Scientific Discovery and the Diabetic Patient: How the Past Century Has Transformed Our Understanding of Diabetes

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The Dynamics of 20th Century Diabetes: An Introduction

Though diabetes, a leading cause of death in the United States, dates back to Ancient Egyptian civilization, significant medical progress was not made until the mid-20th century (A. M. Ahmed, 2002). The discovery and isolation of insulin in 1921 catapulted diabetic treatment options into the modern era. Over the past century, scientific breakthroughs in diabetic research and biopharmaceutical development have provided critical understanding of the mechanisms of diabetes and consequently shaped the treatment and lives of diabetic patients. Prior to modern developments in diabetic research and treatment, patients suffered from poor quality of life and almost certain fatality (White, 2014). Commercialization of both modified and synthetic insulin, by biopharmaceutical companies such as Eli Lilly and Genentech, altered treatment approaches and patient outcomes, which challenged traditional scientific assumptions and established new biotechnological practices (Quianzon & Cheikh, 2012; White, 2014). An analysis of how these research developments contributed to and shaped the scientific community, biopharmaceutical industry, and diabetic patient will highlight the power of scientific understanding and innovation in diabetic treatment. Paradigm shift theory is applied in order to capture and evaluate the change in scientific approach, understanding, and treatment of the disease in response to scientific breakthroughs. The perspective provided by paradigm shift theory showcases the impact of a scientific discovery on the manufacturing approaches of an entire industry, directly affecting the lives of patients. In order to evaluate the changes in the biopharmaceutical industry and its patients, the following question must be addressed: how did scientific breakthroughs in the understanding

of diabetes affect treatment approaches and consequently shape the lives of diabetic patients over the course of the 20th century?

Research Question and Methods

How did scientific breakthroughs in the understanding of diabetes affect treatment approaches and consequently shape the lives of diabetic patients over the course of the 20th century? Historical case studies and documentary research methods aid in addressing this question. Historical case studies connect events in the scientific world to the changes in patients' lives. This form of research helps explain the role of events in shaping a group, in this case the diabetic patient, over time by investigating the dynamics between specific occurrences and resulting impact. This method of evaluation relies on the formation of specifically structured questions and in-depth, holistic analyses of the results over a certain timeframe (Harrison et al., 2017). Documentary research methods study and situate subjects in a social context, providing background and supporting context to the exploration of diabetic treatment and discovery throughout the past century (J. U. Ahmed, 2010). Specifically, these research methods consider studies evaluating the condition and perspectives of patients, physicians, scientists, and pharmaceutical engineers to better understand the shifting dynamics and experiences of these groups.

Research developments on the topic of diabetes throughout the 20th century are evaluated in comparison to the changes in the clinical approaches and treatments of diabetic patients. The impacts of two specific events, Eli Lilly's commercialization of animal-derived insulin and Genentech's development of synthetic human insulin, are investigated and compared with shifts in the treatment and quality of life of patients. A variety of accounts is systematically and chronologically organized to evaluate the dynamics between these two innovations and their impact on patients.

An Overview of Diabetes: From Ancient Egypt to Present

While the first documented case of diabetes emerged in the 16th century BCE in Ancient Egypt, little progress had been made thousands of years later in 1920 towards improving the diagnosis and available treatment. Despite the immense gap in time and resources, the mortality rate across those centuries remained unchanged at 100 percent. With little understanding of the physiology behind the disease, ancient treatment consisted of a cruel diet of bones, wheat, grain, and dirt over a four-day period. Similarly, the only treatment of the early 20th century involved a diet of a few hundred calories to prolong death for as long as possible. Few lived even a year after their diagnosis (Cooper & Ainsberg, 2010).

With the discovery of insulin in 1921 came the start of understanding the pathophysiology of diabetes (White, 2014). Diabetes mellitus, or type 1 diabetes, results from high blood glucose levels. Glucose is the body's primary energy source. In order for the body to create energy from glucose, the glucose must leave the bloodstream and enter cells through active transportation. Insulin, a hormone secreted in the pancreas, regulates blood glucose levels by guiding glucose to the cells for conversion into energy. Type 1 diabetes is an autoimmune disease in which cells that produce insulin in the body are targeted and destroyed. As a result, the pancreas no longer produces insulin and blood sugar has no way of finding transportation to cells for energy production (*Type 1 Diabetes | NIDDK*, n.d.). After centuries of stagnation, the understanding of the mechanisms behind diabetes finally enabled progress in the development of treatment.

The diabetic population is growing and currently includes approximately 200 million people worldwide (Margolis et al., 2011). As a leading killer in the United States with a $30 billion global market, scientific advancements in diabetic research and treatment impact the

quality of life of millions of current and future patients (Heinemann, 2016). The investigation into the development of different therapeutic modalities following the discovery of insulin highlights the impact of pharmaceutical advancements on the diabetic population, as it shapes the understanding of and action taken against disease.

Applying STS: The Perspective of Paradigm Shift Theory

According to Thomas Kuhn, paradigm shift theory is most applicable when a group accepts and implements new practices and routine applications in their field of study (Kuhn, n.d.). This shift results from the re-evaluation and reconstruction of past fundamental assumptions (Pajares, n.d.). Criticism of the paradigm shift theory stems from skepticism regarding the novelty of paradigms. Fenwick English, a distinguished education professor at the University of North Carolina at Chapel Hill, argues that the "new theories" implementing paradigm shifts are simply rebranded "old theories" (English, 2001). Thus, these new theories simply re-center the paradigm without changing in scope or influence, causing the rebranded theories to fall outside of Kuhn's idea of a paradigm. Still, the paradigm shift theory aids in evaluating the contexts of a variety of fields. For instance, Dr. Arch G. Woodside utilized this theory to discuss novel, influential methods of data analysis in business research (Woodside, 2013). The paradigm shift theory proves useful in investigating the impact of approach-altering discoveries on multiple stakeholders, from the researchers, doctors, and manufacturers to the patients.

The application of paradigm shift theory to scientific breakthroughs in diabetes research and pharmaceutical development during the latter half of the 20th century shows the shift in the perspective and practices of scientists. This lens reveals the impact of these discoveries and novel implementations on the biopharmaceutical industry and the diabetic patient. Specifically,

the paradigm shift theory evaluates two events in the scientific development of diabetic treatments in the 1900s. The first is the commercialization of animal insulin by Eli Lilly following the successful isolation of insulin by Frederick Banting and Charles Best in 1921. Previously, the underlying mechanism of diabetes was unknown. The second event being investigated is the creation of recombinant human insulin by Herbert Boyer with Genentech in 1978 (Quianzon & Cheikh, 2012). Genentech's product was the first recombinant therapeutic. Paradigm shift theory uncovers the resultant shift in scientific approach and understanding of disease following these events.

A Paradigm Shift: The Impact of Insulin on the Diabetic World

The discovery of insulin changed diabetes from an acute, fatal disease into a chronic condition, and catapulted doctors, patients, researchers, and pharmaceutical companies into a new era of treatment through collaboration. From the initial commercialization of insulin in 1922 through approximately 50 years of new developments in insulin therapy, the development of formulation and purification processes of insulin have been a crucial aspect in shaping the patient experience. An intricate network of physicians, patients, researchers, and manufacturers efficiently created new insulin analogues and optimized processes. The discovery of insulin caused a multi-level shift in fundamental perspectives of diabetes. Quickly following insulin's commercialization in 1923, diabetic patients no longer universally died and instead could manage the disease long-term (Feudtner, 2004). As a newly chronic disease, patients and doctors formed on-going relationships to manage their condition individually. Doctors no longer had to intricately balance the starvation diet between the most tolerable form of malnourishment and coma. As a result, doctors established the specialization of endocrinology became established (Feudtner, 2004). Researchers turned their attention from searching for the causal compound to optimizing the

patient experience and standardizing treatments (Sinding, 2002). As for manufacturers, a space for biopharmaceutical development in diabetes emerged and exploded. The breakthrough of insulin ignited a total re-definition of diabetes into a complex and promising field for all stakeholders. This redefinition sparked 50 years of near constant innovation in the processing and standardization of insulin analogues. Without embracing close collaboration and a shared emphasis on developing better processes, the development of treatments may not have materialized as efficiently.

The Pre-Insulin Era

Diabetes has plagued the human race since it first appeared 3,500 years ago in Egypt. In those times, treatment consisted of a miserable diet of plants, milk, and beer (White, 2014). Early Indian and Chinese civilizations documented similar cases and therapeutic actions (A. M. Ahmed, 2002; Quianzon & Cheikh, 2012). Yet, at the turn of the 20th century, thousands of years later, there had been little progress on treatment options. Diabetic patients of the early 1900s existed in a state of constant malnourishment, following the only proven treatment at the time: the "starvation diet" (Cooper & Ainsberg, 2010). Treatment revolved entirely around strict measurements of low calorie, high fat foods (Sinding, 2002), a diet that was of no significant improvement compared to those of ancient times (Cooper & Ainsberg, 2010). This strict regimen bought patients up to a couple more years of life at the cost of up to 50 percent of their pre-diabetic body weight (Feudtner, 2004). Pre-insulin era patients all fell into an inevitable sequence once symptoms appeared that led to death (Feudtner, 2004). Type 1 diabetes had a prognosis that ranged from months to a couple of years accompanied by constant torment (Cooper & Ainsberg, 2010; Copenhaver & Hoffman, 2017, p. 1). Through 1919, no individual had survived diabetes and the rate of mortality was 100 percent (Cooper & Ainsberg, 2010; White, 2014).

In December of 1921, researchers Frederick Banting and Charles Best successfully isolated an injectable pancreatic extract to lower diabetic patients' blood sugar levels (White, 2014). Finally, doctors identified a compound that had evaded them for centuries, and the discovery of insulin was quickly considered one of the greatest scientific breakthroughs to date (Sinding, 2002). Doctors administered the first human test injection of animal-derived insulin in January of 1922 which successfully lowered blood glucose levels. With proven effectiveness, the pressure to create a manufacturable process began (Moroder & Musiol, 2017; White, 2014). An efficient collaboration with Eli Lilly & Company enabled production of bovine and porcine insulin samples by 1923 (White, 2014). With this discovery, the paradigm shift of the diabetic world, for patients, doctors, and scientists, began: an uncertain science of balancing a patient on the brink of starvation to put off inevitable death gave way to the pursuit of a specific protein.

From Acute to Chronic

With the discovery of insulin and its commercialization came a new chapter in the history of diabetic treatment (A. M. Ahmed, 2002). Insulin transformed a previously unavoidably fatal disease into a manageable one (Feudtner, 2004). Patient quality of life improved drastically, ending the need for the starvation diet and its ugly side effects (A. M. Ahmed, 2002). For example, a diabetic child on a low carbohydrate vegetable diet weighed 15 pounds prior to the availability of insulin. Just three months later, his body weight had doubled to 30 pounds with insulin injections, enabling him to eat a more substantial 1,500 calories per day (Feudtner, 2004). Pre-insulin era diabetics rarely survived more than two years beyond their diagnosis, with less than five percent living 10 years past their diagnosis. Immediately following the introduction of insulin injections, the diabetic life expectancy extended beyond a decade (Feudtner, 2004). Elizabeth Hughes, one of the first diabetic patients to receive insulin therapy surpassed her pre-insulin life expectancy by 58

years, accumulating roughly 42,000 insulin injections during her lifetime (Cooper & Ainsberg, 2010). Even fifty years following the initial isolation of insulin in 1922, the only commercially available substances originated from the pancreases of pigs and cows. These concoctions were critical in extending the lives of diabetic patients who would have otherwise suffered malnourishment until death (Ladisch & Kohlmann, 1992).

As the pre-insulin era was left behind, diabetes transformed from an acute, fatal disease into a chronic one. This transformation in turn shifted the patient experience and population, the medical approaches, and the culture surrounding the disease (Feudtner, 2004). The success of early insulin commercialization resulted from the collaboration between many doctors, researchers, and pharmaceutical manufacturers that created an effective production process (Sinding, 2002). The transition of the disease into a chronic disorder shifted perceptions of the disease, forcing doctors, patients, researchers, and manufacturers to rethink their practices and the life of the chronic diabetic patient (Feudtner, 2004). In part due to the dismal prognosis and tortuous prescriptions of the pre-insulin era, few doctors specialized in the field. However, by the early 21st century, 5,000 endocrinologists and diabetic specialists dedicated their work to treating diabetes (Feudtner, 2004). This growth in specialization restructured the care provided to diabetics along with their expectations in doctor-patient relationships, marking the initiation of a paradigm shift as diabetes morphed into a chronic condition (Feudtner, 2004).

As diabetic patients lived longer upon graduating from the pre-insulin era, relationships between patients and physicians became more established and grew into a sort of co-dependency. The need for daily, if not more frequent, injections and careful monitoring of glucose levels in patient urine encouraged doctors and patients to interact more frequently and collectively design a personalized treatment management system (Vecchio et al., 2018). Soon after beginning insulin

treatment, patients learned to identify effects of the injections. Of particular concern was hypoglycemia, abnormally low levels of blood sugar, as it was fatal. Diabetics had not encountered this condition prior to the availability of insulin treatments, so patients and doctors collaborated to identify symptoms and adjust dosages (Sinding, 2002). In contrast to the acute diabetic cases prior to insulin, where physicians were entirely responsible for monitoring and care, responsibilities were less clearly allocated between doctor and patient in chronic cases. Patients now had complex, long-standing relationships with their physicians (Feudtner, 2004).

As side effects and inconsistencies with the newly commercialized insulin arose, patient-doctor cooperation was crucial to helping patients, medical care providers, and manufacturers more deeply understand the criticality of standard dosing. Banting, the primary discoverer of the compound, constantly received letters from patients describing the variability in potency and quality of their insulin supply in great detail (Sinding, 2002). Patients documented the details of their eating habits, exercise, volume of insulin injections, the visible characteristics of the solution, the number and severity of allergic or infectious reactions, among other aspects of their regimen (Sinding, 2002). Standardizing insulin, then, was ultimately an intense collaboration between doctors, patients, and manufacturers as they carefully documented and communicated characteristics of each batch of insulin (Feudtner, 2004). While pre-insulin treatment clung to strict diets and urine tests for sugar content, diabetics post-insulin had an entire management system spanning diabetic specialists, scientists, and pharmaceutical engineers with whom they were in constant care and correspondence (Feudtner, 2004). While insulin was a proven effective combatant of high blood glucose levels, researchers had not yet achieved a consistent manufacturing process. Prior to the discovery of insulin, there had been no relationship between physicians, researchers, and pharmaceutical manufacturers because a pharmacological treatment

had not existed. The discovery of insulin brought together these three entities to tackle the standardization of the world's first diabetic therapy.

Standardization and Optimization

In just a couple of years, the research and development efforts of diabetic researchers shifted from searching for a key, yet unknown, substance in diabetes pathology to fine-tuning the commercialization of diabetes' lifesaving pharmacological agent. With this pivot in focus came a clear need to optimize the construction of a newly discovered substance as a medicine. The paradigm shift was near complete, as the focus and understanding of the disease completely changed to one of optimization of product. Where variations in dosage could lead to disastrous effects on the patient, effective standardization of the product was critical (Moroder & Musiol, 2017). Biological standardization is crucial for consistent, reliable management of disease. Simply put, each batch of a drug must yield equal concentration and potency and utmost purity across all lots (Sinding, 2002). At the onset of commercialization, Eli Lilly produced batches that varied greatly in both potency and purity. Potency sometimes spanned a difference in range of up to 25 percent per lot (Quianzon & Cheikh, 2012). Particularly impure samples of insulin caused reactions such as intense swelling at the injection site and allergic reactions due to contaminations (Sinding, 2002). In the fall of 1922, a chief chemist at Lilly optimized a method that enabled insulin samples to precipitate in a consistently purer form than previously achieved (Feudtner, 2004; Sinding, 2002). While this decreased the variation in potency between batches to 10 percent, this range still posed risk of accidental overdose with particular batches (Feudtner, 2004; Quianzon & Cheikh, 2012).

Despite its lifesaving impact on diabetic patients, much improvement could still be made to create a better insulin product. Researchers and manufacturers quickly focused their efforts on

creating longer lasting insulins as commercialized insulin in its initial, quick-release form required several injections each day and often required patients to disrupt their sleep for additional injections overnight (Quianzon & Cheikh, 2012; White, 2014). In 1926, a few years after the discovery of the protein, researchers developed insulin in a crystalized form that allowed for tailoring the treatment to different time-action profiles (White, 2014). In 1950, manufacturers introduced isoforms of insulin with additions of zinc to create more extended release alternatives (Ladisch & Kohlmann, 1992). As the options for different insulins with a variety of characteristics and release profiles emerged, they each carried benefits and risks that demanded specific regimen for the patient to closely follow. While some were rapid response, they lasted for a shorter time period. Others lowered blood sugar over many hours, sometimes risking delayed hypoglycemic reactions whose peak could emerge late in the night and risk severe complications (Feudtner, 2004). As treatment options abounded, so too did the research and pressure for patients to quickly adapt. The focus of developers quickly moved from discovery of a substance to process methods that address new risks uncovered by the introduction of insulin therapy. With this drive to continuously improve the initial product came numerous treatment options with different profiles that patients had to quickly evaluate for their personal treatment plans.

While researchers made critical advancements in optimizing release profiles of insulin products, the need for a therapy that more closely mimicked human insulin became clear. In the half century following the discovery of insulin, all treatments were derived from animals, mainly pork and pig. This production dependence on pancreatic extract from foreign bodies introduced an issue of product shortage and immunological reaction that restricted the treatment of some patients. A number of patients were dying due to a shortage in insulin resulting from a lack of meat availability and the complications of purifying the foreign extract (Feudtner, 2004; Landgraf &

Sandow, 2016). Further, many who received the treatments suffered allergic reactions and biological incompatibility that resulted in inconsistent insulin absorption profiles and complications with the body's ability to maintain healthy fat tissue (Shah et al., 2016). The sample contaminations both heightened pain and inflammation at the injection site. Some patients had to suspend their insulin treatment because of the severity in immunological reactions. Further, inconsistencies with the animal source could lead to unforeseen allergic reactions as some patients could tolerate beef insulin but not pork, for instance (Feudtner, 2004). Clearly, the diabetic population needed an insulin treatment that more closely resembled human insulin.

By creating a therapy that morphed diabetes into a chronic condition, long-term effects of the disease began to appear (Feudtner, 2004). Insulin eradicated diabetic comas and malnourishment, but it unveiled chronic complications such as kidney failure, blindness, and lower limb amputations (Feudtner, 2004). These conditions emphasized that "diabetes, far from being conquered, had been transformed insidiously from an acute to a chronic disease by insulin therapy" (Feudtner, 2004). While the medical intervention of insulin therapy improved hyperglycemia and minimized the chance of coma, it revealed a new set of ailments that now also demanded consideration. The combination and severity of these new factors attributed to chronic diabetes were unique for each patient, as patient experience is a result of both physiological processes and medical intervention (Feudtner, 2004).

To address the immunological reactions and risk of product shortage posed by animal-derived insulins, researchers worked to develop a synthetic human insulin through recombinant DNA (Quianzon & Cheikh, 2012). Through many iterations of purer, extended release insulin in the 50 years following the discovery of insulin, shortcomings related to the source of animal pancreases remained. In 1978, scientists at Genentech, then a biotechnology startup, were able to

engineer recombinant human insulin. This development was made possible by advancements in genetics and molecular biology that could alter native proteins (Brange, 1997). In 1982, Genentech partnered with Eli Lilly to manufacture the first synthetic human insulin product, Humulin (Quianzon & Cheikh, 2012). Recombinant human insulin was "chemically, physically, and immunologically equivalent to pancreatic human insulin and biologically equivalent to both pancreatic human insulin and purified pork insulin" (Ladisch & Kohlmann, 1992). Thus, the body responded much more agreeably to the synthetic human insulin as if it were its own. Two critical advantages of recombinant human insulin compared to animal-derived substances arose: production of synthetic insulin was comparably unlimited, dispelling fears of shortage, and the chances of reactions to allergens or impurities significantly diminished (Ladisch & Kohlmann, 1992).

Since its entry into the market in 1982, recombinant human insulin remains the standard of care for insulin therapy to this day. Recombinant human insulin exceeds its insulin counterparts in purity and consistency across batches. The development of this synthetic insulin "enabled a worldwide human insulin supply of consistent high quality" (Landgraf & Sandow, 2016). Beyond the ability to manufacture this new insulin virtually limitlessly, the comparably lower cost made recombinant human insulin globally available to patients with inadequate resources. With the capability to tweak the protein with desired specificity, a number of different recombinant insulin formulations became possible (Landgraf & Sandow, 2016). These variants enabled true individual treatment, with regimens tailored to each patient that were of upmost effectiveness and safety.

The preceding research and discussion are limited in scope in order to effectively discuss a portion of societal impact of diabetes on the scientific, commercial, health care, and patient realms. A full, extensive analysis of the diabetic world's interaction with the discovery of insulin

was restricted as this project only extended across a seven-month timeframe. Therefore, this study focuses exclusively on the impact of initial discovery and commercialization of animal-derived insulin commercialized by Eli Lilly and recombinant human insulin manufactured by Genentech. Limited details and events were considered due to the constraints surrounding timing, resources, and advisable report length.

Limitations and Future Considerations

Future evaluations of this topic should consider delving deeper into the developments and events surrounding insulin in the 20th century and holistically giving a complete picture of the many insulin analogues available. Insulin analogues, such as the crystallized and zinc-modified insulins briefly discussed above could be explored in more detail to uncover the impact of each individual development and its effect on the scientific, patient, physician, and manufacturing perspectives. Further, while this analysis effectively stops with the first recombinant therapy, a consideration of the impacts of this development on both the diabetic world and the biotechnology industry in general over the past half century, leading up to present day, would be ideal. In this way, the reach of diabetic, therapeutic innovations would be more fully understood outside of its impact on immediate patients.

Diabetes Redefined: A Total Transformation

The discovery of a single protein, insulin, transformed a disease that claimed every life afflicted by it for roughly 3,500 years into a completely manageable disease in the span of a couple of years (White, 2014). This event fundamentally shifted the perspectives of researchers, manufacturers, patients, and doctors. The scientific field changed its focus from the search for an unknown compound to optimization of purification processes. Instead of attempting to find the cause of rapid death of millions of people, they focused on how to create a treatment that offered

optimal ease of use to patients. Patient experience re-centered from one of hopelessness to one of management of a now livable disease, allowing patients to expand their outlook from a couple of years left to decades of life to come. Doctors no longer labored over a perfectly balanced starvation diet in a field in which few dared to specialize. Instead they saw huge growth in endocrinological specialization and long-term relationships with their patients to aid in individual tailoring of insulin treatment (Feudtner, 2004). As for the industry, a pharmaceutical agent for diabetic treatment did not previously exist. Thus, the discovery of insulin unlocked an entirely new area of opportunity. 3,500 years of stagnation in attempts to understand and treat diabetes gave way to 50 years of numerous advancements as a result of the identification of a single protein. Much of the resulting shift in focus and efficient success of manufacturing insulin came from intense collaboration between these entities (doctors, patients, researchers, and manufacturers) to optimize standardization and purification processes of the drug. The discovery of insulin fundamentally shifted professional and patient perspectives alike to emphasize the importance of process optimization and the criticality of success through collaboration across realms to make meaningful progress.

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