Pharmaceutical Innovation: Eli Lilly and Company, the University of Toronto, and the Development of Insulin

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To the glory of God with thanksgiving for the wonder of life.

-Inscription on the grave of Eli Lilly, Indianapolis

In 1918, eleven-year-old Elizabeth Hughes was a healthy, privileged, and adventurous American girl. By 1919, Elizabeth was restricted to just 400 calories per day in order to stay alive. Besides being afflicted with a ravenous thirst, Elizabeth began to show signs of weakness and rapid weight-loss. Her father, the famous statesman Charles Evans Hughes, commissioned two of the leading diabetologists of the age, Dr. Frederick Allen and Dr. Elliot Joslin, to prescribe her forms of treatment for what he suspected was diabetes. His suspicions proved correct, and Dr. Allen severely curbed Elizabeth's diet, bringing her weight from seventy- five to fifty-five pounds within weeks. Though she despised her diet, she almost certainly would have died within the year had she remained untreated. Children such as Elizabeth had little to no hope of leading normal lives, as they were forced to transform themselves into living skeletons to combat the horrors of diabetes. Her weight continued to fluctuate between fifty and sixty pounds, prolonging her life but increasing her suffering by the day. With no curative treatment, Dr. Allen did not expect young Elizabeth to survive past the summer. A sense of hope endured, however, when news came of Dr. Frederick Banting's seeming isolation of insulin within the pancreas in 1921. Issues regarding standardization/potency and high demand quickly zapped Toronto's extract supply--forcing the University to look to American companies, like Eli Lilly and Company of Indianapolis. Thankfully, Elizabeth's story would end quite happily, especially considering such grim circumstances. Most significantly, the child was among the first patients to be administered (and saved by) a miracle drug that would ultimately change the face of medicine.[1]

[1] To read more of Elizabeth's heartwarming story, please see: Thea Cooper and Arthur Ainsburg, *Breakthrough: Elizabeth Hughes, the Discovery of Insulin, and the Making of a Medical Miracle* (New York City: St Martin's Press, 2010).

As the twentieth century approached, academic and industrial institutions were still considered to be at odds; they were viewed as two institutions so fundamentally dissimilar that any ideas about collaboration were not often pursued. Ideal academic institutions are committed to the spreading and enhancement of human knowledge, while industrial institutions must ultimately keep a profit motive in order to be sustainable. This dichotomy discouraged collaboration, and especially open partnership, prior to the twentieth century. Their fundamentally different priorities ironically created new opportunities of mutual benefit, but with this collaboration came problematic situations for both actors involved. Despite this, other forces often played a role in the frequency of academic-industrial partnerships in North America, as well as the increasing quality and safety of medicines. The largest of these was the government, and federal legislation passed by the American Congress just prior to the nation's involvement in World War I was a major determinant of such a frequency. Notably, this was also the time when pharmaceutical organizations had nearly solidified legitimacy apart from chemistry and physiology fields and/or departments.[2] The 1902 Licensing Act required manufacturers of medicines to be licensed by the Secretary of the Treasury, through the Laboratory of Hygiene. Similarly, the well-known 1906 Pure Food and Drug Act sought to regulate the labeling and marketing of drugs and food (thereby ensuring their safety), as well as barring manufacturers from making false claims about the efficacy of their drugs. Perhaps most significant considering the impending war, the 1917 Trading with the Enemy Act permitted American companies to manufacture German patented drugs, encouraging many companies to start forging alliances with universities that might also be committed to bringing American-made products to market.[3]

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[2] John Swann, *Academic Scientists and the Pharmaceutical Industry* (Baltimore: John Hopkins University Press, 1988), 6-10.
[3] Basil Achadellis et al., *Pharmaceutical Innovation: Revolutionizing Human Health* (Philadelphia: Chemical Heritage Press, 1999), 52.

Regardless, the legislation and changing atmosphere set an ideal stage for pharmaceutical companies seeking to increase in-house capabilities and expertise; generally speaking, as war approached, many industries began to rethink their previous positions on utilizing and working with academic institutions for such reasons highlighted above. As American companies were forced to turn to these in-house capabilities, they became more comfortable with the prospect of learning from and working with these emerging research-based universities.

Outside of the United States, a new sort of medical revolution was occurring. Researchers at the University of Toronto had isolated and standardized the internal secretion of the pancreas, known as insulin. Though ultimately focused on manufacturing and distributing the product for medical use from the beginning, their poor capabilities for mass-production led to one of the earliest partnerships of significance in American medicine—that with Eli Lilly and Company of Indianapolis. Eli Lilly and Company's enhanced capacity for mass production led to its ability to help Toronto commercialize the drug, so that patients could benefit as much and as fast as possible. The partnership between Eli Lilly and Company and the University of Toronto was momentous for both academic and industrial institutions. The partnership was among the first born explicitly to bring a new drug to market, and had lasting implications regarding collaboration, academic-industrial relations, and medical progression.

The following paper will discuss the collaboration between Indianapolis and Toronto as a single and comprehensive narrative, something that has not previously been done. It will also take a more in-depth look at the individuals from both cities who were quite instrumental in this process, namely Dr. Banting, Eli Lilly Jr., and Dr. Clowes of Eli Lilly and Company. These mavens were quite visionary and formed connections between and among their respective

industries to bring them increased innovation and efficiency. Were it not for such forward-looking individuals, medical progression and the frequency of academic-industrial partnerships would likely have been pushed back decades.

Prior to 1921, when insulin was discovered, there was no effective treatment or cure for diabetes. *Diabetes mellitus* has been known of and suffered through since antiquity. Greeks and Egyptians recognized the disease thousands of years ago, identifying recurring symptoms such as unquenchable thirst and frequent urination. The word "diabetes" itself comes from the Greek word for pipe-like, as a person becomes diabetic when their body is no longer able to utilize nutrients and metabolize them into energy. Early physicians dubbed diabetes "the sugar disease," as the urine of diabetics had an unusually high sugar content. The essential problem for diabetics is the body's inability to burn much of the simple glucose from food, especially carbohydrates. Instead, this glucose remains in the bloodstream, as the body continually searches for and craves sugar. This often leads to a terrible sense of hunger and desire for nutrients, again, mainly carbohydrates. After diagnosis, the disease itself or complications relating to it caused a relatively quick death for most victims.[4] Without a cure for the disease, physicians at the turn of the twentieth century resorted to limiting their patients' nutritional consumption, restricting daily fat and diet intakes. Following this logic, the diminishing of nutritional intake would not over-burden the body, and would allow the patient to live sugar and carbohydrate-free (and therefore symptom-free). The leading diabetologist in early twentieth century America, Dr. Frederick Allen, advocated for this form of treatment as the most effective and prolonging. Even as many patients were brought to the brink of malnutrition and starvation, the method of treatment was arguably the most popular and effective, just as Dr. Frederick Banting was entering the scene.

[4] Michael Bliss, *The Discovery of Insulin* (Chicago: University of Chicago Press, 2007), 18-20.

A young Frederick Banting, born in Ontario, Canada, first tried his hand in medicine at the University of Toronto, obtaining an M.B in 1916. In 1915, he had made up his mind that he would be a surgeon. His first practical encounters were had as a doctor in the Canadian Army Medical Corps, where he gained experience with handling wounded troops and further familiarized himself with practical medical applications at-large. He was also injured in the line of duty and awarded the Military Cross. Upon his return to Ontario after leaving the army in early 1919, he studied orthopedic surgery and soon became Resident Surgeon at the Hospital for Sick Children in Toronto. He began developing bad habits, such as smoking and drinking, though reported a much more clear and refined sense of purpose and mission in his life after the war.[5] After a number of brief teaching stints, he obtained his M.D. in 1922.[6] Perhaps surprisingly, Banting showed little to no interest in diabetology in his early career. It was only after his late-night reviewing, in preparation for an upcoming lecture, of a 1920 article by Moses Baron discussing ligation and the islets of Langerhans that a revolutionary idea came to him. Below reads an inscription from his 1940 memoir:

> It was one of those nights where I was disturbed and could not sleep. I thought about the lecture and about the article and about my miseries and how I would like to get out of debt and away from worry.
> Finally about two in the morning after the lecture and the article had been chasing each other through my mind for some time, the idea occurred to me…[7]

He postulated that ligating pancreatic ducts of dogs might provide a solution to the long-sought-after question of how to extract insulin from the pancreas before it was destroyed by pancreatic enzymes. After early scientists confirmed that diabetes was related to defects in the pancreas, various researchers established that diabetes was caused by a lack of a protein secreted by the islets of Langerhans, or the region of the pancreas that produces hormone-secreting cells.

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[5] Michael Bliss, *Banting: A Biography* (Toronto: University of Toronto, 1992), 25-41.
[6] Ibid., 43.
[7] Mary Bowden et al., *Pharmaceutical Achievers: The Human Face of Pharmaceutical Research (*Philadelphia*:* Chemical Heritage Foundation, 2003), 87.

It was not long before researchers realized the all-important role of insulin, as the driver behind the metabolism of sugar; lack of it results in the accumulation of sugar in the blood and the excretion of the excess of sugar in the urine. Banting suggested that ligating the pancreatic ducts in dogs would render enzyme-producing cells in the islet ineffective while preventing the destruction of insulin, ultimately leading its isolation and extraction.[8]

After decades of emerging and increasingly extensive research on the causes and effects of diabetes, Banting's idea ignited a flame that would consume the medical world and change the lives of diabetics for humankind. Much of this is due to the receptiveness of Dr. J.J.R. Macleod, the chair of the Physiology Department at the University of Toronto. Though Banting owned a small practice and dabbled in lecturing on medicine, he did not have significant access to medical research facilities or resources. He was hardly known for his relatively limited work, and did not seem to leave a compelling impression on Macleod upon their first meeting in November 1920, in which Banting relayed his idea to the professor. On the contrary, Macleod was an established medical professional whose deferential judgment on diabetes was widely recognized; his first publication on the subject, in 1913, was written while Banting was just beginning medical school. Though Macleod could sense Banting's interest and passion, he was quite incredulous of the young doctor's capacity for medical expertise and conducting highly complex, technically-based experiments. His skepticism remained, yet he offered Banting a young lab assistant and the resources of the physiology labs at the University of Toronto.[9] Beginning in April of 1921, Frederick Banting and his assistant, graduate student Charles Best, began early experiments aimed at isolating the pancreatic extract that was insulin. Most impressively, despite

[8] Bliss, *Discovery of Insulin*, 45-48.
[9] Ibid., 52.

their initial difficulties and tribulations, the two young professionals remained dedicated to the thought of using their extract for beneficial commercial and medical use. [10]

Meanwhile, a similar revolution was occurring in Indianapolis, though this was one of a more industrial nature. Eli Lilly and Company, a rising pharmaceutical manufacturer, was looking for ways to expand marketing and production, improve efficiency and output, and refashion company policies relating to research and development. This firm commitment, realized and implemented earlier than most, distinguished Eli Lilly and Company by the early 1920s. Prior to when these changes were instituted, the company was like hundreds of other American companies. Colonel Eli Lilly, after a stint as a soldier in the Civil War, returned to Indianapolis and established a manufacturer of sugar-coated pills, elixirs, extracts, syrups, and more in 1876. His small retail store on McCarty street relied mainly on handiwork as the primary method of production, as the pills were hand-rolled. These methods made standardization quite difficult, as there was no way to assure the pills came in uniform shapes and sizes. Ironically, the company remained a bit ambivalent about scientific research in its early days. At the turn of the century, its top seller was a *Succus Alterans*, sold as a treatment for syphilis and as a "blood purifier"; it was also purported to be derived from Creek Indians.[11]

Like most early competitors, Eli Lilly was family-owned and managed. When founder Colonel Lilly died in 1898, his son J.K Lilly Sr., took up management of the company. Though J.K Lilly greatly increased personal supervision of the day-to-day workings of his business, it was his son, Eli Lilly Jr,. who most contributed to the company's near meteoric rise. Likewise, the youngest Lilly was the company figure most committed to integrating research and

[10] Please see Bliss's *Discovery of Insulin* for more information on Dr. Banting and Charles Best's early experimentation with insulin.
[11] James Madison, "Manufacturing Pharmaceuticals: Eli Lilly and Company 1876-1948," *Journal of Business and Economic History* 18, no. 2 (1989): 72.

development initiatives into the company's fabric and larger mission. Eli Lilly Jr. was born in 1885 and entered the family company in 1907 as the head and sole member of the Economic Department, upon graduation from the Philadelphia College of Pharmacy. The company and industry that Eli Lilly Jr. entered into were still strikingly similar to the ones his grandfather knew in 1876 and afterwards. Lilly Jr. seemed determined to change this, and even from the start of his career, he was widely interested in roaming the plant, seeking ways to improve production and efficiency and cut costs. He developed a new gadget in the plant's machine shop— a bottle-filling machine that adjusting for different bottle shapes and sizes— saving the company $7500 in spillage the first year the device was used. After detailed observation and analysis, he also concluded that the company's standard wooden barrels caused undue losses through their easy absorption of alcohol. He instituted a switch to copper-lined barrels-- saving the company $15,000 a year.

Aside from the unprecedented efforts he took to improve such things, he also brought his family company broadening success. As head of the Economic Department, he solidified the company's move towards improved output and efficiency by replacing handwritten notes, verbal orders, and individually-typed orders with company-wide blueprints, in which instructions and formulas were outlined and standardized.[12] Also during this time, the young man pored over books and articles examining the art of scientific management, popularized by Frederick W. Taylor (Lilly's obsession and piqued interest in scientific management techniques never left him). Clearly, the business-minded Lilly Jr., had a penchant for improving productivity and efficiency. His father, the president of the company, took notice and promoted him to the head of the newly-created Manufacturing Division in 1909. He quickly acquired even more of a

[12] Ibid., 73-75.

reputation as a "workaholic," eager to please his family members and fellow coworkers by proving the value of his contributions. As head of manufacturing, Eli Lilly Jr., oversaw the greatest expansion of the company to date, mostly by focusing his efforts on the production side. Manufacture of gelatin capsules presented one of the first major challenges for the company; Lilly saw to this by overseeing the installation of fifty Colton machines, and moved them into a newly-constructed capsule plant. Lilly Jr. was instrumental in the inception and construction of Building 13, which opened in 1913; Building 13 was the hallmark of the young man's early achievements, as it encompassed many of his early inventions within a modern industrial gelatin-capsule factory. Additionally, the new machines and the plant to house them were among the most visible signs of significant change at Eli Lilly and Company up to that point. Continuing with his efforts at improving scientific management, Lilly instituted a new merit-based bonus system, as well as inviting in outside consultants to evaluate the company's efficiency and production quotas. He also took measures to improve the company's accounting and inventory systems as well as continue to replace informal means of communication with formal, routinized ones.[13] By the end of World War I, Eli Lilly and Company was well underway in its transformation from local retailer of medicines to a large scale-manufacturing pharmaceutical business. By devoting themselves to in-house research and development much earlier than a vast majority of American companies, and taking measures aimed at increased efficiency, the company primed itself to become the company most suitable and capable for the future Toronto partnership and large-scale manufacture of commercial insulin.

Back in Toronto, Frederick Banting and Charles Best continued early experiments aimed at isolating insulin within the pancreas, as Dr. J.J.R. Macleod headed to his summer home in

[13] James Madison, *Eli Lilly: A Life 1885-1977* (Indianapolis: Indiana Historical Society Press, 2006), 32-36.

Scotland. The rather inexperienced medical devotees planned to conducts pancreatectomies (the surgical removal of the pancreas) on dogs first; the idea was to study the effects of diabetes on the animals after the pancreas was removed. In the meantime, the pancreases of other dogs would have their ducts ligated (rendered ineffective by tying), whereby the pancreas would slowly begin to degenerate. In the first series of Banting's crucial experiments, he would attempt to operate and use these atrophied organs, containing the internal secretion (but, he predicted, not external) to create an extract that might cure the dogs suffering from diabetes with pancreatectomies. A few dogs succumbed to Banting's attempts to undertake and master pancreatectomy operations. The new researchers were forced to take to the streets of Toronto to purchase dogs after all of the ones provided to them had died-- mainly due to improper procedural techniques and infection.[14]

After sensing some progress with a dog in the healing stage of a pancreatectomy, the men resumed experiments by measuring the dogs' blood sugar. It appeared to show diabetic tendencies after its pancreas was removed, but died days after due to abdominal infection. Seven other dogs, however, were showing signs of atrophied pancreases that could soon be used for extract-based experiments after their pancreatic ducts were ligated; only two of these ended up producing any sort of viable extract, and even these were quite crude. By August 1921, this extract had been dubbed "Isletin." Despite slight progress, the research became increasingly difficult to carry out. Extreme heat, limited supplies, lack of space, and mostly discouraging results filled the atmosphere with tension and suppressed frustration. A glimmer of hope overshadowed such concerns as a white terrier was given the aforementioned extract after maintaining solid health post-pancreatectomy. The extract seemed to have a marked effect on the

[14] Bliss, *Discovery of Insulin*, 60.

animal's blood sugar, but satisfactory results could not be reached before the dog died of infection in two days. This was repeated a few times more, with the dogs also dying of infection in a similar timeframe. However, the two men were emboldened, sensing that the results showed "the extract invariably causes a reduction in blood sugar."[15] The experiments also supported the suggestion that ligating pancreatic ducts would isolate the internal secretion from the external, enabling their separate usages. Banting and Best eagerly wrote Macleod of their progress, already discussing their futures in Toronto and further ideas for experiments. Working day and night, in what must have been a highly exciting time for the young scientists, they proceeded to conduct the biggest round of experiments yet attempted. They conducted pancreatectomies on two dogs, but only gave the extract to one. The untreated dog quickly died from diabetes, while the other was seemingly "brought back to life" after being given extracts. The dog continued to withstand various injections of the extract before falling sick. After twenty days, the dog succumbed to complications, with Banting writing: "I have seen patients die and have never shed a tear...but when that dog died I wanted to be alone for the tears would fall despite anything I could do… I hid my face from Best."[16]

After a few weeks, the men received an encouraging response from Dr. Macleod, who urged them to continue experimentation while making sure that the results were precise and reliable. Semi-promising results continued, but could not be proved reliable, as too many dogs died as a result of inconsistent procedures or resulting infections. Nevertheless, Dr. Banting and Mr. Best delivered their first paper on their research in November of 1921, to the Toronto Department of Physiology. Banting, perhaps a bit overconfident in his abilities and findings, demanded larger rooms, a salary from the University, and more dogs and resources. A

[15] Ibid., 72.
[16] Ibid., 78.

dumbfounded Macleod, also frustrated by a lack of consistent results, nevertheless complied, perhaps encouraged by the extract's existing effects. It became clear to Macleod that, though Banting had an unmatched enthusiasm for practical research, he was relatively disinterested in existing medical scholarship; this, combined with his inexperience at experimental research, resulted in capricious and irregular findings. Upon consultation with a number of outside scientists, Banting and Best decided to switch their focus and objectives over to conducting a longevity experiment, i.e. measuring how long the internal extract could prolong the life of a diabetic dog. The researchers also instituted two notable changes: waiting longer for pancreases to degenerate, and using fetal pancreas cells (from pregnant dogs) in obtaining the extract, as it was thought that fetal cells had no chance of carrying the external secretion. This extract was also filtered more carefully, causing it to lose some potency but decreasing the chance of death by infection. Additionally, J.B. Collip, another researcher from the University of Alberta (and recipient of the Rockefeller Travelling Fellowship), joined the Toronto team to assist in refining the extract at the end of 1921.

The dog who received the fetal calf extract saw a consistent lowering of blood sugar levels and continued at a relatively healthy rate. Subsequently, the researchers published their first significant work in the *Journal of Laboratory and Clinical Medicine* in February 1922, in which they offered a sweeping summary of their experiments:

> In the course of our experiments we have administered over seventy-five doses of extract from degenerated pancreatic tissue to ten different diabetic animals. Since the extract has always produced a reduction of the percentage sugar of the blood and of the sugar excreted in the urine, we feel justified in stating that this extract contains the internal secretion of the pancreas.

As Michael Bliss argues in his comprehensive look at insulin, *The Discovery of Insulin*, this assertion ignored many of their prior experiments' inconclusive results and treated such

results as undeniably successful rather than simply impressive and meriting further work.[17] However, it led to one of the most fateful days in the narrative of the Indianapolis-Toronto partnership, as the article was to be presented before the American Physiological Association in New Haven, Connecticut before its publication. The meeting was scheduled to be chaired by the more renowned and experienced Dr. Macleod, late on a Friday afternoon (with Best, Banting, and Collip also present; Banting would be the one to present the paper itself). Though many of the attendees of the conference would be catching trains home during this time, a select few individuals resolved to be present during the presentation-- one of them being Dr. George Henry Alexander Clowes.[18]

Dr. George H.A. Clowes was one of the more remarkable individuals of his time, as argued by his son in the only biography of the scientist to date, *The Doc and The Duchess: The Life and Legacy of George Clowes.* Clowes was born in 1877 in southwestern Britain, part of a Victorian world dedicated to professional, social, and family life. Clowes excelled academically from an early age, and decided to pursue further education in chemistry at the Royal College of Science in London; he graduated with first-class honors in 1897. Germany was the most preeminent country regarding the physical sciences at this time, so Clowes pursued his PhD at the University of Gottingen. While nearing completion, he discovered from a roommate, Dr. Harvey Gaylord, that a new cancer-research laboratory was being established in Buffalo, New York, the first of its kind in America. Dr. Gaylord was being commissioned to study the chemistry of the disease, and recruited Clowes to work alongside him. The over-enthusiastic Clowes could not bear to listen to criticism of fellow colleagues warning that there was no future in cancer research, and that more reputations were ruined rather than created within the field.

[17] Ibid., 92-94.
[18] Cooper and Ainsburg, *Breakthrough*, 117.

They told him that "he would be selling his medical and scientific birthright for a mess of pottage."[19] Despite this, Clowes was entranced by the prospect of a much more personalized and unregulated environment—he travelled across the pond— leaving his home for a land of unrestricted opportunity.

Upon his arrival in Buffalo, Clowes proved instrumental in defining the importance of chemical research in the investigation of cancer. He published a number of works in American and British journals at the turn of the century, further discussing chemistry-based research and immunology. As time passed, however, he began to heed the early warnings he had previously ignored. Research ultimately aimed at clinical care began to overtake the work done by scientists like Clowes, which was aimed at studying the disease itself. He felt his work was viewed as less important, and desired a mix of basic and applied science. While he maintained his desire to advance cancer research, his evolving insights and recent marriage led him away from Buffalo and the Gratwick Institute. In addition to a stint in Jamaica working on applied research regarding the chemistry behind rum fermentation, Clowes continued to conduct research at the American University Experiment Station in Washington and at the Marine Biological Laboratory in Woods Hole, Massachusetts.

Back in Indianapolis, Eli Lilly and Company's management, led by J.K Lilly Sr. and Eli Lilly Jr., recognized the lack of groundbreaking drugs originating from within their company, despite many advances in production and manufacturing. In 1919, Lilly presented a four-year plan to address the situation, with the main stipulations being a revitalization of the Science Division with a shift towards basic research, and the creation of an experimental medicine department tasked with identifying and developing specialty drugs with a high market value.

[19] Alexander W. Clowes, *The Doc and the Duchess: The Life and Legacy of George H.A. Clowes* (Indianapolis: Indiana Historical Society Press, 2016), 22-28.

Such a new direction required leadership of a highly trained scientist who understood and valued research and development initiatives; Eli and J.K. Lilly found such a paragon in George Clowes. He was increasingly seen as an elite scientist—considering his experience with basic research in cancer immunity, colloidal chemistry, and his applied research in Jamaica, among other factors.[20] It seems clear that Clowes was eager to find a position that would allow him to pursue his interests in basic research, earn a living wage, and carry out applied research as needed. Most important, he sought autonomy to pursue research as he saw fit. The Lillys sought a knowledgeable chemist with a solid reputation who would be willing to assist in leading the company in a new direction. These criteria aside, the company was quite willing to take a hands-off approach and eschew the typical close management and supervision of affiliated researchers. While working at Woods Hole, Clowes met with J.K. Lilly Sr., who offered him a position on staff as a biochemist with guaranteed promotion to the Director of Research. Announcing to the pharmaceutical world Clowes' appointment, the company composed:

> The position given Dr. Clowes by Messrs. Eli Lilly and Company represents a somewhat novel departure for a commercial concern and even for a research institution. Realizing the necessity for more fundamental investigation regarding the mode of penetration and function of drugs in the tissues, Messrs. Eli Lilly and Company have provided Dr. Clowes with ample laboratory facilities and assistants, and have given him complete freedom from all routine or commercial work in order that he may devote his time to a continuation of the studies in which he has already engaged in the border-line field between physics and chemistry on the one hand, and biology, pharmacology, and medicine on the other.[21]

As stated, this position would give Dr. Clowes free reign to conduct research for the company's benefit as he saw fit. Once settled into his new position, Clowes worked in conjunction with the Lilly administration to evaluate current progress and expertise, design new

[20] Ibid., 62-64.
[21] J.K. Lilly, Sr., "A Plan for Promoting the Affairs of Eli Lilly & Company during the Years 1920-21-22-23," October 26, 1919, XCAfe, Lilly Archives

research teams, and build a unit of fellow researchers who would focus on both practical and theoretical medical research. The hypothesis they aimed to support was that fundamental research would ultimately lead to practical applications, thereby enhancing not only the company but the medical field at-large. At the time, most American companies were unwilling or unable to reduce focus on short-term revenue and expansion in return for long-term investment and stability strategies. With Clowes' hiring in 1919, Eli Lilly and Company proved quite willing to take the risk.

Returning to New Haven, Connecticut, Dr. Banting had just finished the presentation of his research to members of the American Physiological Association. Many of the attendees, being an experienced, critical group of experts, were impressed by the results but unimpressed with Banting's nervous and halting manner. This did not seem to faze Dr. Clowes, who phoned Dr. Macleod that evening with quite an interesting offer: his company's resources and expertise in helping prepare the insulin extract for commercial use. Though acknowledging the presentation's shortcomings —"It is true that Banting presented his material somewhat haltingly and certainly very modestly," Clowes wrote —he recognized the extent of such a discovery and was eager to insert Eli Lilly and Company into the narrative of evolving diabetes research and development. He continued to Macleod: "Provided the work could be brought to fruition there was every prospect that an important means of treating diabetes would be developed."[22] Macleod, not yet sensing an urgent need for commercial production, kindly declined the offer, while assuring Dr. Clowes that the two men would keep in touch.

Upon the completion of the conference, Dr. Macleod assembled a seven-man team (adding four new members) charged with the further development and standardization of the

[22] Michael Bliss, *The Discovery of Insulin* (Chicago: University of Chicago Press, 2007), 106.

insulin extract in Toronto. The time soon came to test the extract on human subjects; these were mainly individuals so near the brink of death due to diabetes that they had little to lose. While early injections had little to no effect, some patients saw stabilization or slight rises in blood sugar levels. J.B. Collip resolved to settle the increasingly common problem of hypoglycemic reactions (now known as "insulin shock"), which occurs when the blood sugar falls below certain levels. Macleod subsequently assigned him the all-important task of preparing the extract for clinical use. Prior to this time, Macleod was uncertain of the extract's potential commercial capabilities or uses. While he was quite intrigued, and even pleased, with Banting and Best's experiments, their inconsistent and often arbitrary results led him to err on the side of caution. He was much more willing to rely on the expertise and experience of J.B. Collip, who worked tirelessly in the lab, attempting to replicate and standardize a formula for the extracts of Banting and Best's that had been successful experimentally. His challenge lay with producing a purified, yet potent and effective, insulin extract that could be manufactured for clinical use. It was late on the night of January 19th when Collip reported a perfect solution: he had found the ideal amount of alcohol to use as an aqueous solution without destroying the active principle in the extract. Finally, a standard process existed that, when replicated, produced a pure and potent insulin extract that evidently lowered the blood sugar of diabetics.[23] The lives of diabetics around the globe would soon be forever altered, and millions would be given a new sense of hope.

As the trials on human patients began to yield more consistent results, press coverage of the discovery was beginning in Toronto by January 1922; the extract was successfully administered to its first American patient, fourteen-year-old Leonard Thompson, in Toronto during this time as well. Upon his admission to Toronto General Hospital in late December 1921,

[23] Ibid., 116.

Thompson had weighed just sixty-five pounds and was on the brink of death. He continued to worsen even after being administered a strict diet of 450 calories per day; "All of us knew he was doomed," a senior medical student recalled.[24] Miraculously, as the young boy was administered Collip's newly-purified extract, his glycosuria disappeared and his blood sugar levels steadily rose and stabilized. Now armed with evidence that this extract had observable commercial benefits, Macleod negotiated an agreement with the University of Toronto's Connaught Anti-Toxin Laboratories just days after Collip's discovery, aiming to manufacture insulin that would be used by a select number of practitioners.[25] Banting and Best continued to publish and present material about their experiments and the discoveries of their team, as press coverage across North America picked up speed. Dr. George Clowes, refusing to relent, made a formal offer (in writing) to Toronto on April 3, 1922 about the possibility of collaboration for large-scale insulin production on behalf of Eli Lilly and Company; his offer was again refused, as the Toronto associates trusted the capabilities of their newfound partner, Connaught Laboratories. Notably, the responsibility of insulin production shifted from Collip to Charles Best in May of 1922, as Collip returned to the University of Alberta upon the completion of his fellowship.

By this time, the commercial benefits of insulin were clear, and many doctors were incredibly eager to acquire some for their patients. The first widely publicized announcement (also the first time the pancreatic extract was referred to as "Insulin") came with a May 1922 presentation of another joint publication: "The Effects on Diabetes by Extracts of Pancreas."[26] Toronto quickly became overwhelmed by the skyrocketing demand; paired with the limited resources of the small Connaught Laboratory, the problem began to escalate by the day. This

[24] Frank Allan, "Diabetes Before and After Insulin," *Journal of Medical History* 16, no. 3 (July 1972): 39.
[25] *Discovery of Insulin at University of Toronto*. Archival Exhibit from Heritage UofT, University of Toronto Libraries. https://heritage.utoronto.ca/exhibits/insulin (accessed November 2018).
[26] Ibid.

puzzle became much more catastrophic when considering another incredible disaster: J.B. Collip was soon destined to return to Alberta, where he could not make insulin. First, he had great difficulty manufacturing the extract in large batches (at this point, the only suitable solution to such high demand). Additionally, he was unable to duplicate his procedures that had successfully purified and standardized the extract earlier in the year. To the frustration of many of his associates, the scientist had not written down his experimental steps. An insulin famine subsequently occurred in Toronto during the spring of 1922, greatly trying the scientists tasked with solving such an issue, as well as worrying and angering the limited number of doctors who had quickly come to rely on insulin. Though Dr. Macleod was loathe to admit it, he now began to accept the reality: Toronto could theoretically produce the insulin extract, yet in actuality, could not produce it in large quantities sufficient enough for commercial use (and sometimes, in no quantities at all). Pragmatically, it was realized that more assistance was needed.

As the troublesome Toronto spring dawned, Dr. Clowes again wrote Macleod about Eli Lilly and Company's continuing interest in helping develop the insulin extract:

> Public interest in this work will naturally be very great and the demand for the product will be such as to lead to attempts on the part of unprincipled individuals to victimize the public unless some steps are taken to arrange for the manufacture of the product by the procedures recommended by Dr. Collip and the control of the product by means of such tests as you and your associates would consider necessary… I have thus far refrained from work starting in our own laboratories on this question, as I was anxious to avoid in any way intruding on the results of yourself and your associates. I feel, however, that the matter is of such immediate importance that we should take up the experimental end of the question without delay, preferring to cooperate with you and your associates...[27]

As problems abounded, Macleod relented to Dr. Clowes and accepted the proposed assistance. Though troubles and hesitations were present, the need for the expanded manufacture of the extract (with its maximum commercial use in mind) forced the University of Toronto to look elsewhere. On May 30, 1922, an agreement was forged between the Governors of the University of Toronto and Eli Lilly and Company in an effort to manufacture insulin on a large

[27] Michael Bliss, *The Discovery of Insulin* (Chicago: University of Chicago Press, 2007), 132.

scale. As argued by Michael Bliss, it is probable that Macleod felt he had no other option by that point; as Clowes rather politely put it, barring any legally-binding patents, other institutions could very well attempt to replicate the extract themselves. Though Toronto did not have a profit motive, the thought of losing the valuable reputation and recognition they had acquired proved the icing on the cake. Likewise, they considered: if Toronto did not take out a patent on the formula, would someone else? Even worse, what if said organization or individual did possess a profit motive? After realizing the gravity of Clowes' pronouncement, the University filed a patent under the names of Best and Collip as a defensive measure; in fact, the point was to stop individuals who may have been seeking to manufacture the extract in search of a profit. Dr. Banting, in particular, initially viewed the patent as a violation of the Hippocratic Oath, and was reluctant to pursue it. Yet by doing so, the Toronto associates ultimately solidified their aims of medical progression and advancement, and assured that this advance in healthcare would be freely available to humanity.

With Eli Lilly and Company of Indianapolis now fully incorporated into the production process, observers hoped for a larger supply that could be more quickly administered and used. Researchers from both cities dedicated themselves to rediscovering the formula for purified, potent insulin; the Indianapolis chemistry team was headed by lead chemist George Walden. Banting, Best, and the remaining Toronto researchers finally detected that using slightly-acidic acetone as a solution was the most preferable method discovered thus far to maintain purification. Though this lessened the severity of the insulin drought, patients and doctors alike continued to sporadically complain that the insulin was not potent enough, and "effectively useless."[28] The Indianapolis team, too, worked tirelessly to improve the processes of isolation

[28] Thea Cooper and Arthur Ainsburg, *Breakthrough* (New York City: St Martin's Press, 2010), 98-102.

and purification, in order to yield more consistent and beneficial results. An invaluable discovery was made by Walden: that of isoelectric precipitation, which made large-scale production definitively possible.[29] Simply put, this method assured ideal pH levels within acetone, which would prevent a loss of potency while maintaining appropriate standards of purification. Thanks to the collaborative efforts of Toronto and Indianapolis scientists, insulin could now be effectively standardized and purified enough for widespread commercial use; the crucial foundation had now been laid for millions of diabetics to benefit from such a revolutionary discovery.

Though the agreement was unarguably symbiotic and offered clear benefits for medical progression, it was not without conflict or controversy; nearly all of this was internal. Eli Lilly was quite progressive in outlook and equally committed to bringing maximum benefits to diabetic patients. With leaders like Eli Lilly Jr. and Dr. George Clowes, this held especially true and was a significant driver of company policy initiatives. The leadership of the men was crucial in cultivating a culture of innovation within the company, which continued to set them apart from other American companies. Moreover, it allowed them to set the future trajectory of the company and shape its modern vision. However, Eli Lilly was investing huge sums into research and manufacturing, especially because producing the extract in such large quantities was a time-consuming and often laborious process. They still were ultimately forced to maintain a profit motive to sustain themselves; their investment simply had to see a return. Toronto acknowledged this and granted Eli Lilly and Company a one-year monopoly (to expire June of 1923 to produce "Isletin-Lilly." This monopoly, short-lived as it was upon the wishes of Toronto academics, would nevertheless offer Lilly an exponential advantage vis-a-vis other future potential

[29] James Madison, *Eli Lilly* (Indianapolis: Indiana Historical Society Press, 2006), 68.

manufacturers of insulin. The early name-recognition that Lilly acquired would provide lasting benefits. The name of the extract produced by Lilly was also a source of controversy between the two cities. Lilly wanted to market a slightly distinct "Iletin," but compromised with Toronto associates in their acceptance of adding "Insulin, Lilly" to the end of the name.[30] Despite a few trials, the partnership between Eli Lilly and Company and the University of Toronto proved effective; the insulin drought in Toronto officially ended, and shipments began to be distributed to clinics and top specialists throughout the United States. Within a year of the contract, Eli Lilly and Company was producing enough insulin to satisfy the demand in all of North America.[31] Now children such as Thompson and Hughes, as well as long-suffering adults, had a new chance at a long, happy, healthy life.

Though such a partnership's significance cannot be denied, the story of Eli Lilly and Company and the University of Toronto has never been told as a single narrative. Yet, the partnership was among the first borne explicitly to bring a new drug to market, and had lasting implications regarding collaboration, academic-industrial relations, and medical progression. Though insulin is naturally occurring within the body, and therefore not always classified as a "drug," its discovery and isolation were revolutionary. Dr. Frederick Banting (and by association, Charles Best) has traditionally been portrayed as the "discoverer" of the insulin secretion within the pancreas, and should be given much credit for his idea and willingness to continue difficult experimentation in pursuit of an ultimate medical benefit. However, the process of purifying insulin for commercial use was much more of a group effort, led by Dr. Macleod at the University of Toronto, with Eli Lilly Jr. and Dr. Clowes in Indianapolis leading crucial efforts on the manufacturing side. Though the University of Toronto had acquired

[30] Michael Bliss, *The Discovery of Insulin* (Chicago: University of Chicago Press, 2007), 180.
[31] Basil Achadellis et al., *Pharmaceutical Innovation* (Philadelphia: Chemical Heritage Press, 1999), 242.

improved funding and resources immediately prior to the 1920s, the institution was still not considered especially reputable or top-tier. Despite this, the University proved adaptable and willing to dispense these resources in pursuit of something revolutionary. At a time when many academic institutions were uninterested in sponsoring unsupported or potentially inconclusive research, Toronto took the lead in giving such nascent ideas a chance to develop. The associated Toronto General Hospital was also the first major distributor of the insulin extract to diabetic patients. Therefore, the University of Toronto associates were instrumental in the isolation and purification of insulin, and the University was among the first academic institutions in North America to express a firm commitment to advancing the medical field in tandem with pharmaceutical companies.

Eli Lilly and Company was arguably more well-suited to become an actor in this narrative than many other American companies at the time, who were still focused on short-term development and profit initiatives. Much of this is thanks to Eli Lilly Jr. and Dr. George Clowes, who worked to cement their company's position as one of the earliest pharmaceutical manufacturers committed to in-house research.[32] Both have become Indianapolis icons who helped get Eli Lilly and Company on par with efficient and progressive research; both were monumental in priming the company for large-scale insulin production. Because of such a relatively early commitment to research and development, Eli Lilly and Company has grown into one of North America's foremost pharmaceutical manufacturers, with their market capitalization ranked fifth of all American pharmaceutical companies at the turn of the twenty-first century, and profitability also within the top five.[33] Though many other company's endeavors into research and development did not bear fruit until the post-WWII years, Lilly and Company was

[32] Ibid., 53.
[33] Ibid., 132-133.

among the first to bring tangible changes to market, profiting while also assisting in medical advancement. It seems clear that Toronto and Indianapolis found ways to benefit from the other's expertise and resources while also creating maximum benefits for themselves within their respective academic-industrial fields.

The strongest links among science, technology, and industry were forged by such radical innovators as discussed within this paper, and their innovations were commercialized when the scientific knowledge on which they were based was only partially understood. The medicinal properties of such discoveries and inquiries attracted the curiosity of scientists and academics, who worked to further uncover underlying properties or potential uses and purposes. The University of Toronto researches, chief among them Banting, Best, Collip, and Macleod, perfectly represent such an objective. The companies that commercialize such innovations desire to do so in order to improve the quality of products, develop better manufacturing processes, and introduce new products to ever-expanding markets. Likewise, Eli Lilly and Company perfectly exemplifies such a forward-thinking company, committed to funding research projects and developing in-house research expertise in the scientific principles that underlie such radical innovation. As the twenty and twenty-first centuries have progressed, academic and industrial institutions still owe much to the synergies created by academic-industrial research that was popularized during the time under analysis. The direction and pace of North American scientific and technological advances has clear roots in the preliminary partnerships forged in the early twentieth century; Indianapolis and Toronto's narrative is perhaps the most interesting and clear example of such a beneficial construction. Even considering such consequences, perhaps the most relevant takeaway of this partnership is its most contemporarily-cherished: diabetes is no longer a death sentence.

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