"Couldn't Live Without It": Diabetes, the Costs of Innovation and the Price of Insulin in Canada, 1922-1984

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Abstract. This article traces insulin prices in Canada from 1922, just after its discovery at the University of Toronto, to 1984 when production fell out of Canadian control. Connaught Laboratories (part of the University of Toronto from 1914 to 1972) was the first to manufacture insulin and remained the sole Canadian producer. As a public trust, Connaught remained committed to providing insulin at the lowest possible price despite increasing economic pressures. This article analyzes the context surrounding the price of insulin preparations and how they fell from 1922 to 1942, remained unchanged until 1967, and rose during the 1970s.

Keywords. insulin, Connaught Laboratories, price, biotechnology

Résumé. Cet article retrace l'évolution des prix de l'insuline au Canada à partir de 1922, immédiatement après sa découverte à l'Université de Toronto, jusqu'à 1984 lorsque la production échappa au contrôle canadien. Les Laboratoires Connaught (de l'Université de Toronto de 1914 à 1972), ont été les premiers à manufacturer l'insuline et sont demeurés le seul producteur canadien. À titre d'institution publique, Connaught maintenait l'objectif de fournir l'insuline au plus bas prix malgré des pressions économiques croissantes. Cet article analyse les éléments de contexte qui ont joué sur le coût de la préparation de l'insuline, l'affaissement des prix entre 1922 et 1942, leur stabilisation jusque 1967, et enfin leur croissance durant la décennie 1970.

Mots-clés. insuline, Laboratoires Connaught, prix, biotechnologies

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The original discovery of insulin in 1921 by Frederick Banting and Charles Best was recognized in early 2007 as "The Greatest Canadian

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Invention" in a two-hour CBC Television special based on the votes of ordinary Canadians. Insulin topped the telephone [#2] and the light bulb [#3] as inventions Canadians "couldn't live without." While the countdown of the top 50 inventions included many important life-saving achievements (the pacemaker [#6] and the Cobalt-60 Bomb [#11]), and some perhaps less so (five-pin bowling [#4], the Wonderbra [#5] and poutine [#10]), insulin's top placement reflects both its iconic stature among Canadians and its essential life-saving power for diabetics.[1] Further testament to the popular importance of insulin among Canadians was the ranking of Frederick Banting as #4 as "The Greatest Canadian" in a CBC-TV series that aired in 2004.[2]

Insulin's importance to Canadians and diabetics world-wide reflects its "wonder drug" nature, not as a cure for diabetes, but rather as something diabetics require on a regular basis—usually once every day, sometimes more often—to keep them alive. If Banting had discovered a real cure for diabetes that restored the normal function of the pancreas after a few injections, it would have been heralded as a great discovery, but it likely would not have retained its iconic stature over the last 85 years. If insulin were a cure, diabetics would certainly have been willing to pay almost anything to get it. However, as something diabetics "couldn't live without" for the rest of their lives, the price of insulin very quickly became a more complex matter for them and for those who have produced insulin since its discovery. The price of insulin has remained an important matter for the general public and governments as the incidence of new diabetes cases rises at an alarming rate.

While the price of insulin has been an important concern in all countries, for a variety of reasons deeply rooted in the fact that this "wonder drug" was discovered and developed in Canada, the question of insulin's price and how it has fallen and risen over the years has perhaps been the most personally, publicly, and politically sensitive in Canada. Tracking the price of insulin in Canada and providing some historical context surrounding this unusual price sensitivity is the focus of this study.

The dramatic story of insulin's discovery during the summer of 1921 at the University of Toronto by Banting and Best, coupled with the essential physiological and biochemical contributions of J. J. R. MacLeod and J. Bertram Collip, has been well documented, especially in Michael Bliss's definitive, *The Discovery of Insulin* (1982).[3] This story reached a much wider audience when Bliss's book was adapted into a 4-hour mini-series entitled "Glory Enough for All," originally broadcast on CBC-TV in 1988 and since frequently re-broadcast around the world.

The climax of the story took place in January 1922, when news of the first diabetic patients to successfully receive the new pancreatic extract—soon to be christened "insulin"—spread rapidly around the world, draw-

ing unprecedented attention to Canada and to the University of Toronto. This news sparked an unquenchable demand from diabetics around the world somehow to receive a supply of this new "wonder drug" immediately. It was not going to be easy.

In the basement and sub-basement of the same University of Toronto Medical Building in which Banting and Best made their discovery were the modest quarters of a unique and self-supporting part of the University's Faculty of Medicine then known as the Connaught Antitoxin Laboratories.[4] Originally established in 1913 in a humble backyard stable by Dr. John G. FitzGerald, Professor of Hygiene, to prepare a Canadian supply of diphtheria antitoxin for free distribution through provincial health departments, the University of Toronto assumed responsibility for FitzGerald's fledgling enterprise in May 1914 and provided laboratory and processing space in the Medical Building.

During World War I, a global tetanus antitoxin shortage in 1915 prompted the expansion of the Antitoxin Laboratories with the donation of a 58-acre farm site and new facilities some 12 miles to the northwest of the University campus. On 25 October 1917, this unique medical research, biologicals production and public service enterprise was officially christened the Connaught Antitoxin Laboratories after Canada's wartime Governor General and public health patron, the Duke of Connaught. Ninety years later, the Connaught Campus of Sanofi Pasteur Limited, which is the Canadian vaccine component of the global sanofi-aventis group, occupies this same site at what is now the northern border of Toronto on Steeles Avenue West near Dufferin Street. Canada's insulin supply previously produced on the main University of Toronto campus was manufactured on this site from 1970 to the mid-1990s.

By the early 1920s, Connaught produced a growing range of biological public health products—including diphtheria and tetanus antitoxins, smallpox, rabies, pertussis and typhoid-paratyphoid vaccines—on the University campus and "Farm" sites and sold them at cost, primarily to provincial health departments, which then distributed them gratis through local health departments. Some of Connaught's products also were sold on a close-to-cost basis to hospitals, pharmacists and private physicians. Any "profits" earned were put towards research into product improvements and the development of new public health biologicals. During World War I, Connaught also distributed some of its products to other parts of the British Empire, providing the laboratories with important international connections that it would build upon in the future, particularly through its role in the large-scale production and further development of insulin preparations.

In January 1922, Dr. FitzGerald offered Banting, Best, Collip, and MacLeod the assistance of Connaught to work out larger scale production methods and underwrite the costs of preparing the new extract for

clinical trial as well as his negotiating skills to ease some of the personal tensions that had developed among the discovery team. If their efforts proved successful, Connaught would then produce the extract in sufficient quantities to meet the needs of Canadian diabetics.[5] While Connaught soon supplied enough of a fairly crude extract for clinical work at Toronto General Hospital treating severe diabetic cases, particularly to revive patients in diabetic comas, it was clear that a much larger, purer, and more potent supply was needed. At the time Connaught had limited capacity, resources, and experience to expedite the production of insulin on the scale that was necessary to meet the extraordinary Canadian and international demand.

The Toronto discovery and initial clinical success with insulin generated intense interest in the United States. In May 1922 Dr. G. H. A. Clowes, Research Director of Eli Lilly & Co. of Indianapolis, offered to assist Connaught and the insulin discoverers in developing large scale production methods.[6] The University of Toronto Board of Governors also agreed to work with Lilly on how best to protect this monumental discovery through worldwide patents, while at the same time expediting its inexpensive North American and international distribution to diabetics. However, as Clowes stressed to MacLeod in May 1922, this product would take at least a year to develop and even longer to be commercially available. Moreover, "the costs of such work will be great."[7]

Through the summer and fall of 1922, Lilly was able to supplement Connaught's insulin output, which was being directed largely to diabetic clinics in Toronto at no cost to patients. Several diabetic specialists in North America also began to receive small amounts of insulin for experimental clinical work by the fall of 1922.[8] In the meantime, Best was given responsibility for directing Connaught's insulin production, while also consulting with Lilly to expedite its stabilization and standardization, as well as the sharing of any production advances between the two firms.[9]

To help manage the enormous demand for insulin and recoup some of its substantial development expenses, Clowes began selling Lilly's insulin (or "Iletin" as they named it) at cost to diabetic specialists.[10] The first price mentioned for insulin was 10¢ per unit in June 1922, but it is not clear if anyone actually paid that much for it.[11] By the end of 1922, Lilly could no longer afford to give it away and in January 1923 started selling Iletin to individual cases at a price of 5¢ per unit,[12] which if expressed in 2006 currency would be just under 60¢ per unit, or $60 per 100 units, which is how modern insulin preparations are priced.[13] An average diabetic requires about 20 units per day of the type of insulin produced in the early 1920s. Thus, an average diabetic could pay around $1 per day for the first available insulin vials, which would be the equivalent of at least $12 per day in 2006. However, the average per-capita

annual income in Canada in 1923 was close to $500,[14] or less than $10 per week, which meant that most diabetics could spend close to half of their entire income just on daily insulin injections. The limited supply of insulin in Canada and the US in early 1923, however, restricted its use to only the most advanced cases. A 10 February 1923 *Toronto Star* article highlighted the insulin situation in a New York City hospital, which received 2,000 units of insulin from Lilly each week, but could only give it to 1% of the diabetic cases in its care. The main drawback to its expanded use, the article stressed, was its expense.[15]

While the New York hospital was struggling with the limited supply of insulin it could get, through early 1923 Lilly's production levels rapidly increased, leaving it with more insulin available than it could distribute.[16] At the time, only diabetic specialists were qualified to administer insulin or teach patients to inject themselves. It would take time to instruct private physicians in the necessary urine and blood sugar tests for their diabetic patients at the same time as teaching them how to properly administer insulin.

In Canada, however, the insulin production situation at Connaught in late 1922 and early 1923 was much less successful in output levels, primarily due to the limited size of the equipment and production facilities available in the Medical School basement. Lilly was able to supplement Connaught's insulin supplies during this period, although not without some controversy.[17] A delicate situation developed in Canada when it became publicly known that the Canadian institution responsible for the discovery and initial development of insulin could not supply enough of its "wonder drug" to Canadian diabetics, and thus had to turn to the United States to make up the shortfall. In March 1923, the *Toronto Telegram* broke the news of just such "an astounding state of affairs," adding that through an arrangement with Eli Lilly, the treatment of private patients who bought their insulin underwrote the costs of production at Connaught. Public ward patients received free insulin from Lilly also paid for out of private patients' fees.[18]

The major problem was a lack of available funds for expansion of Connaught's insulin production facility. By March 1923 there were calls in Canadian newspapers for the federal government to provide grants to Connaught to expedite a larger Canadian insulin supply.[19] Such calls, however, went unheeded in Ottawa. In the meantime, as Banting outlined during a speech at a hometown tribute in Aliston, Ontario, the Canadian price of insulin had declined to where it cost a diabetic patient from 30¢ to $3 for treatment according to the amount of insulin needed. But he stressed that "every cent being made out of the sale of insulin was being put back into its manufacture with a view to increasing production and lowering the cost." Banting hoped that a philanthropist would come forward with enough money to enable Connaught to produce insulin on

a large scale and "looked forward to the day" when its price could be "lowered to probably 1/5 of the price prevailing today."[20] For diabetics flocking to Toronto in hopes of relief, as one newspaper on 1 March 1923 put it, "miracles" were being "limited by shortages of the extract." For diabetic specialists this situation was extremely difficult emotionally and professionally. They were unable to "treat even all the more severe cases. The result is that if a patient's condition is hopeless for any reason it may be necessary for the medical men in the face of their own consciences and humanity to turn their 'thumbs down' in order that even the smallest amount of the treatment may not be spent on a hopeless case but that it be available for others."[21]

By March 1923, production improvements at Eli Lilly resulted in Clowes confidently writing to MacLeod that Lilly's "overproduction was now so tremendous" that the University of Toronto's Insulin Committee could be "assured of no difficulties supplying any amount that may be required," not only in North America, "but throughout the civilized world."[22] In Great Britain, where insulin production proceeded on an experimental basis at Middlesex Hospital Medical School through an arrangement with the University of Toronto Insulin Committee and the UK Medical Research Council, production improvements had boosted their insulin supply significantly. On 3 March 1923, the Middlesex Hospital announced an immediate reduction in price to about 2 shillings per 100 clinical units; the original price in April 1922 had been 25 shillings per 100 units, and it began to fall three months later to 17s 6d, then to 12s 6d at the start of 1923, and then to 6s 8d in February, at the same time as the extract's potency improved by 40%.[23]

For Connaught, this situation was increasingly difficult, as is clear in a letter from Dr. R. D. Defries to Robert Falconer, President of the University of Toronto. Defries was Connaught's Acting Director while FitzGerald was on a sabbatical leave to the University of California. Defries outlined to Falconer how best to approach the Ontario government for financial support of $20,000 to enable an expansion of Connaught's insulin production capacity. While insulin distribution had increased, Connaught was facing rapidly rising demand. Defries stressed that the laboratories were "assuming the obligation of distribution of this material throughout Canada until June, at least." He also pointed out that "since the material must be used by many persons daily, and since the treatment of many patients and their maintenance will be a problem for the Provincial Governments and the Municipalities a valuable service can be rendered by distribution at the lowest possible prices."[24]

Within a month Connaught's insulin situation had improved, first with a private donation of $10,000 from a patient of a prominent New York City diabetic specialist, and then with news that the Ontario government would provide Connaught with a $25,000 grant in support of its

insulin production. In April 1923, the University of Toronto Board of Governors gave Connaught permission to take over the former University YMCA Building, which had been vacant since its services had moved to Hart House in 1918, and which could be renovated to accommodate a larger insulin production plant. By May, supplemented by $8,000 from Connaught's reserves, extensive renovations and new equipment installations were underway at the old "Y" Building, and as the *Toronto Star* reported on 17 May, the "new plant should be turning out insulin in two weeks." Defries suggested that Connaught would be in a position to produce enough insulin for all of Canada by 1 July 1923, and at a cheaper price. From April to May the price dropped from 5¢ to 4¢ per unit, and by July Defries hoped to be able to offer insulin "practically at cost."[25]

Figure 1

Connaught Laboratories, insulin production facility in the basement of the old YMCA Building, University of Toronto, c. 1923-27 (SP-C Archives, Acc0012).

Banting simultaneously issued a statement expressing the hope that "government aid would be given to medical health departments so that insulin could be administered free in cases where it could be proved that the patient had no means." He felt that "one of the greatest problems facing us today is the permanent care of those diabetics who are unable to look after themselves. This is a great economic problem because when the head of a family is afflicted with diabetes a little help from the government would enable him to resume his earning capacity in a very short time."[26] By mid-August 1923, the Ontario government launched

just such a diabetic program with a booklet entitled *Insulin: Information for physicians regarding the free distribution of Insulin in suitable cases of diabetes.* The Provincial Board of Health would distribute insulin to physicians through its main Toronto laboratory and a network of branch laboratories and local health boards across the province.[27]

By the end of November 1923, Connaught was producing some 250,000 units of insulin weekly in the new building under the direction of Charles Best and assisted by Dr. D. A. Scott and a staff of 26 working day and night shifts. Not only was Connaught now able to supply Canadian diabetics with insulin, it also could ship its surplus extract to Ireland, South Africa, Central America, New Zealand, and Australia, among other countries without their own production plants. Thus with increased output and Connaught's non-commercial mandate, the laboratories were able to further reduce the price of insulin from 3¢ per unit in June to 2¢ per unit in November 1923. To the average Canadian diabetic, such a price meant they could expect to pay about 40¢ per day for their insulin, or almost $3 out of an average per capita weekly income of less than $10.[28]

The 2¢ per unit price for Connaught's "Insulin-Toronto," so named to differentiate it from Eli Lilly's "Iletin," held until March 1924. The price then dropped to 1.2¢ per unit. In June 1924, a further price drop brought Insulin-Toronto down to 1¢ per unit, or an even $1 per 100 units which lasted until December 1924, when it fell to 75¢ per 100 units, a price that remained stable for more than a year.[29] Expressed in 2006 currency, 75¢ per 100 units in 1924 would convert to about $9 per 100 units.

During the mid-1920s the general cost of living in Canada was quite stable, varying only slightly between 1923 and 1930. Thus insulin was increasingly affordable to Canadian diabetics as its price declined while other prices remained stable. At the same time, average annual incomes in Canada rose through this period, from about $507 per year in 1923 to $614 in 1928. The onset of the Great Depression in 1929 however undercut this trend, leaving average annual incomes to fall to $608 in 1929 and then drop dramatically down to $325 in 1933, before rising steadily thereafter.[30]

The price of Insulin-Toronto fell to 65¢ per 100 units in April 1926, although there was some variability of price up to 75¢ per 100 units depending upon the strength of insulin. The next drop in price came in July 1927 when the standard strength Insulin-Toronto sold for 53¢ per 100 units, this price holding until July 1929, when it slipped to 46¢ per 100 units. The equivalent 2006 price would be $5.39 per 100 units. There was little change in the price of Connaught's Insulin-Toronto until September 1932 when the price fell to 43¢ per 100 units, although the more potent type fell at a slightly different rate: 60¢ per 100 units in July 1929, 55¢ in January 1931, and 50¢ in September 1931. The price of Insulin-Toronto continued to fall steadily through the mid-1930s, down to 32¢

per 100 units through until the end of November 1935, which would equate to $4.73 in 2006.[31]

The sharp decline in the price of insulin in Canada was driven by increasing production capacities at Connaught and by higher yields made possible by the development of new production methods. While the laboratory of the renovated YMCA building had expedited a large enough insulin supply to meet immediate Canadian needs, the completion of what became known as the School of Hygiene Building in 1927 made an even larger supply possible. As early as 1922, FitzGerald had approached the Rockefeller Foundation in hopes of financial support towards a new School of Hygiene facility to accommodate the growing Hygiene Department (of which FitzGerald was also Director) and larger facilities for Connaught Laboratories. The Rockefeller Foundation had already granted substantial support towards the establishment of schools of hygiene at Harvard University, The Johns Hopkins University, and the University of London. The Rockefeller Foundation easily accepted FitzGerald's proposal due to Connaught's success and the international prominence of the discovery of insulin at the University of Toronto. Defries's tour of the existing Department of Hygiene and Connaught's facilities with senior Foundation dignitaries in 1923 certainly underscored the need for better facilities.

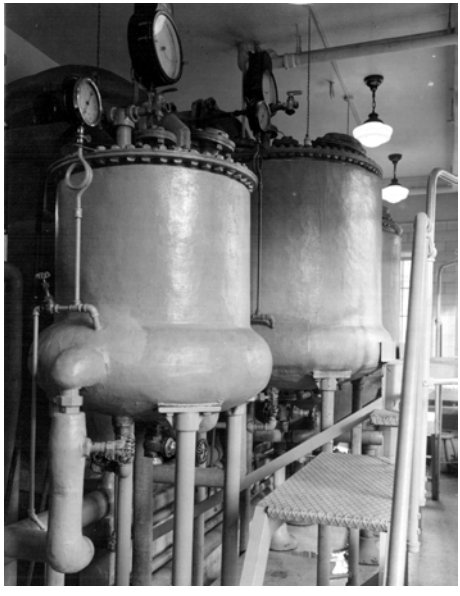
In 1924, the Rockefeller Foundation announced a $650,000 grant (equivalent to about $7.8 million dollars in 2006) to the University of Toronto to establish a School of Hygiene, $400,000 of which was put towards a new building and the balance used as an endowment to create several new hygiene-related departments. Connaught was able to utilize space in the new building for research, production, packaging, and administrative divisions of the laboratories, particularly in relation to insulin.

On 9 June 1927, Connaught's insulin plant moved into two basement floors of the new School of Hygiene Building. In his 1927 Connaught Annual Report, FitzGerald stressed the close proximity of the new insulin plant with the laboratory's other research and public health products production facilities and the various departments of the School of Hygiene. "It may not be out of place to point out again that in no other institution of higher learning in the world is a serum institute an integral part of a School of Hygiene within such an institution, as is the case in the University of Toronto, where the School of Hygiene and the Connaught Laboratories serve a three-fold purpose: research, teaching and medical public service." A key focus of this threefold purpose was the production of insulin, its constant improvement, and its distribution as a public service to Canadian diabetics at the lowest possible price.

In addition to the new and larger insulin plant facilities, Connaught's insulin output was expanded due to advances in extraction technology

and development of insulin crystallization. Small quantities of insulin crystals had been produced at Johns Hopkins University in 1926. After studies on crystallization in 1929 at the University of London, Dr. D. A. Scott returned to Connaught ready to develop a new, more efficient, method of insulin crystallization. Scott's research revealed how zinc, cobalt, and nickel were important components of pancreatic tissues; indeed, he discovered that zinc was an essential element in the crystallization of insulin. He found that if a trace of zinc was removed from insulin, it remained non-crystalline when dried to a powder but still retained its anti-diabetic power. Crystalline-based insulin was purer, but not as long lasting as the original form; more daily injections would be needed. This work was critical to the international standardization of insulin, which would be based on a defined amount of insulin crystals first established at Connaught in 1932. This work was also critical to the development of a new, longer acting, type of insulin in 1936.[32]

Figure 2



Connaught Laboratories, insulin extraction area of the School of Hygiene Building, University of Toronto, c. 1930s. (SP-C Archives, Acc0618).

The first steps toward longer acting insulin were taken in Denmark where Dr. H. C. Hagedorn discovered that a small molecule extracted from fish sperm, known as protamine, when combined with insulin, significantly slowed its action. A diabetic requiring four daily injections of regular insulin, or five injections of the purified type, could manage

with two daily injections of the new protamine insulin, first introduced in 1935 by Nordisk Laboratories in Denmark. Within a year, and building upon their work with insulin crystallization, the Connaught research team of D. A. Scott and Dr. A. M. Fisher discovered that by adding a trace amount of zinc to protamine insulin, a more stable longer-lasting combination was produced, whose effect was prolonged to seven hours and even up to three days. Introduced in 1936, Connaught's Protamine Zinc Insulin was a major advance that was quickly and very widely adopted. It soon became the most popular form of insulin in Canada.[33]

The initial price of Connaught's Protamine Zinc Insulin (PZI) is unknown. However, by February 1939 the price of PZI was set at $1.05 for a 10 cc vial of 40 units per cc strength, or $2 for 80 units per cc strength. This worked out to 26¢ (40 unit strength) or 25¢ (80 unit strength) when expressed in terms of price per 100 units, which in 2006 currency, converts to about $3.50 per 100 units. The price of regular Insulin-Toronto in February 1939 had held at 21.5¢ since April 1938, prior to which it had been 26¢ since December 1935. In April 1942, the base price of Insulin-Toronto fell to 20¢ per 100 units where it would remain for the next 25 years; the equivalent price in 2006 would be $2.43.

During the late 1930s and early 1940s, the average Canadian income rose from just under $400 per year in 1936 to just under $600 per year in 1942, while the cost of living index rose from 98.1 to 117.2 (where the average of the 1935-39 period equalled 100).[34] The ordinary Canadian diabetic's ability to afford insulin continued to improve, although the numbers of insulin-dependent diabetics continued to grow. Within this changing economic climate, exacerbated by World War II, Connaught faced pressures on its insulin prices caused by rising costs of production and changes in prices from other insulin producers, especially Eli Lilly, although Lilly's insulin products could not enter Canada. They did not compete directly, but the prevailing American insulin price sometimes built pressures at Connaught to either raise or lower the price, or to offer discounts, particularly to the Ontario government.

In February 1942 for example, Connaught's Committee on Prices felt that the American insulin price would not be reduced and might even be increased. For Connaught, "It was desired to reduce the price of insulin to both the patients and to the Province of Ontario if such a price reduction was feasible in the light of possible increased costs of production." In the Committee's discussions, "It was pointed out that the present prices might be returned to if costs rose and that this would be in accord with the price-ceiling regulations." The suggested price reductions, which included reducing the price of PZI to 96¢ for 40 units/cc strength (from $1.05) and to $1.85 for 80 units/cc strength (from $2), would result in an annual income reduction to Connaught of $30,809 and a savings of $4,687 to the province on insulin purchases. Such an income reduction was con-

Table 1
Connaught Laboratories—"Insulin-Toronto" Retail Price per 100 units, 1922-1942 and 2006 Equivalent Price

Date	Product	Retail Price per 100 units[a]	Equivalent 2006 Price[b]
Jun 1922	Insulin-Toronto	$10.00	$119.27
Feb 1923	Insulin-Toronto	$5.00	$59.09
May 1923	Insulin-Toronto	$4.00	$47.27
Jun 1923	Insulin-Toronto	$3.00	$35.45
Oct 1923	Insulin-Toronto	$2.00	$23.64
Mar 1924	Insulin-Toronto	$1.20	$14.44
Jun 1924	Insulin-Toronto	$1.00	$12.04
Dec 1924	Insulin-Toronto	$0.75	$9.03
Apr 1926	Insulin-Toronto	$0.65	$7.75
July 1927	Insulin-Toronto	$0.53	$6.38
July 1929	Insulin-Toronto	$0.46	$5.39
Sept 1932	Insulin-Toronto	$0.43	$6.43
Mar 1934	Insulin-Toronto	$0.385	$5.74
Apr 1935	Insulin-Toronto	$0.32	$4.73
Dec 1935	Insulin-Toronto	$0.26	$3.84
Apr 1938	Insulin-Toronto	$0.215	$3.00
Apr 1942	Insulin-Toronto	$0.20	$2.43

[a] Prices quoted are converted from 10 cc vials of 40 units per cc strength products.
[b] http://bankofcanada.ca/en/rates/inflation_calc.html

sidered acceptable when considered against total insulin sales of $360,000 in 1940-41 and total income from all biological product sales of just under $776,000. Thus, after some discussion, the Prices Committee unanimously agreed to introduce the proposed insulin price reductions.[35]

While the price of Connaught's insulin preparations remained stable in Canada from March 1942–1967, maintaining such price levels was difficult. The laboratories faced a variety of external pressures through this period—especially the rising costs of beef and pork pancreas, along with all other aspects of production—at the same time as new developments in insulin production technology afforded opportunities to further improve insulin yields, while increasing international demand for insulin brought new opportunities for export.

Before joining Confederation in 1949, Newfoundland was a separate crown colony to which Connaught exported insulin, among many other biological products. Its close proximity to Canada created some controversy in 1946 when islanders discovered that they were paying signifi-

cantly more, sometimes double the price, for insulin than Canadians. The Canadian press picked up this story, which had been initially prompted when Canadian diabetics visited or moved to Newfoundland and needed to replenish their insulin supply and were surprised at the price. As a Canadian newspaper article stressed, Connaught's 40-units per cc strength regular and Protamine Zinc Insulin sell across Canada "at the strictly controlled price of 96¢ and 83¢ per bottle, respectively," which include an 8% mark-up by pharmacists. However, the corresponding prices in Newfoundland were about $1.90 and $2. The higher prices for insulin, along with other commodities imported into Newfoundland, were due to import duties. The import duty on Canadian insulin was 10%, although most drug items entering from Canada were subject to a 55% tariff. The insulin duty had been 40%, but pressure on the Newfoundland government had prompted a reduction a few years earlier.[36]

During the early post-World War II period, there was growing awareness among Canadians of the great numbers of diabetics across the country and elsewhere, particularly in the United States, and what this situation meant for the future security of the insulin supply. Press reports in 1948, noted the lack of immediate concerns about the Canadian insulin supply, but the numbers highlighted in the article and its headline, "Vital Need For Insulin Spurs U. of T. Campaign," underscored the need for more research in Toronto, "the birthplace of insulin." Furthermore, some 5,000 pounds of beef and pork pancreas were needed to produce eight ounces of purified insulin. At the same time, there were about 3,000,000 people around the world reliant on insulin, one million of whom were American. "What of the future?" the article asked. It was expected that another four million people "will need insulin in their lifetimes. How will demand for insulin be met?"[37]

By 1948, Connaught was operating its insulin plant 24 hours a day, 5 days a week and had built up a reserve insulin supply of 750 million units. Connaught had an arrangement with the Canadian meat packers industry that supplied the laboratories with all of the beef and pork pancreas produced across the country; at that time the price was as high as 27¢ per pound for beef pancreas and up to 45¢ per pound for pork. It was clear that the current Insulin Plant in the School of Hygiene Building (now known as the College Division) would soon be insufficient to meet the insulin demands, despite several expansions and equipment upgrades. Connaught's Executive Committee began considering their options in 1948, debating between building a new production facility at the "Farm" site, which was now called the Dufferin Division, adding to the existing plant, or building a new facility elsewhere on the main University Campus.[38] By early 1949 construction began on an additional insulin plant accommodated in an extension to the Spadina Division (on the main University of Toronto campus), which Connaught had

acquired in 1943 for penicillin and dried blood serum production for the Canadian military.[39]

The additional space and upgraded equipment in the new insulin plant—almost equivalent in capacity to the main plant in the College Division—was the focus of research into new and more efficient insulin production methods. Dr. Gordon Romans developed the "salt-alcohol" method in 1949-50, which proved successful in raising insulin extraction efficiency from beef pancreas to 1200 units per pound, although the results were less substantial with pork pancreas.[40]

The increased insulin production capacity put Connaught in a better position to respond favourably to the growing number of requests for insulin from international laboratories and pharmaceutical firms and foreign governments. In February 1949, Connaught's Prices Committee met to develop an insulin export policy, prompted by a request from Burroughs Wellcome in the US for 10 million units of insulin in bulk crystals. The Prices Committee recommended that Connaught agree to sell up to 25 million units of insulin to Burroughs Wellcome for a "suggested special price" of 7.7¢ per 100 units, which they accepted. In April 1949, after Brazil inquired about buying finished insulin, it was clear that growing international demand rendered it essential that Connaught "sell insulin preparations in foreign markets for the Labs are now producing insulin at 3 times the rate at which the product can be used in Canada." Yet there were concerns about the impact such exports would have on the price of pancreas in Canada, as well as concerns about what prices to charge for exported insulin. By early 1950, however, the increasing insulin surplus prompted Connaught to become pro-active, sending letters to other insulin manufacturers and "any responsible lab" in countries such as Denmark, Great Britain, Australia, and the US, asking if they needed additional bulk supplies of zinc insulin crystals to meet their needs. It was sometimes a difficult sell as a global surplus of insulin was building through the early 1950s. In some countries there was interest, but difficulties getting currency complicated sales.[41] In the meantime, Connaught's insulin surplus continued to build; in May 1952 there were 1.2 billion units in stock, but the laboratories only sold about 600 million units in Canada per year.[42]

By October 1950, it was clear that Canadian pancreas prices would rise. Nevertheless, Connaught's Prices Committee voted to maintain the existing prices for Insulin-Toronto and for Protamine Zinc Insulin. However, the introduction of a new type of insulin, known as NPH Insulin, which was intermediate in its action between regular insulin and Protamine Zinc Insulin, provided an opportunity to offset the rising costs with a new product. NPH Insulin was originally developed at the Nordisk Laboratories in Denmark in 1946 but not licensed in Canada until 1950. Connaught officially added NPH Insulin to its product line on

1 December 1950, introducing it at a price of $1 for 10 cc at 40-unit strength and $1.90 for 10 cc at 80-unit strength, which were 4¢ or 5¢ over the price of Protamine Zinc Insulin.[43] The NPH prices were equivalent to 25¢ per 100 units for the 40-unit strength type, and 24¢ per 100 units for the 80-unit strength, which if expressed in 2006 currency would be $2.11 (40 unit) and $2.03 (80 unit) per 100 units.

During the late 1940s and early 1950s, the cost of living index in Canada rose from 124.5 in 1946 to 185.4, while the average annual income rose from just over $900 in 1946 to just under $1,500 in 1951.[44] Under these economic conditions, the cost of insulin for the average Canadian diabetic would have been more affordable than it had ever been. For Connaught, however, maintaining such a low price became increasingly difficult.

Connaught's insulin production increased from the mid-1950s and into the 1960s, driven by the need to process the beef and pancreas it bought at controlled prices, which was the entire Canadian supply (totalling over 1.25 million pounds annually), provide all available insulin preparations to Canadian diabetics at the lowest possible price, and maintain a substantial stock and secure emergency reserve. Such a large insulin production machine at Connaught, with production that had doubled every seven years and totalled 1.3 billion units in 1955, operated "around the clock" with close co-operation of Canadian pharmacists and the meat packing industry and continuous research in the laboratories. By 1957 Connaught's insulin exports accounted for about 23% of domestic distribution.[45]

Through this period, Connaught's insulin sold at lower prices than in the US (in 1955 a 10 cc vial of 40-unit strength of regular insulin was 83¢ in Canada and from $1.19 to $1.39 in the US) and at about the same price as in Great Britain. European insulin prices, however, were generally cheaper.[46] As Connaught produced more insulin that it could sell in Canada, the export market became increasingly important, particularly in Japan, South America, and parts of Europe, as well as to countries "behind the Iron Curtain." As noted by Connaught's Executive Committee in September 1955, "While such distribution will return only a small margin to the Labs, it would further our objective of reducing our inventory by about 500,000,000 units."[47] Such export sales helped, but did not ease the financial pressures that were building at Connaught, leading to another suggestion at a late November 1955 meeting of the Prices Committee to raise insulin prices. However, as had been the case previously, "after considerable discussion," the Committee "agreed that from the standpoint of the Laboratories and from the standpoint of patients, it was desirable that there be no increase in price at this time."[48]

One factor that may have influenced the decision against an insulin price increase, and similar to the introduction of NPH Insulin five years

earlier, was the pending addition of another type of insulin to the product line, known as Lente Insulin. Developed at Novo Laboratories in Denmark in the late 1940s, Lente Insulin was another variation of insulin combined with zinc, but without any other protein added that slowed the action of insulin. There were actually two additional special types of Lente Insulins known as Semilente and Ultralente. Semilente was soluble in blood and acted nearly as fast as unmodified insulin (such as Insulin-Toronto), while Ultralente was insoluble in blood and acted very slowly, much like Protamine Zinc Insulin.[49] After arranging approvals from Novo Laboratories late in 1955, Connaught applied for a Canadian licence for Lente Insulin. While awaiting the licence, Dr A. M. Fisher worked out the production methods and on an experimental basis distributed Lente Insulin to Canadian physicians for free.[50] The licence was granted in December 1956 and Connaught sold Lente Insulin in 10 cc vials of 40 and 80 units per cc concentrations for $1.10 and $2.10 respectively, or 27.5¢ or 26.25¢ per 100 units respectively, which was slightly more that NPH Insulin; their 2006 values would convert to $2.02 and $1.94 per 100 units.[51] By early 1963, Connaught had introduced the Semilente and Ultralente Insulin preparations, which sold at the same price as Lente Insulin; their price in 2006 would convert to $1.81 and $1.74 per 100 units.[52]

While Connaught had imported the rights to produce the Lente Insulins and NPH Insulin earlier, during the late 1950s and early 1960s a small research team at Connaught, led by Dr. P. J. Moloney, undertook unique studies into the immunochemistry of insulin and specifically the problem of insulin resistance. Repeated injections of insulin prepared from beef or pork pancreas potentially can be perceived by the human body as a foreign protein and in some cases sufficient antibodies can develop that inhibit or counteract its intended effect. Fortunately, insulin very rarely acts as an antigen in human diabetics. However, Moloney was able to demonstrate this type of reaction to insulin in experimental animals and in a few diabetic patients, who had become increasingly resistant to insulin. Though rare, likely some diabetics died of the disease when undiagnosed insulin resistance led to their condition becoming uncontrollable.

By 1962, Moloney's team had discovered a way to prepare a modified type of insulin that they called Sulphated Insulin, which in reasonable doses acted as regular types of insulin normally did. Moloney initially found seven patients with insulin resistance for whom Sulphated Insulin was offered for free. Soon, however, it became clear that this type of insulin resistance occurred more often than originally thought. A larger supply was thus needed, leaving Connaught with the challenge of preparing and providing a new product targeted at an unusually small market at an affordable price. In 1965 Sulphated Insulin was licensed and sold for $12 per 100 units, an unavoidably much higher price than regular types of insulin.[53] Converted to 2006 currency, the price would be $77.23 per 100 units.

Table 2
Connaught Laboratories, Insulin Preparations Launch Prices and 2006 Equivalent, 1923-1965

Date	Product	Retail Price per 100 units[a]	Equivalent 2006 Price[b]
Feb 1923	Insulin-Toronto	$5.00	$59.09
Feb 1939[c]	Protamine Zinc Insulin	$0.26	$3.63
Dec 1950	NPH Insulin	$0.25	$2.11
Dec 1956	Lente Insulin	$0.275	$2.02
Jan 1963	Semilente Insulin	$0.275	$1.81
Jan 1963	Ultralente Insulin	$0.275	$1.81
1965	Sulphated Insulin	$12.00	$77.23

[a] Prices quoted are converted from 10 cc vials of 40 units per cc strength products.
[b] http://bankofcanada.ca/en/rates/inflation_calc.html
[c] Protamine Zinc Insulin was launched in 1936, but I was unable to find a reference to its initial price, although it was unlikely to be much higher than the 1939 price.

During the mid-1960s it became clear at Connaught that an insulin price increase was unavoidable. In April 1967 the price of 40-unit strength 10 cc vials of Insulin-Toronto rose by 7¢ (or 8.4%), 80-unit strength rose by 15¢ (or 9.3%) and 100-unit strength by 20¢ (or 10%). The price of Protamine Zinc Insulin rose by 19¢ (or 19.8%) for 40 unit strength vials and 40¢ (or 21.6%) for 80 unit strength vials. The prices for the other more specialized types of insulin also rose by similar amounts.[54] After holding the prices on these key types of insulin for 25 years in the face of the economic pressures highlighted earlier, Connaught's price increases were not unreasonable.

On 24 June 1970, the official opening of the new Defries Building at the Dufferin Division marked the beginning of a new era of insulin production for the laboratories. With inflationary pressures accelerating during the early 1970s, it was more difficult for Connaught to prevent further insulin price increases. However, as Dr. A. M. Fisher noted in an article titled "The Cost of Insulin" published in the *Newsletter* of Canadian Diabetes Association in 1972, the effect of the 1967 price increase for average diabetics reliant on 40-unit strength Insulin-Toronto meant a rise from about 8.3¢ per day to 9.0¢ per day, while users of 40-unit strength NPH Insulin paid not more than 12¢ per day. Still, as Fisher stressed, despite the price increase in 1967, insulin prices "are substantially lower than those in effect in 1938, and for Insulin-Toronto, no higher than the price in 1942."[55]

An important factor that made it more difficult for Connaught to absorb rising insulin production and other costs during the 1960s and 1970s was the loss of royalty income that had been generated by various insulin patents. In particular, there were four American patents managed by the University of Toronto Insulin Committee, which generated

Figure 3

Opened in June 1970, Canada's insulin supply was produced in the Defries Building at Connaught Laboratories' Dufferin Division, Steeles Avenue West, Toronto (SP-C Archives, Acc1043).

substantial revenues. The original Banting, Best, and Collip patents, which expired in 1940, generated net royalties of $2,400,304 for the University of Toronto, half of which was assigned to the Insulin Committee Trust Fund to support research in Banting's and Best's research laboratories, and the other half split three ways to support the research work of Banting, Best, and Collip in their respective institutions.[56]

Of more direct significance to Connaught were Scott's patent for the crystallization of insulin, which expired in January 1956, and Scott and Fisher's patent for Protamine Zinc Insulin, which expired in November 1956. From 1937–57 the PZI patent yielded $4,492,373 and after paying the expenses of the Insulin Committee, the royalties totalled more than $3,500,000, half of which went to the Insulin Committee Trust Fund and divided similarly as the Banting, Best, and Collip patent. Connaught received the other half, with over $970,000 then granted to the School of Hygiene between 1929 and 1972 out of a total of more than $2,400,000. "To a significant extent, Connaught's insulin sales paid for the School of Hygiene's operations." For Connaught itself, the steady stream of predictable revenues from insulin royalties and sales "allowed a development of staff and research which has been the envy of similar institutes of public service, like the Lister Institute and the Wright-Fleming Institute in England." Indeed, Connaught "was lucky to have insulin."[57]

By 1972, despite Connaught's successes with insulin, as well as other products, notably the Salk and Sabin polio vaccines, the University of Toronto decided to sell Connaught Laboratories to the newly established federal crown company called the Canadian Development Corporation.[58] By the end of June 1972, Connaught had become a profit-oriented commercial company, a transformation that generated concerns on many levels, not the least of which from the Canadian Diabetic Association, worried about the potential impact Connaught's sale would have on insulin prices and supplies. In petitioning the Ontario government to halt the sale of Connaught to the CDC, the CDA pointed out that Connaught sold its insulin to Canadians at prices that were 25 to 35% cheaper than American companies did south of the border. However, the Ontario government did not interfere with the sale and Connaught Medical Research Laboratories became Connaught Laboratories Limited, the Chairman of the CDC assuring diabetics that "insulin prices would not rise in the foreseeable future."[59]

In 1974, dramatic spikes in the price of beef and pork pancreas made it impossible for Connaught to avoid insulin price increases that year. Meanwhile, Eli Lilly was forced to implement its first insulin price increase in 28 years, pressured by pancreas price rises of 129% since 1968, and 85% since 1973, along with wage costs rising 50% since 1968.[60] In October, facing similarly dramatic pancreas price increases, Connaught had no choice but to raise its insulin prices by about 10%.[61]

Amidst the news of pancreas prices rising alarmingly and prospects of global pancreas shortages and further price instability in the future, it was reported that there had been a breakthrough in the chemistry of human insulin at the Swiss pharmaceutical firm, Ciba-Geigy AG, "by achieving the total synthesis of the vital hormone." This significant development pointed to the large scale production of insulin based on a synthesized human form of the hormone, although "several more years of work" were needed.[62]

Following an 11% increase in July 1976, Connaught's largest insulin price increase, 20–24%, was implemented in January 1977. The retail price of Insulin-Toronto (beef) thus went up to $4.20 per 100 units and to $6.70 per 100 units for pork-based. Protamine Zinc Insulin and NPH Insulin types each rose to $5.90 (beef), $6.70 (pork) and $5.20 (pork and beef) per 100 units, while each of the Lente types of insulin sold for $5.50. When the 1977 insulin price increases were announced, which brought the average daily cost of insulin up to about 15¢, the CDA appealed to the federal and provincial governments for some financial assistance to diabetics who were on fixed incomes.[63] As stressed in press reports, the latest insulin price change resulted in Canadians paying more for their insulin than Americans, although such reports did not mention the differences in production scales that favoured US produc-

ers.[64] For the *Toronto Star*, the situation with insulin provided an "overwhelming reason to get Connaught out of CDC hands and back to the University of Toronto." It was clear that the sale to the CDC was "a mistake," since "profit and medical research are simply not compatible." Connaught should thus be publicly owned and receive "the subsidies it needs to restore its reputation as a centre of research and for the production of life-saving biological substances."[65]

In January 1979, after a further 6% hike in Connaught's insulin prices, CBC-Radio host and *Toronto Star* columnist Peter Gzowski profiled the story of a diabetic entitled, "A Diabetic's Luck: Illness and Bills." This particular diabetic, a 55-year-old successful self-employed sales agent whose name was Syd, required 94 units of Lente insulin, which he administers at 7:30 a.m. every morning, although the dosage for the average diabetic was closer to 30 units. For Syd, the new price of Lente insulin "really won't make that much difference." "The increase is, as almost everyone involved in bringing it down explained, just about a penny a day. It will raise the cost to the average diabetic to 18 cents a day, from 17." Gzowski's column, however, also highlighted the other costs associated with managing diabetes, such as: $13 for a box of 100 disposable needles; $3 for a 60 day supply of alcohol swabs; $7.85 for a bottle of sticks to test sugar levels in urine (three sticks per day were used). For Syd, his total expense for managing his diabetes was about $6 per week, which he felt he could easily afford, although he had little choice but to pay such costs, none of which were borne by Ontario public health insurance. At the time, Prince Edward Island was the only province in Canada that gave out insulin for free. In Ontario, "if you're old or poor you get help with the cost of insulin, otherwise you pay for the bad luck of getting diabetes yourself."[66]

The start of the 1980s marked the symbolic end of an era for insulin in Canada and the start of a new reality for Connaught Laboratories' insulin production operation. In 1980, after some 57 years as Canada's sole supplier of insulin, Eli Lilly was granted permission to sell its American made insulin in Canada. The licence applied only to a new purified type of single-peak "Iletin" insulin—purer than Connaught's—aimed at 6 to 7% of Canadian diabetics who were sensitive to ordinary insulin.[67] As noted in a 1980 *Toronto Star* report, Lilly's entry into the $7 to $8 million Canadian insulin market seemed quick and "surprisingly easily" after submitting its application in August 1979 and having the licence granted in December 1979.[68]

By 1980, Eli Lilly controlled about 60% of the global insulin market and was very active in developing and testing a new recombinant-DNA based biosynthetic form of insulin. Most of the remaining 40% of the global insulin market was controlled by Novo Laboratories of Denmark, which was making faster progress than Eli Lilly in developing and marketing a

new generation of human biosynthetic insulin products. Joined by Nordisk Laboratories, also of Denmark, Novo and Lilly entered into a major insulin war built around the new forms of human insulin.[69] For Connaught, there was little it could do during the early 1980s except watch the battle from the sidelines as it did not have the resources to compete effectively in the development of the new biosynthetic insulins, nor be able to keep the price of its insulin products as low as it had in the past.

Indeed, a 1983 newspaper article noted, the growing international insulin competition had "forced Connaught up against a wall over the past 10 years."[70] Rather than face an uncertain future of rapid change in the global insulin market and risk losing control of the Canadian market, in the fall of 1983 Connaught agreed to join forces with Novo Laboratories. Formally launched in January 1984 under a 10-year agreement, Novo established a Canadian subsidiary, Novo Industries Ltd., which would take over Connaught's existing insulin production facilities. Connaught and Novo would also create a new company together, Connaught Novo Ltd., which would assume control of marketing, clinical research, and medical services for Novo products made in Canada. It was expected that this new joint venture would not affect jobs at Connaught or the price of insulin in Canada. By July 1984, the first Connaught Novo human insulins were launched in Canada: Actrapid (similar to Insulin-Toronto in its action), Montotard (similar to Lente) and Protophane (similar to NPH Insulin).[71]

In May 1985, Health and Welfare Canada hosted a symposium entitled "Status of Diabetes in Canada," whose final report provided a useful snapshot of not only the incidence of the disease—there were estimated to be 160,000 Type I diabetics in Canada dependent on insulin—but also the changed status of insulin in Canada. There were at least 15 insulin manufacturers in the western world, three of which supplied insulin in Canada: Connaught-Novo had 87% of the market, Lilly 12%, and Nordisk 1%, together providing some 2.5 million vials of insulin annually in Canada, with this amount increasing 2 to 4% annually. In 1985, the wholesale price of beef or pork-based insulins was about $9 per 100 units, or $13.50 per 100 units for pork-based or human insulins. Each type was subject to a 10 to 40% mark-up at pharmacies. The report estimated that the average annual cost of insulin in Canada was about $250 per patient and with a total population of 250,000 insulin-dependent diabetics, the annual retail expenditure for insulin in Canada was approximately $60 million, most of which was spent on either regular or NPH types of insulin. When converted into 2006 currency, the average annual cost of insulin in Canada would convert to just under $430, while the total annual Canadian expenditure for insulin would convert to about $103,000,000.[72]

While Connaught Laboratories divested itself of a direct role in insulin production in 1984, for the next decade it maintained its interest in Connaught Novo Ltd., after which it shifted into only a distribution role for the insulin products produced by the newly merged firm of Novo Nordisk. Connaught's move away from insulin during the 1990s was driven by its 1989 corporate take-over by Institut Mérieux of Lyon France, which transformed it into the Canadian component of "Pasteur Mérieux Connaught." (or simply PMC), the primary focus of which was the development and production of human vaccines.[73] A decade later, Rhone Poulenc, the France-based parent company of PMC, merged with Hoechst of Germany to create a new company known as "Aventis." PMC was thus re-branded as "Aventis Pasteur" and its Canadian component designated the "Connaught Campus." In 2004, the acquisition of Aventis by Sanofi Synthélabo of France resulted in the creation of Sanofi-Aventis and the transformation of Aventis Pasteur into sanofi pasteur.[74]

Through all these shifts in name, the identity of the Canadian site known as the "Connaught Campus" has remained remarkably consistent, reinforced by its deep Canadian roots, a major component of which grew out of the essential role it played in the development and production of insulin since its discovery. Coupled with its unique organization through most of its history as a self-supporting part of the University of Toronto dedicated to medical research, biologicals production and public service, Connaught was able to provide a similarly unique service to diabetics in Canada and globally, based on innovation and a dedication to providing all types of insulin at the lowest possible price. This was successfully accomplished as the company avoided price increases from 1942 through 1967 while constantly innovating production technologies and expanding outputs in the face of economic and other challenges. As much as Canadian diabetics couldn't live without insulin, for most of the 20th century, they could not have lived without Connaught Laboratories.

NOTES

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74 The official corporate policy of the global organization is to use all lower cases when writing "sanofi pasteur" in all internal and public documentation. However, the legal name of the Canadian component, "Sanofi Pasteur Limited" retains the capitals.