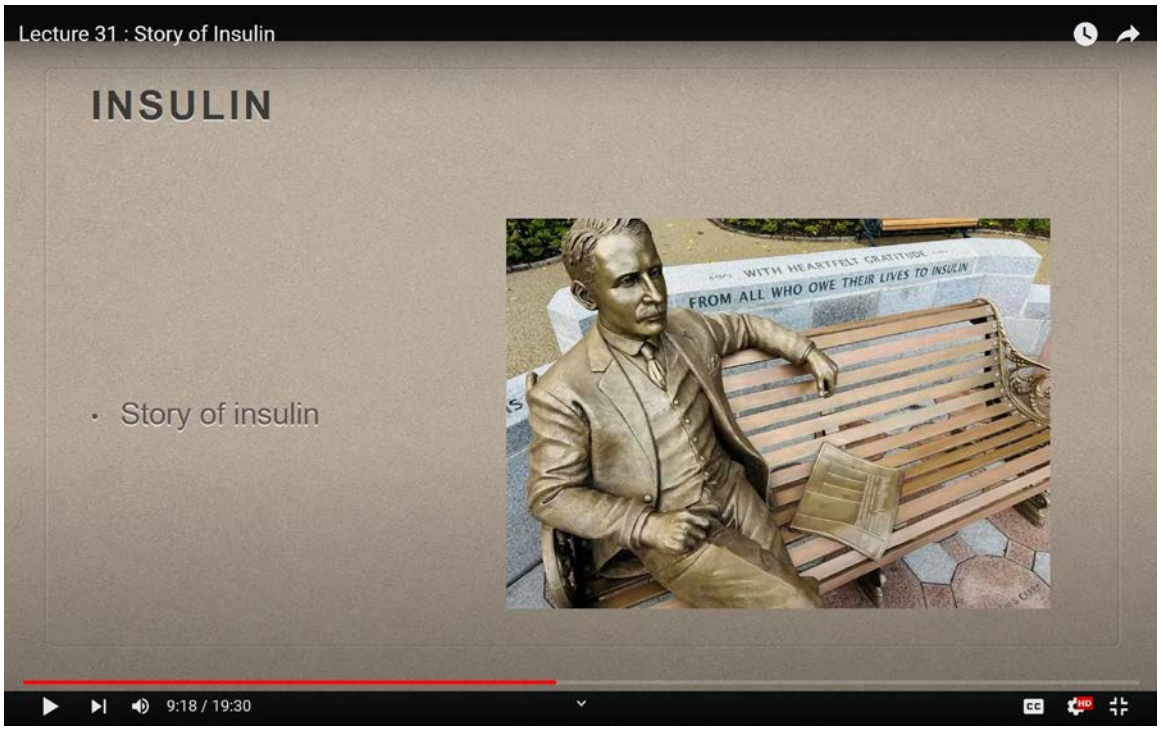

Insulin therapy is crucial for many diabetes patients, as their bodies are either unable to produce insulin or cannot effectively metabolize sugar. Over the next few classes, we will work to unravel the mysteries of insulin. I understand that many of you come from diverse academic backgrounds, so my goal is to make the story of insulin accessible and clear to everyone.

The history of insulin spans over 150 years and is rife with scientific breakthroughs, controversies, and dramatic turning points. The discovery of insulin and its subsequent use as a treatment for diabetes is a story filled with intrigue. It includes the lives of the scientists behind the discovery, the controversies surrounding them, and the recognition they received with the Nobel Prize, the highest honor awarded to scientists. The story also touches on how pharmaceutical companies, particularly one giant, Eli Lilly, played a role in the commercialization of insulin, and how this revolutionized the lives of diabetes patients.

However, as insulin became more widely used, the cost of insulin therapy began to take a

toll on patients, raising concerns about the economic burden faced by those who depend on it for survival. There are also different types of diabetes, Type 1 and Type 2, and we will explore what differentiates these conditions. Moreover, from the 1950s until today, there have been highly controversial cases involving the use of insulin as a murder weapon, illustrating that insulin, while life-saving for many, can also be deadly in the wrong hands.

In the upcoming classes, we will work to demystify the story of insulin, its discovery, its impact on medical science, and the controversies that have followed it throughout history. On the slide, you'll see a model, written by all who owe their lives to insulin, with heartfelt gratitude, symbolizing the profound importance of this hormone in saving countless lives.

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The gentleman you see in this image is John Macleod, one of the often overlooked yet pivotal figures in medical science, particularly in the development of insulin therapy for diabetes. When we reflect on the history of insulin, the narrative frequently centers around four individuals: Frederick Banting, Charles Best, James Collip, and John Macleod. These four researchers from Toronto played an instrumental role in discovering and purifying

insulin, ultimately providing a life-saving treatment for diabetes. But the story of insulin's discovery is far from simple.

Today, I will begin to share the remarkable journey of these four individuals. In the early 1920s, under John Macleod's direction at the University of Toronto, Frederick Banting and Charles Best made the breakthrough discovery of insulin. With the expertise of James Collip, insulin was successfully purified, making it available for effective treatment of diabetes. For their contributions, Banting and Macleod were awarded the Nobel Prize in 1923. However, the story is far more complex than just these few accolades.

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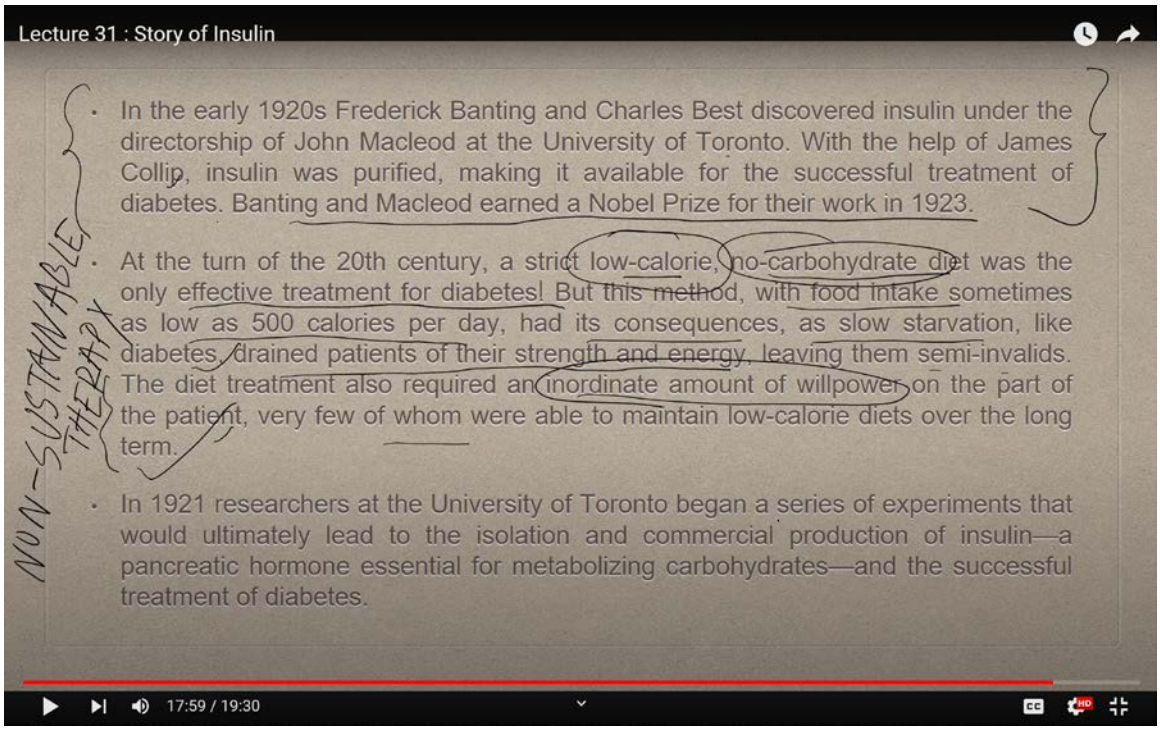

At the turn of the 20th century, specifically around 1900, the only treatment available for diabetes was a strict calorie-controlled, no-carbohydrate diet. The logic was simple: if your body couldn't process carbohydrates, then you simply avoided them. This was the only therapy available at the time, complete abstinence. But while this may sound reasonable in theory, the brain relies solely on glucose for energy. Without it, a person experiences intense cravings for food and runs the risk of fainting. This is why, when people experience

a diabetic episode, they are often given glucose water, to provide a quick and easily absorbed energy source for the brain.

Though this explanation may sound straightforward, history reveals that there are many more intricacies at play. Glucose is vital for brain function and survival, and the body prioritizes its absorption. However, the diet therapy of the early 1900s, which often involved consuming as few as 500 calories a day, led to slow starvation. Patients with diabetes were left physically drained, with little strength, often living in a state of semi-invalidity. Adhering to such a restrictive diet demanded immense willpower, and only a few patients could maintain it long-term. This was clearly not a sustainable solution, far from it.

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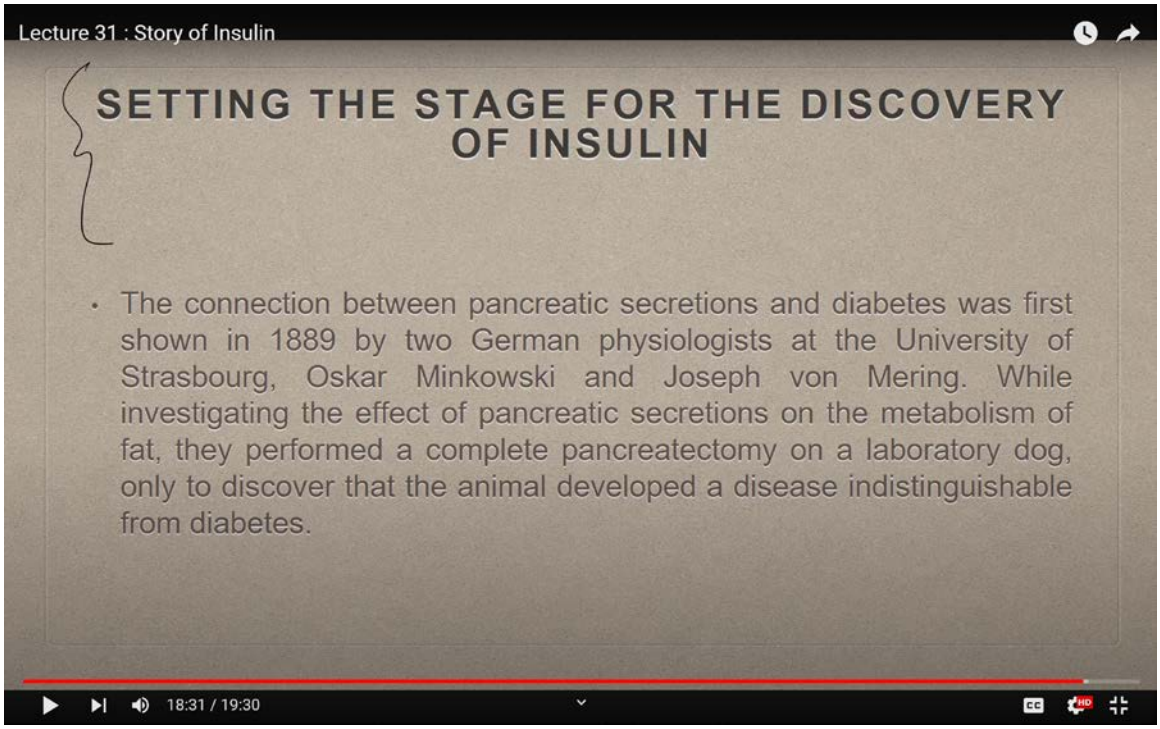

Then, in 1921, researchers at the University of Toronto embarked on a series of groundbreaking experiments that ultimately led to the isolation and commercial production of insulin. This pancreatic hormone is essential for carbohydrate metabolism, and its discovery changed the course of diabetes treatment forever. The successful application of

insulin was nothing short of revolutionary, but the journey to this point is what we will now focus on.

In the next class, we will explore the foundations of insulin's discovery, starting from the state of medical knowledge before 1900. We will examine how humanity's understanding of diabetes, despite being fragmented, laid the groundwork for one of the most significant medical breakthroughs in history. From these early insights came the commercial production of insulin, a development that saved countless lives and addressed one of the most critical health challenges of the time. Thank you.