Insulin at 100: Indianapolis, Toronto, Woods Hole, and the "Insulin Road"

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Abstract: "Insulin at 100" joins a body of new scholarship being produced globally to commemorate the discovery of insulin. The paper brings to light a new perspective on the collaboration between two North American institutions, the University of Toronto in Canada and Eli Lilly & Company in the United States. It focuses on the collaboration's complexities, actors who have not been examined previously, and implications for both parties and the general public. The article contributes to existing scholarship by expanding the collaboration story to include central actors at both Eli Lilly and Company and the University of Toronto in a continuous and collaborative cycle.

Keywords: Insulin, innovation, University of Toronto, Eli Lilly and Company

In 2021 the world commemorates the 100th anniversary of insulin's discovery. The discovery remains one of medicine's most celebrated stories, told and retold, approaching a mythical account of heroism and man's triumph over nature. Michael Bliss's *The Discovery of Insulin* (1982) remains the definitive study, exhaustively researched and exquisitely written. Interpretations that build on Bliss's work examine key aspects of the discovery and subsequent medical advances in the treatment of diabetes. Academic and popular literature as recent as 2017, however, continues to linger over the four University of Toronto scientists, their relative contributions, Nobel prize controversy, personalities, and legacies. When Lewellys Barker declared at Toronto's 1923 Nobel Prize dinner, "In insulin there is glory enough for all," he meant glory enough for the four discoverers: Frederick Grant Banting (1891-1941), John James Rickard Macleod (1876-1935), James Bertram Collip (1892-1965), and Charles Herbert Best (1899-1978).[1] The four scientists and the unique discovery story are no doubt remarkable in and of themselves. The collaboration between the Toronto team and U.S. pharmaceutical manufacturer, Eli Lilly and Co., while thoughtfully examined in Bliss, *The Discovery of Insulin*, Sinding, "Making the Unit of Insulin" (2002), and Swann, *Academic Scientists and the Pharmaceutical Industry* (1988), remains overshadowed in the canon of insulin scholarship.[2] Studies continue to emphasize the *discovery* – the new idea – over the *innovation* – the combination of financial, human, and material capital that makes the new idea useful to society.[3] Scholars, moreover, have overlooked large-scale production challenges and economic impacts in "miracle" drug histories.[4] This essay argues that glory enough for all the discoverers *and* the innovators exists. The essay, therefore, contributes to existing literature by expanding the collaboration story to include central actors at both Eli Lilly and Co. and the University of Toronto in a continuous cycle represented in Figure 1:

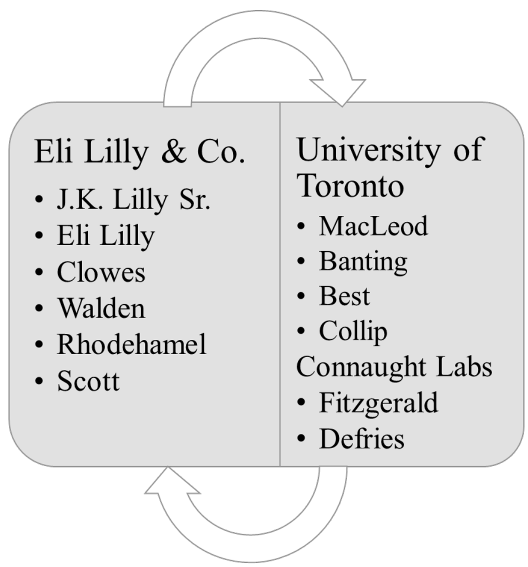


*Figure 1: Eli Lilly and Co. and University of Toronto central actors in insulin discovery and innovation.*

Extant scholarship does not address the complexities and challenges of taking medical discoveries to large-scale production. The penicillin studies further remind us that innovation is iterative, failures inevitably precede an ultimate success, and lesser known actors may play significant roles in the outcome. Accordingly, Gelijns and Thier (2002) noted that the partnership roles of universities and industrial firms are seldom studied. They argued that the traditional image, that "academic faculty generate fundamental knowledge that industry in turn develops and markets" does not do justice to the intimate and interdependent collaboration that occurs.[5] Pickstone (2001) considered pharmaceuticals a as science, technology, and medicine field in which knowledge development, or "ways of knowing," included ways of production. Technoscientific networks, such as the academic-industrial collaboration that brought insulin to the market, began after 1870. The Lilly-Toronto collaboration exemplifies the "technoscientific complex" phenomenon that Pickstone articulated.[6]

Achilladelis (1999) explored pharmaceutical innovation, noting that industrial research gradually outpaced academia after the early 1900s. Most innovation occurred in academic settings before the pharmaceutical industry existed, prior to 1880. As the industry emerged between 1880 and 1920, innovation rapidly shifted domains with an upswing in industrial "radical," or highly original innovation, as presented in Table 1:[7]

| Time Period | Academic | Industrial | Total Innovations |
|---|---|---|---|
| 1800-1900 | 56 | 24 | 80 |
| | *70%* | 30% | |
| 1900-1920 | 15 | 48 | 63 |
| | 24% | *76%* | |

Achilladelis examined the sources of innovation but not academic-industrial collaboration, but we can locate insulin as a "radical" innovation that pioneered collaboration just as pharmaceutical research departments were forming – creating precedent for the coming decades. Chin-Dusting et al. (2005) found that the nineteenth-century view of German *Wissenschaft* (pure research) vis-à-vis pharmaceutical profit making remains widely held, especially in academic circles. They noted that drug innovation since World War II in fact resulted from multiple origins and highly collaborative environments.

Figure 2 reveals the research organizations in which 32 new drugs originated between 1945 and 1990:

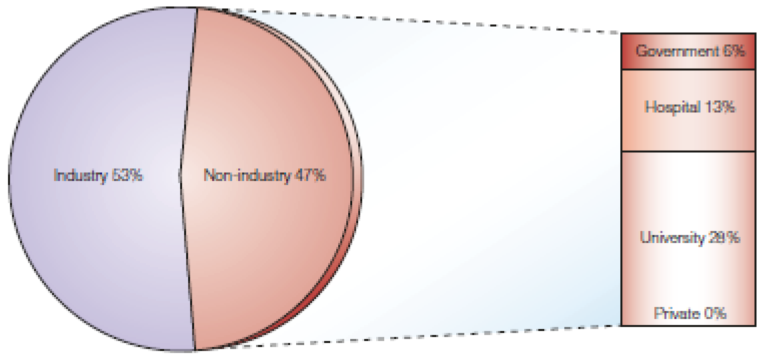


*Figure 2: Who Contributes to the Making of Innovative Drugs?* [8]

A closer examination of academic-industrial collaboration in medical innovation allows us to understand the 1920s insulin collaboration as the prototype for future innovation across the United States pharmaceutical industry. The insulin innovation gave rise to not only Eli Lilly's "corporate technology tradition," but created the blueprint for its peers to emulate.[9] Studies of penicillin's discovery, for example, have demonstrated that bringing the miracle drug to patients was far more complex, multi-party, and international than Alexander Fleming leaving the window open only to discover mold.[10] This broader framing allows for a deeper understanding of the extensive interaction, bidirectional transfer of knowledge, and complementary intellectual contributions of Eli Lilly and Co. (Lilly) and the University of Toronto and its Connaught Antitoxin Laboratories (Toronto) between 1921 and 1923 to bring insulin to patients. In addition, a closer examination of Lilly's own interdependent scientific and organizational innovations around 1920 further illuminate the insulin story.[11] With scientists from both teams making *at least* 35 train trips between Indianapolis, Toronto, and Woods Hole in 1922 alone, the discovery, refinement, standardization, and production of insulin was a phenomenon of what this essay calls "the insulin road."[12]

In the nineteenth century Western Europe and the United Kingdom led the world in biochemical and physiological research with the Pasteur Institute (founded 1887), the Robert Koch Institute (founded 1891), and the Lister Institute (founded 1893) together representing the pinnacle of medical science. Laboratory medical research in North America had emerged slowly, appearing first in universities. Toronto stood at the forefront just as medicine's "center of gravity" was beginning to tilt across the pond to Canada and the United States, having expanded by 1900 in recognition of laboratory medicine as the wave of the future.[13] The famous Flexner Report (1910) singled out the University of Toronto's clinical and laboratory resources as comparable to the world's best.[14] Academic disrespect for industry, especially the pharmaceutical industry, ran high in the wake of suspicious patent medicines and outrageous flim-flam advertising. Academic scientists claimed the moral and ethical high ground based on the foundation of pure research for the public good, untainted by profit motives. The academic laboratory existed to discover and to pursue new knowledge as the highest good. Smithsonian President J.J. Carty wrote in 1916 that the institution was just beginning to appreciate the relationship between academic and industrial research. While both cohorts contributed to society, he noted, he clearly reflected the zeitgeist that pure scientists worked for the joy of discovery, industrial scientists for practical application and utility.[15] Philanthropy, moreover, reinforced the binary by funding discovery over innovation. Rockefeller Foundation President Raymond Fosdick reflected that the foundation preferred studies "likely to add to man's understanding of the living world," not the degree to which they promised an "immediate practical result."[16] To observe new phenomena and to develop medicines stood worlds apart.

Hoping to sharply distinguish academic researchers from those housed in pharmaceutical concerns, the 1908 American Society for Pharmacology and Experimental Therapeutics founders barred anyone "in the permanent employ of any drug firm" from membership.[17] The disdain that academic scientists held for industrial researchers was so pervasive that Sinclair Lewis depicted the moral divide in *Arrowsmith* (1924). Martin Arrowsmith's hero, Max Gottlieb, symbolized the utter reverence with which pure researchers held German *Wissenshaft*. When Gottlieb, the world's most distinguished immunologist joined a reputable pharmaceutical firm, his former colleagues wailed and cried, "*Voila*! He is dead."[18]

Legitimate scientists nonetheless pursued the commercial route and the U.S. pharmaceutical industry established research operations in lockstep with academia. During the nineteenth century, the industry evolved from small apothecary shops to local family businesses to large firms with greater geographic reach. Liebenau identifies the decades between 1890 and 1930 as the years in which the industry grew into its modern form, with Lilly as one of eight leading firms that emerged. Leading firms embraced the scientific revolution to elevate their image, signal legitimacy, distinguish themselves from controversial patent medicines, develop new products, and expand into new markets – patterned after the Pasteur and Koch models.[19] After 1890, this coterie of firms overtook small competitors by offering a full range of standard products and by engaging scientifically trained staff in systematic fashion. Pharmaceutical leaders accessed newly available capital for manufacturing expansion, laboratory development, and strategic additions to human resources. The scientific revolution further improved the industry by sorting out inferior suppliers. Product standardization, achieved through mechanization and laboratory quality control, allowed leaders to force small, less reputable manufacturers out of the market.[20] Federal regulation arrived with the Pure Food & Drugs Acts of 1902 and 1906, but leading firms were well on their way to establishing quality standards in advance of legislation.

Such use of science and technology allowed Eli Lilly and Co. to emerge as an industry leader. Colonel Eli Lilly (1838-1898) founded Eli Lilly and Co. in 1876 as an integrated manufacturer and wholesaler. The founder's son, Josiah Kirby Lilly, Sr. (1861-1948), succeeded him as president in 1898 and presided over five decades of growth, innovation, and modernization. J.K. Lilly in 1882 had graduated *cum laude* from the Philadelphia College of Pharmacy and returned to the business imbued with high expectations to place the pharmaceutical business on "equal footing with medicine."[21] By 1910, the firm had complied with the Food & Drug Acts with minimal disruption and was one of the first pharmaceuticals to receive government certification. It added the first of fifty automatic capsule making machines (1913) and an entire science building (1911), which later earned recognition in *Scientific American*.[22] J.K. Lilly's eldest son, Eli Lilly (1885-1977), also a Philadelphia College of Pharmacy graduate, introduced Frederick Taylor's scientific management to the business in the 1910s.[23] J.K.'s senior management executed what he described as "conservative progressivism" that became the hallmark of the J.K. Lilly years.[24]

Chandler (2005) characterized Lilly as the "most successful American producer in expanding its capabilities as new technologies enlarged existing paths of learning."[25] Chandler based his assertion on more than a century of history. J.K. Lilly, who a close colleague described as a true "captain of industry," laid the foundation formally in 1899 with the proclamation, "to contribute to the progress of medicine by developing new and superior agents through research."[26] University departments of chemistry, biology, physics, anatomy, and physiology were sufficiently developed that forward looking pharmaceuticals had a pool of educated and trained scientists from which to draw.[27] J.K. Lilly deliberately hired botanists, chemists, pharmacologists, biologists, and clinicians to undergird his research commitment.

As pharmaceutical houses built their research teams and laboratory facilities, the role of research director emerged in select firms, first in Europe and later in the U.S. In Germany, Bayer hired chemist Heinrich Hörlein (1882-1954) in 1902 and he quickly rose to manage the firm's pharmaceutical-scientific labs and an 82-person staff. Hörlein defined the research manager as liaison between Bayer and the scientific and medical communities. He became the archetypal research manager, with a holistic, systematic, long-range view of the need for special interactions among researchers and their organizations to achieve optimal results. Scientists in isolation, he advocated, could not achieve success without cooperation.[28]

Lilly, similar to Bayer, placed its systematic research agenda and resources within the purview of its executive leadership team, a move that predated most of its peers.[29] The industrial laboratory of only a few corporations deliberately connected invention and development.[30] In 1916 Lilly's chief of research, Dr. Frank Eldred, invited Dr. George Henry Alexander Clowes (1877-1958) to deliver a lecture on electrolytes.[31] While in Indianapolis, Clowes met President J.K. Lilly and Vice President Eli Lilly, which brought together three of the dynamic leaders who would transform Lilly into a modern, international corporation.

Clowes hailed from England with a Ph.D. in chemistry from the University of Göttingen. His resume included research positions at several prestigious institutions, including the Marine Biological Laboratory at Woods Hole, Massachusetts.[32] His wide-ranging research interests positioned him to contribute uniquely to Lilly's future. Fermentation studies translated to scaling for production and development of antibiotics. Clowes' focus on cancer research may have intrigued J.K. Lilly above all, as Colonel Lilly had died of cancer.

Clowes possessed insatiable curiosity for discovery and an aptitude for applied science. After a period of courtship, J.K. Lilly hired Clowes in 1919 and promoted him in 1920 to Director of Biochemical research. Lilly announced the position as a "somewhat novel departure for a commercial concern and even for a research institution."[33] Clowes put into action the research and development agenda that J.K. Lilly had foregrounded in 1899. Clowes would have ample laboratory facilities, staff, and carte blanche to pursue avenues of interest in physics, chemistry, biology, pharmacology, and medicine – or an intersection among the fields. Clowes could divide his time between Woods Hole from June to October and Indianapolis the balance of the year such that Indianapolis and Woods Hole developmental research programs became interdependent.[34] Lilly scientists, Lilly laboratory assistants, and university graduate students joined Clowes at Woods Hole to work on extended projects in summer months. Clowes' believed nothing less than the "welfare and advancement of mankind" were at stake, thus never wavered from his commitment to "fundamental research."[35] Even as a pharmaceutical executive, Clowes recognized the crucial value of pure research claiming "the necessity of securing the recognition, respect and confidence of scientific and medical organizations and individuals … For this reason it may pay to spend a great deal of time on the scientific intricacies of problems from the solution of which there may be no immediate commercial return."[36] Clowes was one of only a handful of researchers who moved easily among universities, industry, and government agencies.[37]

Clowes became the lynchpin to J.K. Lilly's strategic plan launched in 1920. The plan captured the state of the firm, effects of World War I and the influenza epidemic, and strategies and tactics for growth (capital requirements, marketing and sales, product development). The war years meant rising raw material prices and falling sales, but the armistice rocketed sales up 50%. Drugs fell into one of three divisions: pharmaceutical, biological, and scientific. Pharmaceutical and biological production, a roster of hundreds of medicines, was at capacity, projected to double with increased material and human capital and greater geographic distribution.[38] Clowes oversaw a staff of 50 in the scientific division, charged to "prepare for one or more Pharmaceutical preparations of large possibility." J.K. Lilly called for all departments to "revolutionize our methods."[39] The research plan had to build on Lilly's drug portfolio of extracts, liquids, tablets, syrups, ointments, and tinctures, many of which diminished symptoms rather than cured diseases. J.K. Lilly singled out glandular extracts in particular for development into a "broad line," unique among peer pharmaceutical houses, presciently believing that research funding could produce significant results.[40]

Clowes brought academic-industrial boundary spanning ability to Lilly that was unique for the time. His Woods Hole installation placed Lilly as the only pharmaceutical lab nestled among university laboratories: Stanford, Harvard, Yale, most eastern schools, and some from the Midwest.[41] His vitae included publications in the prestigious *Journal of*

*Experimental Medicine* and *Science*, and papers presented to the American Chemical Society. His mentor, Dr. Wilder D. Bancroft, edited the *Journal of Physical Chemistry* and served twice as president of the Electrochemical Society. Clowes' network of medical contacts numbered in the dozens.[42] J.K. Lilly commended Clowes on his first publication as a Lilly employee in the *Journal of the American Medical Association*, adding that it should "break their precedent of refusing to publish scientific work done in commercial laboratories."[43]

It is unremarkable, then, that Clowes heard rumors of Banting and Best's Toronto experiments from his peer Lewellys Barker, a University of Toronto graduate. Nineteenth-century scientists had linked the pancreas with diabetes. Langerhans, Mering, Minkowski, and Sharpey-Schafer had learned that the pancreas contained separate clusters of cells and that pancreatic function included both internal and external secretions, but no one had isolated the internal secretion: insulin. Research had progressed iteratively ever since, although World War I halted diabetes research, especially in Germany where scientists were close to discovering the hormone.

On Sunday, October 30, 1920 Banting reviewed the extant literature to prepare for a class lecture on the pancreas the next day. During the night he envisioned a surgical technique to isolate the internal secretion. J.J.R. Macleod, head of physiology at the University of Toronto, provided Banting with a small lab, several dogs, and the assistance of biochemistry and physiology student Charles Best. They began grueling experimentation in May; by November 1921 the Toronto team planned to present their preliminary findings outside of the university.[44] Deeply entrenched in the scientific milieu, Clowes learned of Banting's upcoming presentation at the American Physiological Society annual meeting on December 30, 1921. J.K. Lilly, Eli Lilly, and Macleod all encouraged Clowes to attend the conference. With Eli Lilly's pithy "Go for it!" in mind, he boarded a train for New Haven on Christmas Day 1921 – the insulin road's inaugural trip. Clowes listened to the findings and proposed collaboration to Macleod on the spot.[45]

Macleod, Banting, Best, and Clowes discussed potential collaboration. Clowes pointed out "that before long their problem might well be one of large-scale production, in which case they would need the help of chemical engineers, who were not to be found at that time in any university group."[46] Macleod declined as he had recruited biochemist J.B. Collip, on sabbatical from the University of Alberta. Macleod also leveraged the university-based laboratory and modest biologicals manufacturing facility, Connaught Antitoxin Laboratory (Connaught).[47]

In January 1922 Connaught's leaders John G. FitzGerald (1882-1940) and Robert D. Defries (1889-1975), formalized a research and development agreement between Connaught, Banting, Best, Collip. and Macleod. The agreement stipulated that the collaborators not file patents with a commercial pharmaceutical firm during an initial working period and that no modification to the research proceed without all parties' agreement. FitzGerald offered Connaught's facilities, its expertise, and $5,000 to expedite insulin development and production. FitzGerald acknowledged that it would "consider subsequently the question of commercial production of the extract or extracts if and when its (or their) merit has been established and its (or their) method of preparation has been given to the world."[48] Collip directed initial extract production work with satisfactory small-scale production results, but subsequent experiments on any scale soon proved impossible to consistently duplicate.[49]

The complementary strengths of Lilly (industry's human, financial, material capital and significant capacity) and Toronto (academia's pure research, Connaught's biological research, development and production experience, and limited capacity) had developed sufficiently to be deployed in a collaborative framework. Although research expertise in both entities existed, Toronto initially perceived risks to collaboration, in addition to the moral divide, that outweighed rewards. Potential collaborative rewards for both parties appear obvious: the thrill of discovery, intellectual exchange, recognition, paths to new research, and – most importantly – lifesaving treatment for a horrific illness. For Lilly, an academic partnership promised legitimacy that further distanced it from less reputable peers.[50] Risks and unanswered questions, however, loomed large. No precedent existed in North America that could guide either Lilly or Toronto. The parties barely knew each other so trust, an essential element in any collaboration, had not developed. Each party brought competing goals and priorities as well as cultural, ideological, and organizational biases. No models for the proper length and scope of an agreement, nor the sharing of resources, costs, and intellectual property, could inform the collaboration. One party's subpar performance could damage the other's reputation. Industry's business development motive could inhibit knowledge dissemination within academia. Which party would establish the drug's cost to the end user once it went to market, and how would revenue be shared?[51]

Toronto's initial reluctance to collaborate with Lilly was bound up with conflicting philosophies on patenting medical innovation. Medical practitioners' ethics at the time held that profits from medicines return to the public in some way, so the practices of patenting, discovery, and innovation were intertwined. Industry viewed patents' benefits as translating discoveries into innovations, protecting the public from inferior quality products, and rewarding scientific research through recognition. Opponents in medicine and academia feared patents fostered jealousy, rewarded profit over pure research, and inhibited free market competition. German manufacturers routinely patented medical innovations to protect their market share for new drugs, even in the United States. The practice, which North America researchers considered taboo, lagged behind Germany until after World War I. U.S. pharmaceutical firms at the time didn't embrace patents strategically but instead focused on market development, production, and distribution.[52] The U.S. patent context exacerbated the philosophical divide as patent struggles characterized industrial inventions in the early twentieth century. Legal disputes raged over patent rights and contained highly normative questions of public interest: whom should patent law benefit and who should control goods and services?[53]

Each party independently prepared for potential collaboration. Toronto scientists prepared to file their first insulin patent during spring 1922 and sought a U.S. entity to which it would assign the patent to enable production. Toronto preferred a university to hold the patent "for the purpose of controlling the manufacture of Insulin" in that country.[54] Toronto assumed responsibility for controlling insulin in Canada and the U.S., as no U.S. organization was willing or able to accept patent rights on its terms. Only two precedents existed for patenting a medicinal extract derived from a natural hormone: adrenalin and thyroxine. Thyroxine's inventor, American chemist E.C. Kendall, had shared his patent with the Mayo Clinic and the University of Minnesota, stipulating the university organize the commercial production in the interests of the medical profession. The university established an *ad hoc* committee to administer the patent, transfer the invention to industry, assign license to a pharmaceutical firm (Squibb and Sons), thus retaining control over preparation, sale, and retail price.[55] Macleod modeled insulin's agreement and committee after thyroxine's.

Toronto formed the Insulin Committee to "undertake to issue licenses to those commercial firms that prepare 'Insulin' for sale, and to collect from them a royalty, the proceeds of which shall be used to establish a research fund in the University." Accordingly, Toronto would maintain "strict supervision over its production." Collaboration, it concluded, with "one pharmaceutical firm, rather than several … would likely prove more efficient than a divided one. Hewing to the prevailing academic ideology toward medical patents, Toronto protected itself from accusations of unethical behavior.[56] Once large-scale production was underway, Toronto could issue licenses to qualified firms to manufacture insulin.[57] The Insulin Committee prided itself as the "first example of a university undertaking to administer a university invention for the public good," although Minnesota with thyroxine had been the first.[58]

Lilly prepared for potential collaboration in significant ways. Clowes stayed in continuous communication with Macleod as Toronto's research and Connaught's attempts at production progressed. Clowes' research team introduced "intermediate scale experiments between the laboratory and the factory so as to anticipate factory problems and difficulties in advance and to give the workers in both fields a better acquaintance with one another's problems."[59] J.K. Lilly Sr. and Eli Lilly earmarked $250,000 in seed capital for large-scale production, 6% of the firm's capital and the equivalent of $3.2 million today.[60]

J.K. Lilly's multidisciplinary research team included George B. Walden (1895-1982), who had joined Lilly's research department in 1917 as an analytical chemist in organic research. Clowes described him as "not just a chemist but a chemical engineer," a "great rarity" in university labs at the time.[61] Walden came to Lilly with a bachelor's degree in chemistry from Franklin College and several summers of graduate study in chemistry and electrical engineering at the University of Wisconsin. He served for a year in the Army Signal Corps during World War I, then rejoined the research program on vitamins, hydrogen peroxide, and analysis of existing Lilly lines that included over 20 glandular products.[62] Fortuitously, Lilly chemists George Walden and his future wife Eda Bachman were conducting independent research on proteins at Woods Hole. The Walden team's basic science program on isoelectric precipitation involved new applications of a well-known principle.[63] Walden was working to determine the isoelectric points of materials in several of Lilly's products such as ipecac and squill. Although the experimental program did not involve insulin initially, it would be crucial to insulin production.

In May 1922, Toronto applied for its first U.S. patent and invited Lilly to collaborate. Macleod informed the university's president that Toronto needed a "commercial house" to execute production that had proven fraught with difficulties at Connaught. Toronto chose Lilly as it was "well equipped and properly staffed," and Clowes "a well-known scientist of high standing." Macleod moreover noted that the proposed collaboration could "not be criticized as unethical … or as in any way prejudicial to the free manufacture of insulin."[64] Accordingly, the collaboration meant that Toronto and Lilly would share all their knowledge. Lilly received a one-year exclusive to "make, use and sell" insulin in the U.S., Mexico, and South America, thus presumably recover its research and development costs. Lilly agreed to apply for new patents if it demonstrated that it "develop, improve, or simplify methods of producing" insulin (known as process patents), and only in Canada – not in the U.S.[65]

The collaboration involved large-scale clinical tests in Canada and the U.S. with Lilly supplying insulin free of charge in the one year "experimental stage" in which patient trials were underway, then selling at cost. Toronto prohibited Lilly from divulging production process details to other manufacturers. Toronto did not impose this restriction on itself as it intended to publish Connaught's production method so that qualified firms could produce insulin after May 30, 1923, the end of Lilly's exclusive period.[66] The resulting collaboration laid the foundation for the first major pharmaceutical academic-industrial collaboration, which was at best a fledgling concept.[67]

Events moved swiftly: travel on the insulin road began in earnest, Lilly and Toronto signed the first indenture, and Lilly ramped up for production.[68] Clowes named Walden supervisor of insulin production and assigned chemists Harley Rhodehamel and Jasper Scott, creating the team to carry out concurrent projects of experimental and large-scale production. Harley W. Rhodehamel (1884-1952) had graduated from Purdue University and joined Lilly's Analytical Department as a biochemist in 1907. As part of the department of approximately 60 people, he worked on the first standardized vitamins, barbiturates, and various synthetic organic compounds. He developed the manufacturing formulas for alcresta ipecac and oxyl-iodine, important new Lilly specialties.[69] An experienced chemist when the insulin opportunity arose, Rhodehamel traveled to Toronto early in 1922 (prior to the indenture agreement) to meet with Macleod. He foregrounded to Macleod that Toronto's major challenge, large-scale production, would require both chemists and engineers to accomplish.[70] Jasper P. Scott (1897- 1953) like Walden, graduated with a degree in chemistry from Franklin College. After serving in the U.S. Navy during World War I, Scott joined Lilly in 1920 as a research chemist.

The ink hadn't dried on the indenture before Walden, Rhodehamel, and Scott began daily experimental runs in June, repeating Toronto's small-scale insulin production experiments and scaling for production based on both cow and pig pancreas. By the end of August, Lilly had delivered more than twice the amount of insulin to which it had committed.[71] Clowes invited Best to Indianapolis to study the large-scale equipment and meet with Lilly's engineers, so that Connaught could duplicate the installation if desired.[72] Walden and Rhodehamel worked literally around the clock through the summer modifying the alcohol concentration, temperature, and extraction process, and laying out new equipment as it arrived. Rhodehamel recalled that "every available person was put to work on Insulin."[73] By September, however, complications arose: production yielded impure insulin and patients' side effects were troubling. The unrelenting pressure to perform took its toll. Clowes forced Walden to take a vacation before he collapsed and deployed Scott to take over. Scott did collapse eventually and had to take time off.[74]

Weeks of experimentation followed, then George Walden's science program at Woods Hole broke the production logjam and created the first contentious matter in the collaboration. Walden discovered that isoelectric precipitation could be employed to purify insulin in large yield by reducing its nitrogen content.[75] Walden's breakthrough proved extraordinarily valuable in two ways: it catalyzed insulin's high-volume production and it showcased innovation's role in bringing discovery to public benefit. During fall 1922, Lilly's insulin stability issue was traced to varying pH levels between batches. Walden closely tracked these levels and discovered that the weakening of the insulin solution was due to the gradual formation of a precipitate in the solution that also contained the active principle, the effect of which was to reduce the activity of the remaining insulin solution. It appeared that at the "wrong" pH, insulin was being precipitated out of the insulin solution. Walden realized that the precipitate was indeed far purer and potent than had been seen. And as Walden stressed, it was "a product having a stability many times as great and a purity ranging from ten to a hundred times as great as the best product hitherto obtainable."[76]

Another challenge in large scale pharmaceutical production, unique to industrial innovation, arises in supply chain management, which today is a well understood phenomenon; not so in 1922. Insulin production depended on a consistent, reliable supply of pancreas from slaughtered pigs or cows, material resources that academia would have no reason to marshal on its own. Lilly's headquarters sat squarely in the heart of the livestock packing industry. Indiana and the surrounding midwestern states boasted abundant agricultural resources to grow livestock feed, land on which to raise animals, and railroad lines that converged on Indianapolis. At the turn of the century, slaughtering and meat packing was Indiana's leading industry; in 1919 Indianapolis ranked as the fifth largest meat-packing city in the nation.[77] The state's largest firm, Kingan and Company, had pioneered ice and artificial refrigeration, making year-round slaughtering and packing possible. Its main plant was located exactly one mile from Lilly's factories.[78] Within less than 200 miles, and linked to Indianapolis by railroad, lay the meatpacking giants of Cincinnati and Chicago.[79] Securing sufficient pancreas quantities for experiments and trials was one challenge; establishing supply for large-scale production proved to be far greater.

By the 1890s leading U.S. meatpackers employed chemists to develop proprietary organotherapies from their own extracted animal glands and had developed the techniques to harvest glands. The packing industry built its by-product field urgently to meet pharmaceutical demand, with Lilly's supply chain arrangements setting the precedent for similar partnerships. Any animal's pancreas will yield insulin, but not with sufficient volume or human attributes for production. Neither pig nor cow insulin was identical to human insulin, as pig insulin varied less and created fewer skin reactions for patients. The early patient trials demonstrated pig insulin as the preferable source by the end of 1922.[80] To yield the 208,000 pounds of ground pancreas Lilly purchased in 1923 required over one million animals. Lilly's immense demand for pancreas required collaboration including Kingan, Chicago's Armour and Swift, and eventually a "far-flung" national network of packing house partners – an aspect of insulin's innovation that medical historians have overlooked.[81] When demand for pancreas (one of eight significant glands for pharmaceutical use) skyrocketed, its procurement had to come from packers that wielded high volume and extraction expertise, skilled chemical control, temperature, humidity, sterility, and quality regulation. Such expertise in extraction assured the preservation of the gland's active secretion, insulin.[82] Without rigid temperature control, the pancreas glands' inherent enzymes would destroy the insulin. Lilly's purchasing director Austin H. Brown (1890-1954) led the collaboration and skill development between the two industries, packing and pharmaceutical. As Brown established the first procurement system, he trained packers to harvest, handle, and preserve glands for production.[83] Lilly's research increased yield in manufacturing which "kept us just ahead" of inconsistent or inadequate supply.[84] Walden recalled scientists investigating alternative sources of insulin, even fish and whale, to assure adequate supply. Once Lilly's supply chain stretched across the country, individually frozen pancreas arrived by rail for inspection and processing. Also in 1922, Lilly simultaneously designed, purchased, and installed manufacturing equipment for storage, distillation, filtration, purification, concentration, and standardization in anticipation of production. Each unit of insulin required testing on mice or rabbits, numbering in the tens of thousands annually.[85] Production required manpower, so Lilly retained additional employees for all aspects of manufacturing.

Toronto faced the same supply chain concern, despite its unlikely historic moniker "Hogtown." Harris, a crucial local packer, exploited the previously nonexistent market for pancreas and sold the glands to a British buyer for a premium price. Toronto scientists diverted orders to at least three other local packers to assure pancreas supply. Toronto faced temporary limitations until the team made arrangements for consistent and sufficient supply.

By the end of 1922, Lilly was producing high purity insulin in high volume and Toronto adapted Lilly's methods so that the two concerns together comfortably met demand from diabetes specialists in the U.S. and Canada. By January production was so efficient that Lilly was building up reserves.[86] J.K. Lilly and Eli Lilly asserted the firm's lack of "consideration to the matter of expense" had been "sensible" but could not last indefinitely.[87] Walden later recalled that Lilly was ideally positioned as the industrial collaborator: years of glandular research experience, facilities, equipment, personnel, and "management who was willing to spend any amount of money" necessary to bring insulin into large-scale production. Lilly recognized from the outset that insulin had to be affordable to patients, so the pure science, or purification of insulin "to its nth degree," had to balance with the reality of cost-efficient manufacturing.[88] At Clowes' urging, Walden in March 1923 filed to patent the "New and Useful Purified Antidiabetic Product and Process of Making It" – in the U.S.[89]

Just as Walden filed the process patent, the collaborators clashed over insulin's trade name. It is a commonplace in today's pharmaceutical industry that patenting and branding are equally essential in creating and maintaining market share. Lilly marketed insulin under the trade name "Iletin" without Toronto's express consent, assuming tacit consent because of the indenture's ambiguity regarding trade names and the common references to "Iletin" in Toronto-Lilly correspondence. J.K. Lilly insisted that instantly recognizable brand names were fundamental, natural, and proper in the industry. The collaborators negotiated that Lilly could label the product "Iletin (Insulin, Lilly)" in the U.S.[90]

The schism over trade name and patent nearly ended the collaboration. Swann (1988) characterized the turbulent weeks that followed Walden's patent application as "full of moves and countermoves."[91] From March to June 1923 intertwined contractual matters, untested in academic-industrial collaborations, brought the conflicting ideologies on patents, unitage, retail price, trade name and public good into full relief. Toronto's attorney found Walden's patent so far reaching – with thirty product and process claims –that if sanctioned "it would give Lilly an absolute monopoly for the manufacture of Insulin in the U.S."[92] Both Toronto and Lilly struggled for control. Both parties had devoted significant resources to producing and distributing a sufficient supply of clinical-grade insulin as quickly as possible and could see success just around the corner.

Several accounts of the discovery cast the subsequent disputes over the Walden patent and trade name as Lilly's aggressive overreach, fueled by profit motive and unbridled competitiveness. Almost a year of collaboration had not sufficiently convinced Toronto to trust Lilly, much less the pharmaceutical industry at large. Toronto interpreted any of Lilly's attempts to resist its tight controls as automatically suspect and only motivated by profit.[93]

Clowes, therefore, continually emphasized to Macleod the human, financial, and material investments that Lilly had made, particularly the myriad staff innovations.[94] U.S. courts had defined "invention" and distinguished, through case law, between "breakthrough" and "incremental improvement."[95] Skyrocketing patent applications in the late nineteenth century had produced a deluge of litigation, so invention, innovation, patents, and the law were in constant dialogue.[96] A body of law that could translate invention and innovation into practice and property rights, therefore, had been forged by the time the Walden patent landed in the U.S. Patent Office.

Clowes vigorously defended the Walden patent for two reasons: Lilly scientists had been "principally responsible for the rapid development on a large scale" and Lilly had underwritten "very heavily the cost of development" from which other firms would benefit.[97] He asserted Lilly's moral right to take out "the strongest possible patents on our discoveries," dismissing concerns that Lilly would do "anything that might embarrass Toronto University."[98] Toronto's patent attorney asserted that Lilly deliberately sought a monopoly and failed to adhere to Toronto's utilitarian goal of "doing the greatest good for the greatest number."[99]

The collaborators orchestrated a pathbreaking compromise, with Toronto assuming control over an intricate patent pool that allowed the university, prior to government, to fill a regulatory role. Historians do not agree on which party first suggested the patent pool design, but it is clear that Lilly and Toronto hammered out the patent pool without a model to guide them. The pooling concept required that all licensed manufacturers assign any future patents related to insulin to the university so that product and process knowledge would be shared among Toronto, Lilly, and future collaborators. Dutfield's study of intellectual property rights found the insulin breakthrough to have set the precedent for patent pools in the life sciences. Toronto, he noted, asserted its "rights in the aggressive way that subsequently became the norm in the industry."[100] Lilly maintained its exclusive license for the duration of the experimental period; Toronto maintained control over manufacturer regarding product quality, price, and royalties.

Toronto and Lilly signed a new indenture, effective June 13, 1923 in perpetuity, the captured the *quid pro quo* solutions to the hotly contested disputes over patents and trade name. The new agreement required Lilly to assign the Walden patent to Toronto in exchange for open ended manufacturing license and rights to the trade name "Iletin (Insulin, Lilly)" in the U.S. and "Insulin" elsewhere in the world. The indenture unambiguously required that Lilly's future patents and any other licensees' patents on insulin product improvements be assigned to the pool controlled by Toronto.[101] J.K. Lilly delivered the final document with "a great deal of pleasure" in December 1924.[102]

Sinding (2002) examined thoroughly the negotiations over unitage and standardization that produced heated exchanges between the collaborators during 1923, with Toronto holding the "scientific and moral authority."[103] More contentious than the trade name or standard unitage, positioning for patent advantages produced the most vehement disagreements and generated tension that lingered the longest in the collaboration. More than a decade later, Lilly's proposal to introduce a new slow-acting protamine-insulin combination resurrected anew the highly contentious patent dispute. Eli Lilly, the founder's grandson and now company president, reminded Toronto of the longstanding patent pool agreement and the Walden patent's value to the public. He politely but with conviction defended Lilly's right to produce insulin's new iteration as the *quid pro quo* of patent for trade name was long ago settled.[104] The matter resolved within days but reveals that the ideological divide regarding patents persisted into the 1930s.[105]

Lilly executives travelled the insulin road well into the 1920s as additional research, sales agreements, and further details of the collaboration evolved. Money, as well as people, flowed along the same route through patent revenue (royalties) repatriation, government funding, and philanthropy. This enduring public benefit of collaboration, in another continuous cycle, invites further examination and is represented in Figure 3:

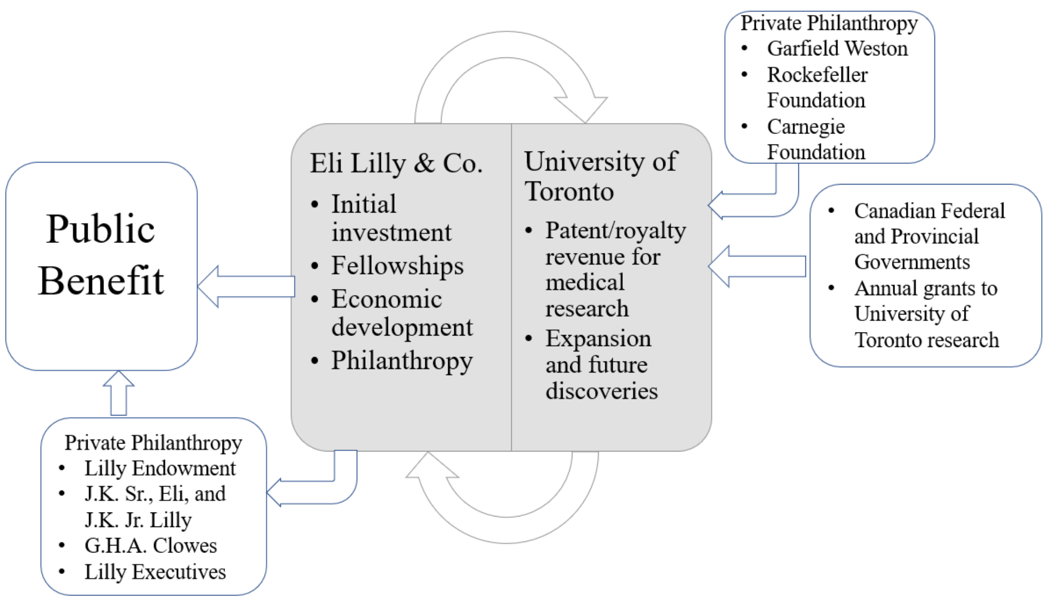


*Figure 3: Eli Lilly and Co. and University of Toronto public benefit funds flow following insulin discovery and innovation.*

Both parties benefited financially and reputationally. The Insulin Committee's license agreements with manufacturers required that five percent of patent royalties be remitted to the University of Toronto. Edward Shorter finds that once insulin's license agreements went into effect, the "proceeds from the patent license fueled medical research in Toronto for the decades to come."[106] The Insulin Committee administered patents and patent royalties until the final royalty payment in 1956 when the Insulin Trust Fund was valued at C$3 million and lifetime royalties totaled C$8 million.[107]

Philanthropy had supported the discovery, providing seed money that produced enormous payoff to medical research, and philanthropy continued to support individuals and institutions. A Rockefeller Travelling Fellowship had funded Collip's sabbatical that brought him to Toronto. After the discovery, Collip received grants and donations from the College of Physicians and Surgeons of Alberta, Rockefeller Foundation, and Carnegie Foundation. He returned a portion of his royalties to launching, staffing, and supporting his future research.[108] In Best's final year of medical school, he received a university fellowship, a Connaught research grant, and a Rockefeller fellowship.[109]

Robert Defries (1889-1975) became director of both Connaught and the School of Hygiene when FitzGerald retired in 1940. Defries later recalled Connaught's capacity constraints and insufficient capital to fund plant and equipment at scale.[110] By 1923 Toronto met most Canadian demand for insulin while it sought funding for facility expansion, including individual donors and the Ontario government. The Rockefeller Foundation in 1924 granted $650,000 to create Canada's first School of Hygiene (Public Health) at the University of Toronto.[111] Banting's and Best's prestigious reputations drew funding and honors for the rest of their lives, accruing to the benefit of the University of Toronto and the public. The university created the Banting and Best Department of Medical Research (BBDMR) in 1930 with Banting as chair, its first department in which the faculty were relieved of teaching to focus solely on research.[112] The BBDMR has been a "discovery powerhouse" in since its inception.[113] Housed within the Department of Physiology, the BBDMR embarked on a "pioneering strategy" of forming collaborative partnerships, inspired by the insulin academic-industrial cooperation.[114] Lilly made grants to the BBDMR from its inception until Best's death in 1978.[115]

A private funder endowed in 1925 the Banting Research Fund C$600,000, also at the University of Toronto. The Canadian Federal Government earmarked C$60,000 annually to university for scientific research; the Ontario Provincial Government granted C$10,000 annually for Banting and Best research.[116] Lilly donated US$50,000 upon the fund's creation.[117] Government support created a "crowding in" effect, with both Banting and Best attracting substantial grants from Eli Lilly and numerous private donors.[118] In 1960 a private donor donated C$1 million to form the Charles H. Best Foundation.[119]

The careers of Banting, Best, Collip, Macleod, and Clowes have been well documented. The roles of Lilly's Walden, Rhodehamel, and Scott have been overlooked yet cannot be overstated in the history of insulin's innovation. Their contributions to insulin innovation catapulted each man's career. Walden held executive positions, retiring in 1960 as vice president of biochemical manufacturing and board member. His research and leadership included liver extracts to treat pernicious anemia, penicillin purification and production, and blood plasma production during World War II. Walden patented six additional innovations and received honorary doctorates from Franklin College and the University of Toronto.[120] Rhodehamel retired in 1949 as executive director of Lilly's Research and Control Function that encompassed 1,400 executives, scientists, technicians, inspectors, and production staff. He contributed to the development of liver extracts, ephedrine, and barbiturates, patented three innovations, and combined executive positions with designing specialized equipment for chemical research and production. Rhodehamel served as Lilly's liaison to the American Medical Association.[121] Scott also contributed to development of vitamin products, liver, parathyroid, and pituitary extracts. He held positions of increasing responsibility, retiring as executive director of operations planning. Scott was awarded one patent and an honorary doctorate from Franklin College.[122]

Lilly executives' role in the collaboration rarely appears in insulin's history. J.K. recalled that "insulin revolutionized our place in the industry," underplaying leadership's role in propelling the organization forward.[123] J.K. and Eli Lilly demonstrated remarkable entrepreneurship in forging the Toronto collaboration, evincing substantial risk tolerance, investment, and a quality known as "adaptive capacity" that allows leaders to embrace adversity and learn from it.[124] Both J.K. and Eli spearheaded the new Lilly Research Laboratories, which opened with great fanfare in 1934. Banting's address at the lab's opening closed by thanking Lilly for joining Toronto in their "ideal of providing insulin to the greatest number of diabetics at the lowest possible price."[125] J.K. Lilly served as president of Eli Lilly and Company until 1932, when Eli Lilly succeeded him. J.K. Lilly then led the firm as chairman until his death in 1948. Under his governance, Lilly expanded geographically to achieve global presence; created and hired for executive leadership in sales, finance, and advertising; and permanently embedded a broad research agenda.[126] As president from 1932-1948, Eli Lilly led the corporation through the Great Depression with sales increasing ninefold from $13 million to $117 million.[127] By the 1940s, Lilly wielded one of the largest research operations among pharmaceuticals, with over seventy scientists trained in multiple disciplines.[128]

Bliss characterized insulin's academic-industrial collaboration as a "fascinating and instructive" study in cooperation.[129] Few in academia or the pharmaceutical industry widely adopted the precedent-setting collaboration until World War II catalyzed similar partnerships to bring sulfa drugs and penicillin into large-scale production during the so-called "therapeutic revolution."[130] Smith, Kline's Vice President of Research noted in 1943, perhaps hopefully, that academic institutions were "just beginning" to trust "first-class commercial houses" although psychologic differences still necessitated "real effort toward tolerance and understanding."[131]

Fresh from what one physician described as the "scrimmage era," however, Lilly and Toronto proceeded with collaborations more quickly than their peer institutions.[132] Clowes governed Lilly's research agenda until his 1945 retirement with steadfast commitment to academic-industrial collaboration. He described and implemented what he called the long stride from invention to innovation: Laboratory recognition => developmental research => clinical observation => large-scale production tests => standardization tests => stability tests => production.[133] By 1925 Lilly had entered into a remarkable *twelve* new collaborative agreements with universities and medical schools.[134] A 1927 partnership with Harvard University on pernicious anemia, to which Walden contributed another patent, delivered almost immediate results.[135] Lilly instituted a robust annual scientific fellowship grant program, with grants ranging from $1,000 to $5,000 in 1930 to individuals at eighteen universities.[136]

Lilly capitalized symbolically, as well as financially, on the cultural capital created through its Toronto and Harvard collaborations, parlaying success into building future academic-industrial partnerships. A 1936 *Journal of the American Medical Association* advertisement headlined "A VALUED PRIVILEGE" claimed a "harmonious" relationship with clinical investigators as "conducive to real medical progress."[137] Select U.S. pharmaceuticals in the 1930s created in-house research laboratories, although the majority of long-established manufacturers concentrated more on marketing than research and development through the interwar years.[138] By the 1940s, Lilly's scientific staff routinely called on universities and medical schools throughout the U.S. and overseas to cultivate collaborative relationships. Cultivating networks produced results. In 1939 alone, Lilly introduced twenty-five new products, fourteen of which came directly from cooperation with outside researchers.[139] Lilly also augmented its in-house research staff through university fellowships, university faculty consultants, and awards to scientific societies.[140] Upon his 1949 retirement, Rhodehamel called relationship development "one of the most important duties" of scientists, chronicling over twenty pharmaceuticals that had resulted from academic-industrial partnerships since the insulin landmark.[141] At mid-century, Lilly epitomized what Pickstone called the technoscientific complex of the future.[142]

Distinct cultures will define academia and industry for the foreseeable future, with the extent of the blurring of boundaries ebbing and flowing. Achilladelis described innovative productivity as a complex admixture of systematic research, luck, serendipity, and development.[143] In addition, massive organizations – whether academic or industrial – may stagnate or stifle innovation. Langowitz and Graves (1992) found that smaller firms in the 1980s were more innovative than pharmaceutical giants that are subject to the "creative backwardness of bigness."[144] The hybrid incubators for startups appear to be the organizational form of the twenty-first century that bring the combined assets of both sectors to bear. Essential seed capital and risk appetite remain the province of industry, which is often overlooked in public criticism of pharmaceutical corporations. Lilly in the 1970s provided initial capital and technology to launch the startup Genentech, Inc. one of the earliest and leading biotech research firms in the U.S. Lilly and Genentech collaborated to produce another "miracle" drug, human insulin in the laboratory, a result of recombinant DNA research.[145]

Scientists and biotech entrepreneurs convened in 2019 to reflect on the topic, "How Academic Research Matures to Breakthrough Medicines." Lessons from the 1920s insulin innovation foreshadowed the themes of 2019: industry informs research laboratories and vice versa, seed capital and scientific networks are essential to move from invention to innovation, academia and pharmaceutical firms operate symbiotically but will always have competing priorities. Academic scientists focus on initial breakthroughs, large firms on innovation and scaling. The 2019 convening and insulin's 2021 centennial remind us that end goal for all scientific researchers, whether housed in academia and industry, remains singular: to harness the power of medical technology to improve human lives.[146]

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[1] "Banquet to Nobel Prize Winners Pinnacle in Medical Appreciation," *Toronto Star*, November 11, 1923, p. 28; Michael Bliss, *The Discovery of Insulin* (Chicago: University of Chicago Press, 1982); Sisir K. Majumdar, "Glimpses of the History of Insulin," *Bulletin of Indian Institution of the History of Medicine* 31 no. 1 (January 2001): 57-70; Jesse Roth, et al., "Insulin's Discovery: New Insights on its Ninetieth Birthday," *Diabetes/Metabolism Research and Reviews* 28 (2012): 293-304; Ian Whitford, Sana Qureshi, and Alessandra L. Szulc, "The Discovery of Insulin: Is There Glory Enough for All?" *Einstein Journal of Biology and Medicine* 28 (2012): 12-17; Jeannette Y. Wick, "Insulin: Almost a Century of Lifesaving," *Consultant Pharmacist* 32, no. 4 (April 2017): 190-200.

[2] Bliss, *The Discovery of Insulin*; Christiane Sinding, "Making the Unit of Insulin: Standards, Clinical Work, and Industry: 1920-1925," *Bulletin of the History of Medicine* 76, no. 2 (Summer 2002): 231-270; and John P. Swann, *Academic Scientists and the Pharmaceutical Industry: Cooperative Research in Twentieth-Century America* (Baltimore: Johns Hopkins University Press, 1988). Shortt carefully examined the contested simultaneous discovery of Banting and Ernest Scott, not the innovation or production, in S.E.D. Shortt, "Banting, Insulin and the Question of Simultaneous Discovery," *Queen's Quarterly* 89, no. 2 (Summer 1982): 260-273.

[3] For the helpful distinction between discovery and innovation see Louis Galambos and Jeffrey L. Sturchio, "The Pharmaceutical Industry in the Twentieth Century: A Reappraisal of the Sources of Innovation," *History and Technology* 13, no. 2 (1996): 84. This paper adopts the definition of collaboration, "to work together especially in a joint intellectual effort," from Jaye Chin-Dusting, Jacques Mizrahi, Garry Jennings and Desmond Fitzgerald, "Finding Improved Medicines: The Role of Academic-Industrial Collaboration," *Nature Reviews* 4 (November 2005): 891-897, quote on 891.

[4] Robert Bud, *Penicillin: Triumph and Tragedy* (New York: Oxford University Press, 2007), 45; Wai Chen, "The Laboratory as Business," in *The Laboratory Revolution in Medicine*, ed. Andrew Cunningham and Perry Williams, p. 245-295 (New York: Cambridge University Press, 1992); John E. Lesch, *The First Miracle Drugs: How the Sulfa Drugs Transformed Medicine* (New York: Oxford University Press, 2007), 7-8.

[5] Annetine Gelijns and Samuel O. Their, "Medical Innovation and Institutional Interdependence: Rethinking University-Industry Connections," *Journal of the American Medical Association* 287, no. 1 (January 2002): 73-77, quote on 72-73.

[6] John V. Pickstone, *Ways of Knowing: A New History of Science, Technology and Medicine* (Chicago: University of Chicago Press, 2001), 3 and 14.
[7] Basil Achilladelis, "Innovation in the Pharmaceutical Industry" in *Pharmaceutical Innovation: Revolutionizing Human Health*, pp. 1-148, ed. Ralph Landau, Basil Achilladelis, and Alexander Scriabine (Philadelphia: Chemical Heritage Press, 1999), 36-37.
[8] Chin-Dusting, et al, "Finding Improved Medicines": 891-897, quote on 891-2.
[9] "Corporate technology tradition" in Achilladelis, "Innovation in the Pharmaceutical Industry," 53.
[10] Robert Bud, *Penicillin: Triumph and Tragedy* (New York: Oxford University Press, 2007); Gladys L. Hobby, *Penicillin: Meeting the Challenge* (New Haven: Princeton University Press, 1985).
[11] Business historian Alfred D. Chandler, who studied the modern corporation including the pharmaceutical industry, asserted the core proposition that technological and organizational innovation are interdependent. Gary P. Pisano, "The Evolution of Science-Based Business: Innovating How We Innovate," *Industrial and Corporate Change* 19, no. 2 (April 2010): 465-482.
[12] Swann indicated Clowes made at least 25 trips to Toronto and Best made at least 9 trips to Indianapolis. Swann, *Academic Scientists and the Pharmaceutical Industry*, 131. In addition, Banting visited Indianapolis multiple times. J.K. Lilly, Eli Lilly, George Walden, Charles Lynn visited Toronto; Dale and Dudley traveled from the UK to Indianapolis; DeFries and Riches visited Indianapolis. Toronto scientists made multiple trips to the Lilly laboratory at Woods Hole, Anna Hickson interview, Eli Lilly and Company Corporate Archives, Lilly Corporate Center, Indianapolis IN (hereafter ELCCA).
[13] Edward Shorter, *Partnership for Excellence: Medicine at the University of Toronto and Academic Hospitals* (Toronto: University of Toronto Press, 2013), 23-24.
[14] Michael Bliss, *The Making of Modern Medicine: Turning Points in the Treatment of Disease* (Chicago: University of Chicago Press, 2011), 70.
[15] J.J. Carty, "The Relation of Pure Science to Industrial Research," Annual Report of the Board of Regents of the Smithsonian Institution (Washington D.C.: Smithsonian Institution, 1917), 523-531.
[16] Raymond B. Fosdick, *The Story of the Rockefeller Foundation* (New York: Harper, 1952), 274. Rockefeller Institute staffer Paul de Kruif's biting critique of medicine noted, "the place for the study of disease is in the [academic] laboratory." Anonymous, "Our Medicine-Men, By One of Them," *Century* 104 (1922): 425; Charles Rosenberg, "Martin Arrowsmith: The Scientist as Hero," *American Quarterly* 15, no. 3 (Autumn, 1963): 447-458.
[17] The ASPET constitution did not allow industrial pharmacologists as members until 1941. K. K. Chen, ed., *The American Society for Pharmacology and Experimental Therapeutics, Incorporated: The First Sixty Years, 1908-1969* (Washington, DC: ASPET, 1969), 11; John Parascandola, "Industrial Research Comes of Age: The American Pharmaceutical Industry, 1920-1940," *Pharmacy in History* 27, no. 1 (1985): 12-21, quote on 19; Nicolas Rasmussen, "The Moral Economy of the Drug Company-Medical Scientist Collaboration in Interwar America," *Social Studies of Science* 34, no. 2 (April 2004): 161-185, quote on 162-164. Lawrence examines the same moral divide in 1920s Edinburgh, Scotland. Christopher Lawrence, *Rockefeller Money, the Laboratory, and Medicine in Edinburgh 1919-1930: New Science in an Old Country* (Rochester, NY: University of Rochester Press, 2005).
[18] Sinclair Lewis, *Arrowsmith* (New York: Harcourt, Brace & World, 1924), 140.
[19] Pickstone, *Ways of Knowing*, 177.
[20] Jonathan Liebenau, *Medical Science and Medical Industry: The Formation of the American Pharmaceutical Industry* (Baltimore: Johns Hopkins University Press, 1987), 1-10, 30, 131.
[21] Gene E. McCormick, "Josiah Kirby Lilly, Sr., the Man (1861-1948)," *Pharmacy in History* 12, no. 2 (1970): 57-67, quote on 60.
[22] *Scientific American* 117 (September 15, 1917) referred to in Josiah K. Lilly, *Eli Lilly & Company, The History in Chronological Order* (Unpublished manuscript, ca. 1950, 30–40 ( ELCCA).
[23] Frederick W. Taylor (1856-1915), founding father of scientific management whose approach is often referred to as Taylorism. His major publication, *The Principles of Scientific Management* (1911), was highly influential in manufacturing and management.
[24] R. C. Buley and Gene E. McCormick, *The Red Lilly: A History of Eli Lilly and Company, 1876–1966* (Unpublished manuscript, 1964–1982), 193-194 (ELCCA); McCormick, "Josiah Kirby Lilly, Sr.," 64; James H. Madison, *Eli Lilly: A Life, 1885–1977* (Indianapolis: Indiana Historical Society, 1989), 31-33.
[25] Alfred D. Chandler, Jr., *Shaping the Industrial Century: The Remarkable Story of the Evolution of the Modern Chemical and Pharmaceutical Industries* ( Cambridge: Harvard University Press, 2005), 193.
[26] "Captain of industry" in Nicholas Noyes interview by Gene McCormick, October 1967 (ELCCA); "to contribute to" in Buley and McCormick, *The Red Lilly*, 176 (ELCCA)

[27] Robert E. Kohler, "Medical Reform and Biomedical Science: Biochemistry – A Case Study," in *The Therapeutic Revolution: Essays in the Social History of American Medicine*, ed. Morris J. Vogel and Charles E. Rosenberg, 27-66 (Philadelphia: University of Pennsylvania Press, 1979); John P. Swann, "Universities, Industry, and the Rise of Biomedical Collaboration in America," in *Pill Peddlers: Essays on the History of the Pharmaceutical Industry*, 73-91, ed. Jonathan Liebenau (Madison, WI: American Institute of the History of Pharmacy, 1990), 76.
[28] Hörlein was instrumental in developing Luminal (phenobarbital) for epilepsy treatment. Lesch, *The First Miracle Drugs*, 44-49.
[29] Squibb hired its research director in 1915, Abbott, Hoffmann-La Roche, Merck, and Parke-Davis hired directors after 1920. Swann, "Universities, Industry, and the Rise of Biomedical Collaboration," 80-81. .
[30] Pickstone, *Ways of Knowing*, 171-172.
[31] Eldred had joined Lilly in 1901 as Director of the Analytical Laboratory. Buley and McCormick, *The Red Lilly*, 198 (ELCCA).
[32] In 1885 the first U.S. Fish Commissioner established a permanent research station, the Marine Biological Laboratory, in Woods Hole, Cape Cod, Massachusetts. The lab continues today as a private, nonprofit research institution. Its research has contributed to more than 50 Nobel laureates: https://www.mbl.edu/mbl-facts/.
[33] Clowes' appointment announced in internal newsletter *The Budget*, June 1919 as quoted in Alexander W. Clowes, *The Doc and the Duchess: The Life and Legacy of George H.A. Clowes* (Bloomington: Indiana University Press, 2016), 66.
[34] Biographical information (ELCCA); Clowes, *The Doc and the Duchess*, 56-66, 106; George H. A. Clowes, Jr., "George Henry Alexander Clowes, PhD, DSc, LLD (1877-1958): A Man of Science for All Seasons," *Journal of Surgical Oncology* 18 (1981): 197-217.
[35] G.H.A. Clowes, *Milestones in Medicine*, 1933 film produced by Eli Lilly (ELCCA).
[36] "G.H.A. Clowes Preliminary Report, Research Department, 1921" as quoted in Swann, *Academic Scientists and the Pharmaceutical Industry*, 39.
[37] Pickstone, *Ways of Knowing*, 181.
[38] Biologic manufacturing depends on micro-organisms, including viruses. Inspired by Pasteur's germ theory, Lilly in 1913 purchased 100 acres of prairie land; built a lab, greenhouse, and livestock; and staffed the campus with scientists. Buley and McCormick, *The Red Lilly*, 203, 282 (ELCCA). J.K. equated "scientific" with experimental.
[39] Staff of 50 in Buley and McCormick, *The Red Lilly*, 367 (ELCCA). "Revolutionize our methods" emphasis in original. J. K. Lilly Sr., "A Plan for Promoting the Affairs of Eli Lilly & Company during the years 1920-21-22-23," October 26, 1919 (ELCCA).
[40] Buley and McCormick, *The Red Lilly*, 282, 290 (ELCCA). The study of glandular secretions first appeared in journals and textbooks between 1910 and 1916 as North American physiologists contributed to the emerging field of endocrinology and clinical medicine. Shortt, "Banting, Insulin and the Question of Simultaneous Discovery," 269.
[41] Anna Hickman interview March 1972 (ELCAA).
[42] Wilder Dwight Bancroft (1867-1953) https://www.electrochem.org/bancroft. 1917-1920 correspondence between Clowes and Bancroft in Box 1, Folder 19; list of medical contacts in Box 1, Folder 3, Clowes Family Collection, 1842 – 1998, Collection #M1028, Indiana Historical Society.
[43] Buley and McCormick, *The Red Lilly*, 209 (ELCCA).
[44] M. Weatherall, *In Search of a Cure: A History of Pharmaceutical Discovery* (New York: Oxford University Press, 1990), frontispiece and 89-91. Chapters 1-3 provide a complete explanation of endocrine medical research prior to 1921 and the Macleod, Banting, Best experiments in 1922. Bliss, *The Discovery of Insulin*.
[45] Buley and McCormick, *The Red Lilly*, 291 (ELCCA); Clowes, *The Doc and the Duchess*, 71-72; Henry F. DeBoest, "Lilly: The Train Trip That Was a Turning Point," *Nation's Business* (January 1971): 72-73.
[46] George H. A. Clowes, "The Banting Memorial Address," *Proceedings of the American Diabetes Association* 7 (1948): 53.
[47] Christopher J. Rutty, "Personality, Politics and Public Health: The Origins of Connaught Medical Research Laboratories, 1888-1917," in E.A. Heaman, Alison Li, Shelley McKellar (eds.) *Figuring the Social: Essays in Honour of Michael Bliss* (Toronto: University of Toronto Press, 2008), p. 273-303.
[48] John G. FitzGerald Memorandum in reference to the co-operation of the Connaught Antitoxin Laboratories in the researches conducted by Dr. Banting, Mr. Best and Dr. Collip, January 25, 1922. Archives and Records Management Services, University of Toronto: University of Toronto. Board of Governors. Insulin Committee.
[49] Michael Bliss, "Resurrections in Toronto: Fact and Myth in the Discovery of Insulin," *Bulletin of the American Academy of Arts and Sciences* 38, no. 3 (December 1984): 15-36.
[50] Alison Li, *J.B. Collip and the Development of Medical Research: Extracts and Enterprise* (Ithaca, NY: McGill-Queen's University Press, 2003), 42.

[51] Gelijns and Their, "Medical Innovation and Institutional Interdependence," 75-76; Swann, *Academic Scientists and the Pharmaceutical Industry*, 5, Swann, "Universities, Industry, and the Rise of Biomedical Collaboration," 85.
[52] Graham Dutfield, *Intellectual Property Rights and the Life Sciences Industries: A Twentieth Century History* (Burlington, VT: Ashgate Publishing, 2003), 113-116; Li, *J.B. Collip*, 77-78; Liebenau, *Medical Science and Medical Industry*, 109-110; Swann, *Academic Scientists and the Pharmaceutical Industry*, 31-35; Charles Weiner, "Patenting and Academic Research: Historical Case Studies," *Science, Technology, & Human Values* 12, no. 1 (Winter 1987): 50-62, quote on 50-51.
[53] Patent disputes consumed notable U.S. inventions such as the telephone, telegraph, electric lights, cotton gin, mechanical reaper – and even barbed wire. Christopher Beauchamp, "Who Invented the Telephone? Lawyers, Patents, and the Judgement of History," *Technology and Culture* 51, no. 4 (October 2010): 856-857.
[54] Statement read by J.J.R. Macleod at the Insulin Committee meeting regarding patents and royalties, April 28, 1924. Archives and Records Management Services, University of Toronto: University of Toronto. Board of Governors. Insulin Committee.
[55] Maurice Cassier and Christiane Sinding, " 'Patenting in the Public Interest:' Administration of Insulin Patents by the University of Toronto," *History and Technology* 24 (2) (June 2008): 153-171, quote on 154.
[56] J.J.R. Macleod, J.G. FitzGerald, F.G. Banting, C.H. Best to Robert Falconer, May 25, 1922, Box 13, file 11 (ICUT).
[57] J.J.R. Macleod, J.G. FitzGerald, F.G. Banting, C.H. Best to Robert Falconer, May 25, 1922, Box 13, file 11 (Archives and Records Management Services, University of Toronto: University of Toronto. Board of Governors. Insulin Committee; hereafter: ICUT).
[58] Shorter, *Partnership for Excellence*, 56.
[59] As quoted in Clowes, *The Doc and the Duchess*, 69.
[60] Swann, *Academic Scientists and the Pharmaceutical Industry*, 133. Capital amount in Lilly, *Eli Lilly & Company*, 67 (ELCCA). 2020 dollars calculated using https://www.usinflationcalculator.com/.
[61] G.H.A. Clowes, "In Retrospect," *Physician's Bulletin*, September 1946 (ELCCA). Walden, Rhodehamel, and Scott were credited with educational attainment beyond chemistry and awarded degrees in chemical engineering based on their industrial experience. Talk given by Harley W. Rhodehamel, October 25, 1949 (ELCCA).
[62] Interview George B. Walden Sr., November 5, 1968 (ELCCA).
[63] Buley and McCormick, *The Red Lilly*, 286 (ELCCA).
[64] J.J.R. Macleod letter to Sir Robert Falconer May 25, 1922, Box 13, F11 (ICUT).
[65] Toronto denied Lilly's appeals for either a short-term monopoly or a longer term exclusive license. Indenture May 30, 1922 (ELCCA).
[66] Indenture May 30, 1922 (ELCCA).
[67] Hobby, *Penicillin*, 12; Swann, *Academic Scientists and the Pharmaceutical Industry*, 3, 23.
[68] Indenture effective May 30, 1922, executed by Toronto June 28, 1922 and by Lilly July 7, 1922 (ELCCA).
[69] Buley and McCormick, *The Red Lilly*, 289 (ELCCA).
[70] Talk given by Harley W. Rhodehamel, October 25, 1949 (ELCCA).
[71] G.H.A. Clowes, "Report on Iletin," (Fisher); Gene E. McCormick, "The Discovery and Manufacture of Insulin" ca. 1971 (ELCCA).
[72] G.H.A. Clowes letter to J.J.R. Macleod September 17, 1922 (The Discovery of Insulin Manuscript Collections, Thomas Fisher Rare Book Library, University of Toronto; hereafter: Fisher).
[73] Talk given by Harley W. Rhodehamel, October 25, 1949 (ELCCA).
[74] "all night work" in J.K. Lilly letter to Eli Lilly July 26, 1922 (ELCCA); "heavy day-and-night work" in G.H.A. Clowes letter to J.J.R. Macleod September 5, 1922, Box 12, F12a (ICUT); "strain on staff" in G.H.A. Clowes letter to J.J.R. Macleod September 23, 1922 (Fisher); McCormick, "The Discovery and Manufacture of Insulin" (ELCCA).
[75] The isoelectric point was a well-known principle to chemists, defined by the pH of a medium at which a protein carries no net charge and thus will not migrate in an electric field. At this specific isoelectric point, proteins readily precipitate, or fall out of solution, a property useful for separating mixtures of proteins or amino acids. McCormick, "The Discovery and Manufacture of Insulin" (ELCCA).
[76] Interview George B. Walden Sr., November 5, 1968 (ELCCA).
[77] Clifton J. Phillips, *Indiana in Transition: The Emergence of an Industrial Commonwealth, 1880-1920* (Indianapolis: Indiana Historical Bureau and Indiana Historical Society, 1968), 279-281.
[78] Cathleen F. Donnelly, "Kingan and Company," in *The Encyclopedia of Indianapolis*, ed. David J. Bodenhamer and Robert G. Barrows (Bloomington: Indiana University Press, 1994), 870-871; "Nearly Eight Years Ago," *Indianapolis Star*, December 31, 1923.

[79] Leo E. Landis, "Meatpacking," in *The American Midwest: An Interpretive Encyclopedia*, ed. Richard Sisson, Christian Zacher, and Andrew Cayton ((Bloomington: Indiana University Press, 2007), 1216-1218. Illinois, Indiana, and Ohio together produced the largest number of swine for packing in the U.S., *Fourteenth Census of the United States Taken in the Year 1920*, v. 5 (Washington D.C.: Department of Commerce, 1922), 693-694.
[80] Toronto and Lilly formed a Canadian/U.S. clinicians' advisory group, in tandem with production, to conduct patient trials. Stephen S. Hall, *Invisible Frontiers: The Race to Synthesize a Human Gene* (New York: Atlantic, 1987), 7; Gene E. McCormick, "Insulin: A Hope for Life" 1979 (ELCCA).
[81] *Lilly News*, September 11, 1954 (ELCCA).
[82] One hog pancreas weighed approximately 3 ounces. Pounds of pancreas ground 1923 (ELCCA). Small producers and farms did not have the expertise to harvest pancreas when butchering livestock. Rudolf Alexander Clemen, *American Livestock and the Meat Industry* (New York: Ronald Press Company, 1923), 206-209, 214-215; Wilson J. Warren, *Meat Makes People Powerful* (Des Moines: University of Iowa Press, 2018), 95-96.
[83] "American Meat Institute Honors A. H. Brown," *Lilly Review*, October 1949 (ELCCA).
[84] Interview George B. Walden Sr., November 5, 1968 (ELCCA).
[85] DeBoest, "Lilly: The Train Trip That Was a Turning Point," 72; F.C. Felter, "Medical Paper Article Led Banting to Insulin," 1935 (ELCCA); "Insulin: Its Modern Manufacture" (ELCCA).
[86] G.H.A. Clowes letter to J.J.R. Macleod January 17, 1923, Box 12, F12a (ICUT).
[87] J.K. Lilly letter to G.H.A. Clowes January 3, 1923 (Fisher).
[88] Interview George B. Walden Sr., November 5, 1968 (ELCCA).
[89] George B. Walden Patent Application, March 2, 1923, United States Patent Office (ELCCA).
[90] J.K. Lilly letter to Eli Lilly, January 1923 (ELCCA).
[91] Swann, *Academic Scientists and the Pharmaceutical Industry*, 144.
[92] "Thirty product and process claims" in Swann, *Academic Scientists and the Pharmaceutical Industry*, 145; Meeting, University of Toronto Insulin Committee, April 2, 1923, C.H. Riches letter to J.J.R. Macleod, April 3, 1923, Box 1, F15 (ICUT).
[93] Sinding, "Making the Unit of Insulin," 243.
[94] G.H.A. Clowes letter to J.J.R. Macleod March 7, 1923; March 14, 1923 (Fisher); G.H.A. Clowes letters to J.J.R. Macleod December 12, 1922; January 17, 1923; April 10, 1923, Box 12, F12a (ICUT).
[95] Beauchamp, "Who Invented the Telephone?: 860.
[96] Beauchamp, "Who Invented the Telephone?: 876.
[97] G.H.A. Clowes letter to J.J.R. Macleod March 7, 1923 (Fisher).
[98] G.H.A. Clowes telegram to J.J.R. Macleod, April 8, 1923 (Fisher).
[99] Cited in Cassier and Sinding, " 'Patenting in the Public Interest": 159.
[100] Graham Dutfield, *Intellectual Property Rights and the Life Sciences Industries: A Twentieth Century History* (Burlington, VT: Ashgate Publishing, 2003), 116-117. Inter-organization patent pools and "thickets" of overlapping patent rights also became more common in technology and manufacturing industries. Beauchamp, "Who Invented the Telephone?: 878.
[101] Indenture June 13, 1923 (ELCCA).
[102] J.K. Lilly letter to F. Lorne Hutchison, December 29, 1924, Manuscript Collection 473, Box 1, Folder 2 (Fisher).
[103] Christiane Sinding, "Making the Unit of Insulin: Standards, Clinical Work, and Industry: 1920-1925," *Bulletin of the History of Medicine* 76, no. 2 (Summer 2002): 243. This paper's valuable contribution clearly outlines the negotiations over standardization and unitage, but relegates Clowes to the role of field worker.
[104] Eli Lilly letter to F. Lorne Hutchison, November 2, 1936, Manuscript Collection 473, Box 1, Folder 1 (Fisher).
[105] Toronto granted Lilly use of the labels "Protamine & Iletin (Insulin, Lilly) in 1936 and "Protamine Zinc & Iletin (Insulin, Lilly) in 1937. Clowes, *The Doc and the Duchess*, 101-102.
[106] Shorter, *Partnership for Excellence*, 54.
[107] Shorter, *Partnership for Excellence*, 55; Swann, *Academic Scientists and the Pharmaceutical Industry*, 148.
[108] Collip went on to research pituitary and placental hormones, and collaborated with other pharmaceutical firms throughout his career. Li, *J.B. Collip*, 150 and 174. Collip's research lab and Lilly also collaborated on an anti-tumor cancer treatment based on the periwinkle plant in the 1950s. Jacalyn Duffin, "Poisoning the Spindle: Serendipity and Discovery of the Anti-Tumor Properties of the Vinca Alkaloids (Part I)," *Pharmacy in History* 44 , no. 2 (2002): 64-76.
[109] Henry B.M. Best, *Margaret and Charley: The Personal Story of Dr. Charles Best, the Co-discoverer of Insulin* (Tonawanda, NY : Dundurn Group, 2003), 99.
[110] Robert D. Defries, *The First Forty Years, 1914-1955: Connaught Medical Research Laboratories, University of Toronto* (Toronto: University of Toronto Press, 1968), 70.

[111] Christopher J. Rutty, " 'Couldn't Live Without It": Diabetes, the Costs of Innovation and the Price of Insulin in Canada, 1922-1984," *Canadian Bulletin of Medical History* 25, no. 2 (2008): 407-431, reference on 411 - 415.
[112] Banting died in 1941; Best chaired from 1941 to 1965. Shorter, *Partnership for Excellence*, 413.
113 "History of the Banting and Best Department of Medical Research," https://www.thedonnellycentre.utoronto.ca/history-banting-and-best-department-medical-research.
[114] Irving B. Fritz, "The Banting and Best Department of Medical Research at the University of Toronto," *BioEssays* 9, nos. 2 & 3 (August-September 1988): 92-97; Shorter, *Partnership for Excellence*, 419.
[115] Swann, *Academic Scientists and the Pharmaceutical Industry*, 149.
[116] Shorter, *Partnership for Excellence*, 282.
[117] Lilly, *Eli Lilly & Company*, 75.
[118] Michael Bliss, *Banting: A Biography* (Toronto: McClelland and Stewart, 1984), 239; Shorter, *Partnership for Excellence*, 413.
[119] Shorter, *Partnership for Excellence*, 414.
[120] George B. Walden biographical information (ELCCA); patents at: https://patents.google.com/?inventor=george+b+walden&oq=george+b+walden&sort=old.
[121] Harley W. Rhodehamel Sr. biographical information (ELCCA); patents at: https://patents.google.com/?inventor=harley+rhodehamel&oq=harley+rhodehamel+&sort=old.
[122] Jasper P. Scott biographical information (ELCCA); patent at: https://patents.google.com/patent/US1699479A/en?inventor=jasper+scott&oq=jasper+scott.
[123] J.K. Lilly memo to G.H.A. Clowes, Eli Lilly, and George Walden, quoted in E.J. Kahn Jr., *All in a Century: The First 100 Years of Eli Lilly and Company*, Indianapolis: Eli Lilly & Co., 1976, 100.
[124] Craig E. Johnson, *Meeting the Ethical Challenges of Leadership: Casting Light or Shadow*, 5th ed. (Los Angeles: SAGE Publications, 2015), 96-97.
[125] Diabetes specialist Dr. Elliot Joslin, Harvard University Medical School, spoke of insulin's transformational effect on his patients. Eli Lilly and Company, *The Celebration of the Dedication of the New Lilly Research Laboratories*, Indianapolis: Eli Lilly and Company, 1934, 20.
[126] J.K. Lilly served as trustee of the Philadelphia College of Pharmacy and Purdue University, and received eight honorary graduate degrees. "J.K. Lilly Dead at 86," *Indianapolis Times*, February 19, 1948, p. 1.
[127] "Mr. Eli Lilly, 1885-1977," Lilly News (ELCCA).
[128] Swann, *Academic Scientists and the Pharmaceutical Industry*, 36.
[129] Bliss, "Resurrections in Toronto": 32.
[130] Hobby, *Penicillin*, 233-235; Lesch, *The First Miracle Drugs*, 269. "Therapeutic Revolution" in Chandler, *Shaping the Industrial Century*, 179.
[131] Francis Boyer, "The Pharmaceutical Manufacturer and Academic Research," *The New England Journal of Medicine* 228, no. 17 (April 1943): 529-532, quote on 529. Smith, Kline employed eight researchers. Swann, *Academic Scientists and the Pharmaceutical Industry*, 38.
[132] Boyer, "The Pharmaceutical Manufacturer and Academic Research," 529.
[133] G.H.A. Clowes, *Milestones in Medicine*, 1933 film produced by Eli Lilly (ELCCA).
[134] J.K. Lilly detailed eleven partnerships: University of Alberta, University of Minnesota, New Haven Hospital, Cornell University, Presbyterian Hospital (New York), University of Kansas, University of Kansas Medical School, Columbia University, Bellevue Hospital, St. Mary's Hospital (St. Louis), and University of Maryland. Lilly, *Eli Lilly & Company*, 75. Lilly created a research program at Indianapolis General Hospital, clinical home of the Indiana University School of Medicine. Clowes, *The Doc and the Duchess*, 107.
[135] Clowes, *The Doc and the Duchess*, 110.
[136] Lilly, *Eli Lilly & Company*, 91-92.
[137] Advertisement quoted in Rasmussen, "The Moral Economy of the Drug Company-Medical Scientist Collaboration in Interwar America": 175.
[138] Chandler, *Shaping the Industrial Century*, 179.
[139] Lilly, *Eli Lilly & Company*, 132.
[140] Swann, *Academic Scientists and the Pharmaceutical Industry*, 51-54.
[141] "A Talk Given by H.W. Rhodehamel, October 25, 1949 before the Division Representatives Group" (ELCCA).
[142] Pickstone, *Ways of Knowing*, 163.
[143] Achilladelis, "Innovation in the Pharmaceutical Industry," 5.
[144] Nan S. Langowitz and Samuel B. Graves, "Innovative Productivity in Pharmaceutical Firms," *Research Technology Management* 35, no. 2 (March-April 1992): 39-41.

[145] "Following Genentech agreement, Lilly to develop commercial production of insulin from bacteria," *Lilly News*, October 1978 (ELCCA).
[146] First author's notes from Fourth Annual Indiana University Innovation and Commercialization Conference: How Academic Research Matures to Breakthrough Medicines, presented by Johnson Center for Innovation and Translational Research, November 2019.