The Discovery and Manufacture of Insulin

By Gene E. McCormick, Historian
Eli Lilly and Company, 1971

At the annual meeting of the American Physiological Society held during the Christmas holidays of 1921 at New Haven, Connecticut, a young Canadian physician reported that he and an associate had isolated from the pancreas an internal secretion that lowered the blood-sugar level of depancreatized dogs to normal and that by periodic injection of the substance and special dietary measures, they had maintained the animals diabetic free for several weeks.\(^1\)

The discovery of insulin by Dr. Frederick Grant Banting and his student assistant, Charles Herbert Best, was profound at that point in time in the field of medical science. Their work conclusively demonstrated that the pancreas, by internal secretion, serves a direct function in carbohydrate metabolism, and, thus, a thirty-year search of international scope to find the elusive, hypothetical hormone was culminated.

The discovery of insulin also established the unitary nature of diabetes and, consequently, brought together the observations and explorations of many who had struggled over the millennia to understand the disease and assuage its ravages.\(^2\)

Diabetes was not a widespread disease at the time Banting conceived his surgical method of isolating insulin—a method he was unaware others had tried. For by 1920, life expectancy was too short to manifest the major incidence of its maturity onset. But the disease was vicious and implacable. Little could be done to check the victim’s unquenchable thirst, excessive urination, gnawing hunger and gradual wasting away. Although the starvation diets devised a few years before Banting’s discovery did prolong the diabetic’s life somewhat—a little more than two years on the average—the suffering they imposed was almost as cruel as the disease itself. This was as far as the nutritional concept of diabetes therapy had evolved after 200 years of trial and error to restore balance in the bodily conversion of food into energy.

In fact, until the advent of insulin, diabetes generally was a fatal disease. The body, unable to metabolize carbohydrates, turns to its fats as an energy source and, in the process of burning them in conversion, produces by-products that eventually smother internal processes. At this stage, the body is forced to derange its precious chemical balance to counteract the disruptive congestion of its environmental pathways. This radical effort to survive brings its final destruction. The heavy
gulping of air by the unconscious victim to expel the smothering ketones of burning fat cannot stave off the fatal coma. Thus, 50 years ago, the conquest of diabetes was defined as the prevention of coma, and the unusual severity of the disease in children gave particular urgency to that conquest. The death throes of diabetes most frequently occurred in the young.

Scientists and physicians the world over fully appreciated the need of specific therapy for diabetes. As late as 1920, while many noted authorities were skeptical about the existence of an internal pancreatic secretion—and in face of the numerous failures to isolate it since the turn of the century—there were others who were intrigued by indications increasingly coming to light since the work of Oskar Minkowski and Joseph von Mering in 1889. Dr. G.H.A. Clowes was among the latter, and aware of the investigation of Banting and Best almost four months before their first report to the outside world at New Haven, he was in the audience to hear what Banting had to say. Impressed by the experimental conclusiveness reported on the action of insulin and with authorization from Eli Lilly, the vice president of Eli Lilly and Company, he promptly offered to Banting and Professor James J.R. Macleod, head of the department of physiology at the University of Toronto, under whose auspices Banting had pursued his work, the services of the pharmaceutical company for the large-scale production of the vital hormone.

It was not until the middle of the following May, however, that Macleod accepted the offer of collaboration on behalf of the university. Aware of the importance of the discovery of insulin to patients with diabetes, and likewise, the obligation to prevent fraudulence and exploitation, the University of Toronto had much to do before making commitments of any kind. Testing of the extract in human cases had not started at the time of Clowes’ overture; development of manufacturing procedures from laboratory methods had barely begun; and the means to administer control of product efficacy, clinical trials and licensing had to be resolved.

During this period, the university took measures to establish an advisory group of its representatives and officials of the Connaught Antitoxin Laboratories affiliated with the university to oversee the development and distribution of an effective, standardized agent. It also obtained, in gratuity patent rights, that which had been applied for on insulin and its process of manufacture. Vested as an official body responsible to the university for the insulin program, the advisory group was formally established as the Insulin Committee toward the end of 1922.
While these affairs were in process, the first clinical trial of insulin was yielding encouraging results. On January 11, 1922, Banting and his associates at the Medical Service of the Toronto General Hospital, Drs. Walter R. Campbell and Almon A. Fletcher, had administered insulin to Leonard Thompson, a 14-year-old boy suffering from juvenile (severe) diabetes. The initial injections did not produce notable response, but with the use of more potent extracts administered two weeks later, there was marked improvement, and the boy soon was restored to normal life. He died 11 years later from broncho-pneumonia resulting from a motorcycle accident.

Six additional patients were put on clinical trial as laboratory supply of the precious extract increased. In a preliminary report published in March, the investigators said, “It is difficult to put into words what is meant by clinical improvement.” Tentative though it was, the advance was unique. For the first time in man’s existence, there was promise of liberation from this dreaded disease. “With bright news from Toronto,” said Dr. Elliott P. Joslin, eminent American diabetologist, parents who had scrupulously made their children follow strict dietary discipline were now rewarded with “a hope for life, which they hardly dared to anticipate.”

Attempts at Toronto to devise a standard extraction procedure for large-scale manufacture were not successful however. From March to May, there was no production of acceptable material. Dr. James B. Collip, professor of biochemistry on leave from Edmonton University who had been engaged by Macleod to develop process standards, declared he was unable to solve the problem of potency loss and instability that accompanied increased yields and withdrew from the project. The fact that seven diabetics were now supported by insulin was, of course, a crucial matter. But in the wider view, it was also important to the university to establish reliable extraction standards for the purposes of licensing—since it recognized that it had neither the funds nor the facilities to support the manufacture of insulin on a scale equal to general demand. Accordingly, the university concluded that development work must now turn to outside assistance, and on May 15, Macleod invited Clowes to come to Toronto to discuss the collaboration proposed at New Haven. Two weeks later an agreement was committed to paper as an “indenture” pertaining to experimental production and clinical supply and was signed by the university and the company. The agreement stipulated, among several things, that:

- Lilly had one year in which to develop an agent complying with university standards, during which time the company had exclusive right to make, use, and sell the extract in the United States, Mexico, Cuba, and Central and Latin America only

- batches of the product acceptable to both parties on the basis of approved testing could be distributed on a cost basis or gratis to physicians and institutions selected by agreement between both parties
Lilly was to provide the university 28 percent of each approved lot of insulin when distributed gratis and 12 percent when supplied at cost.

All clinical reports received by Lilly were to be submitted to the university and company use of them would be governed by the discretion of the university for both professional and promotional purposes.

There was to be full collaboration between the two parties on the divulgence of production methods and testing and on improvements either might make, in which case if Lilly developed patentable methods, it was to assign U.S. patents in gratuity to the university “upon being requested to do so.”

After successful conclusion of the experimental period, Lilly was to be granted a license and pay a five percent royalty on net sales to the university.

The university agreed not to divulge to others any information provided by Lilly within the time limit of the indenture and assured the company that the licensing of other firms would be on the same terms as it would receive. (9)

In the development of safe and effective medicine, the stipulations of the agreement were without precedent and, as far as is known, signified the first voluntary, cooperative endeavor among an academic institution, the medical profession, and a commercial house to apply a major therapeutic advance on an international scale.

Clowes lost no time. He assigned George B. Walden, the supervisor of insulin production, and placed under him Harley W. Rhodehamel and Jasper P. Scott, thus forming a team of three to carry out the concurrent projects of experimental and factory-scale processing. (10) Based on protocols by Collip and Best— and some modifications of its own—Lilly began experimental runs almost daily during early June and on the nineteenth of that month sent Banting its first insulin, a shipment of 50 units, which he found satisfactory. (11) The first factory-scale lot was made on June 26 and the second on July 5—the latter amounting to a yield of 30 units from 75 pounds of fresh hog pancreas and a potency of one unit per cc.

By the end of July, production averaged 1,200 units a week as a result of various modifications of alcoholic concentrations, temperatures, extraction steps, and lot combinations, and potencies as high as two units per cc. were being achieved. By the first of September, the company had produced a cumulative total of 5,390 units, of which 2,985 had been shipped to Toronto, or a little more than twice the percentage specified in the indenture. (12)

Connaught production, on the other hand, was...
beset with difficulties and when Banting visited J.K. Lilly, Sr., president of the company, in Indianapolis in the latter part of July, he said there was not a drop of insulin in Toronto. Now that he had charge of a large clinic, wrote Mr. Lilly to his son, Eli, “He certainly was in trouble. We had 150 units ready for him and when I told him that he could take it back with him Monday night, he fell on my shoulder and wept, and when I told him that on Tuesday evening we would send him another 150 units, he was transported into the realm of bliss. Banting is really a fine chap and we must back him to the limit.”

The night and day work Walden and his team had given to the insulin program since the first of June brought highly encouraging results by September. The amount of active material being extracted reached new levels of 90 to 120 units per pound of gland and total output of September was as much as had been produced in July and August combined. In August, equipment for large-scale production had begun to arrive and Rhodehamel—who had been bending full-time effort toward layout of facilities in Building 20—was busy with installation that, hopefully, would be in regular operation by the first of October. It was expected that, based on the experience of previous increasing yields and potencies, the output from the shakedown phase of large-scale production would amply fill the needs of the 16 Canadian and American clinicians now supplied by Lilly and the commitment to Banting of 500 additional units per week. The exhausting, frantic effort on everyone’s part, however, was not rewarded. The final product from the new process deteriorated badly—50 percent and more—which meant that, in spite of greater yields, production would have to be doubled to make up the loss. In addition, clinicians began to report extremely variable patient response to different lots and incidence of abscesses, in duration and sensitivity at the injection site—all of which denoted a highly impure product.

In an effort to overcome production problems in general, Walden worked himself to the verge of collapse, and Clowes insisted he take two weeks off. Scott, who took over in Walden’s absence, did suffer a breakdown and remained off the job for three weeks. Because of all the setbacks, J.K. Lilly, Sr., instructed Clowes to release Walden from experimental work and assign him exclusively to pressing production needs. Clowes also decided to return to the initial extraction protocol since house samples from that process had retained full potency since June.

It was believed that the problem of deterioration in the large-scale method was the cumulative result of errors not unlikely to occur in
initial development attempts. In brief, Lilly was encountering the same difficulties that had harassed Collip and which were still frustrating production at Connaught. It was apparent to both parties that potency loss in the final product had to be surmounted before production and clinical work could be advanced.

Out of this necessity came a startling revelation. In noting that stability was dependent upon the hydrogen ion concentration of the solution from which the final product was obtained, Walden discovered that most of the deterioration did not result from destruction of the insulin hormone in processing but rather from the slow formation of the precipitate in the final product solution. These determinations were fundamental and, moreover, radical, for they revealed that insulin activity was not in the solution—the premise upon which both Connaught and Lilly extraction methods were based—but in the very precipitate heretofore considered a contaminant and discarded during the extraction process. Carrying this finding further, Walden found that the rate and extent of the formation of the hormone-bearing precipitate was governed by the hydrogen-ion concentration of the solution, and this suggested that, by pH adjustment of the solution, an optimum point could be established at which the insulin hormone would split off from the bearing precipitate. In other words, it was discovered that iso-electric precipitation could be employed for the purification of insulin. Its nitrogen content could be significantly reduced, and equally important, as high as a 90 percent recovery of insulin activity became possible. A way had been found to achieve high purity with large yield.\(^{15}\)

What Walden unearthed in the exasperating month of September 1922 was followed by many weeks of trial and error in application before the highly pure material could be produced in large volume. But in early 1923, production problems had been largely overcome. By April of that year, the weekly rate was running at a little more than 180,000 units—a sharp contrast to the 2,500 rate seven months earlier. Potency also had risen to 20 units or more per cc.

Such progress did not come without financial burdens. A large investment had been made without assurance of returns for some time or of protection against obsolescence. The matter of arranging for and maintaining proper icing of glands at a time when artificial refrigeration was still in its infancy imposed heavy costs in shipping and storage. To assay insulin required many hundred rabbits, and yet the few animal suppliers there were could not consistently provide animals of uniform size and weight or assure normal health—factors that vitally affected test data. And feeding and caring for the animals under proper conditions required special provisions on a scale the company had never faced before. During the latter half of 1922, more than 100,000 rabbit assays were conducted.

Determination of the value of the unit of insulin, highly complicated by wide variability of animal response, was a subject of great debate between Lilly and the Insulin Committee over a period of several months. While it was not technically possible at the time to derive precise value—
which was the crux of the debate—it, nevertheless, was a basic factor interlocking the economics of yields, capacity projections, and future facility demands. In the first six months of production at Lilly, unit standards were modified four times. Believing it had absorbed all the expense it could, the company requested and obtained Toronto’s approval to sell insulin to clinicians at cost, and distribution on this basis began in late January 1923.\(^{(16)}\) Shipment was direct to physicians, but billing was handled through the drug trade in keeping with the company’s established policy. At the time, Lilly was supplying sixty clinics in Canada and the United States.\(^{(17)}\)

The extension of the clinical program to this level within a year after the first administration of insulin by Banting seems remarkable considering the small output of insulin during the period. All clinical work had been dependent upon insulin from Lilly until the end of 1922, when Connaught Laboratories finally overcame equipment problems and swung into initial mass production. Considering, too, that unit potency was low, relatively large daily dosages were necessary to maintain a patient. Since the action of the hormone was not a precisely known entity, much precaution had to be taken in selecting physicians for clinical work. Assignment of specific investigators to hospital-affiliated laboratories in major urban areas had to be planned in order to gather data most efficiently from a limited supply of insulin. The value of the unit, based on the original rabbit assay unit, also had to be raised to better indicate clinical response. All of these considerations were worked out along deliberate lines.

At the behest of Clowes, the Insulin Committee agreed to the creation of a team of American investigators to put clinical work on a systematic basis in the United States according to committee requirements and over which it was to exercise authority. The desire of the committee to have this priority was fully appreciated by the Americans and carefully observed throughout the clinical program.

On November 22, 1922, a roundtable meeting was held at Toronto, attended by the Canadian clinicians, members of the Insulin Committee, representatives of Connaught and Lilly, and six American physicians—all noted authorities on diabetes management—to plan distribution control procedures, special studies, and unit standardization. The American doctors overseeing clinical work in the United States in liaison with the Insulin Committee were:

- Dr. Elliott P. Joslin, Boston
- Dr. Frederick M. Allen, Morristown, New Jersey (after whom the Allen Era of dietary management, 1914-1921, was named)
- Dr. H. Rawle Geyelin, New York (an authority on juvenile diabetes)
- Dr. John R. Williams, Rochester, New York (the first American physician to use Banting’s extract)
- Dr. Rollin T. Woodyatt (a brilliant clinician from Chicago)
- Dr. Russell M. Wilder, of the Mayo Clinic, Rochester, Minnesota.

It was at this meeting that clinical trial development was set up to provide the greatest number of cases for test information within the limits of available supply. The plan of individual patient therapy followed Joslin’s philosophy. “It has been our policy to treat many rather than few diabetics. We have felt it more...
humanitarian to prolong the lives of many old and faithful patients rather than attempt to secure marvelous results with a few."

Drs. Banting, Campbell, and Fletcher published in the January 6, 1923, issue of The British Medical Journal their findings on insulin therapy with 50 cases, a paper that was the first comprehensive report of the Canadian trials, and by agreement with the Insulin Committee, the American investigators subsequently published their findings. These appeared in late May in a series of papers in The Journal of Metabolic Research, which, including the above Canadian report, discussed experiences with approximately 600 cases since the inception of clinical work in January 1922.¹⁸

Brought to light by scientific data was reliable evidence that insulin did have widespread value therapeutically when the specific requirements of the individual patient were recognized in the administration of the agent. Though the number of reported cases was small in relation to the estimated million people with diabetes in the United States at the time, this collective experience was an enormous advance. By virtue of the stringent controls exercised in treating variable manifestations of the disease, the basis was laid upon which the practicing physician could hope to bring patients with diabetes under control, and through carefully calculated diet, regulated insulin dosage, and proper exercise, guide them toward a normal way of life. For the first time, there was extensive practical knowledge available for attacking the disease.

As one of Joslin’s early insulin patients wrote, a professor of Greek at the University of Vermont, “If the true Christian be the close imitator of Christ, then the discoverer, and the one who applies the discovery, should feel that they are literally following the one who said: ‘I am come that they might have life, and that they might have it more abundantly.’”²⁹ Also among Joslin’s cases was an indefatigable researcher at Boston who was within a few years to discover treatment for pernicious anemia, George Richards Minot.

By the time the findings of the American investigators had been published, the company had distributed more than seven million units of insulin and, in conjunction with Connaught, was supporting about 10,000 patients with diabetes. The Insulin Committee in early spring of 1923 arranged that Lilly ship quantities of insulin to the British Isles to support the program there under patents granted to the public domain by the University of Toronto, and the Committee also permitted broadened clinical work in the United States.

Lilly was allowed to submit names of physicians who had interest in insulin and were qualified to use it, so that the Committee could rule on additional eligibilities. Such, in brief, were the events behind the official June announcement by the Insulin Committee that a safe and standardized product was available in large volume and that firms could be licensed for the manu-
facture of insulin. Thus, in a 12-month period, a clinical entity of wholly new origin and value had been developed into a useful and, for many, a lifesaving product. Of the role of Eli Lilly and Company in this achievement, the Committee announcement said, “Without this collaboration, it is unlikely that a non-irritating product of such satisfactory potency and durability could have been produced in adequate amounts to meet the demand of the medical profession in this comparatively short time.”

On the last day of June, the University of Toronto prepared a license contract for Lilly for the manufacture and sale of insulin in the countries specified in the original indenture agreement, and the license was approved and accepted by the company’s board of directors on July 11. However, approval for the company to begin commercial distribution did not come until the following October, after the unit value disagreement had been resolved (the Committee insisted that its standards had to prevail); additional clinical evidence had been gathered; and approval had been given of the company’s literature and label copy, an approval based on rigorous control.

On October 15, Iletin®, the company’s brand name for its insulin, was released for distribution through regular drug trade channels available on physician prescription. Simultaneously, a price reduction was made—the third since it was first sold on a cost basis ten months earlier—and it amounted to a 66 percent decrease. It was estimated that 7,500 physicians were treating 25,000 diabetes patients with Iletin. At the close of 1923, Lilly had sold almost 60 million units during the year.

With the introduction of Iletin, the company prepared an extensive literature program to provide the practicing physician useful guidelines on dosage determination, suitable potencies, dietary measures, and urine and blood analyses and also developed a variety of accessories for the patients with diabetes self-care needs. It also introduced, within the following year, new potencies of the amorphous material so that it had on the market in 5- and 10-cc vials strengths of U-10, U-20, U-40, and U-80. Part of the motive behind this attempt at wide market development was, to be sure, the likelihood of competition, which began to materialize in 1925. But more pressing was the critical matter of overproduction. Diabetic treatment was still largely confined to hospital or clinical supervision by the very nature of the disease and so consumption did not rise commensurately with the estimated incidence of diabetes. As experience with diabetes management extended through the medical profession, however, and the company was allowed to sell insulin in certain other foreign countries, demand for it rose. By 1925, units distributed amounted to 217,681,150, thirteen million of which went into export.
1926 considerably reduced the return on the line but a profit continued to be made as unit sales increased. The eighth reduction was made in 1932, when unit sales reached 792,451,300, and resulted in a cumulative decrease of 90 percent from the original price in January 1923.

With the collaborative development of insulin, the battle against diabetic coma ended and there began the long campaign against the complications of the disease arising with the prolonged life span of diabetic victims. The role of Eli Lilly and Company and others in this campaign—which has been waged in ever-widening circles to this day—remains to be accounted for in later chapters; only the beginning has been given in these few pages. Writing to J.K. Lilly, Sr., in December 1930, Joslin spoke of the many happy homes there were at Christmastime because of the contribution of Eli Lilly and Company, and to this, Mr. Lilly replied:

The great and refreshing discovery through this experience was that the really great men in any line of endeavor are the most approachable, simple, and direct in their reasoning and contacts. Both in letter and in spirit, we have endeavored to indicate to you how precious our relations have been with you and your associates, and sometimes we are haunted with a fear that probably we have not been able to do our part in as full measure as it was humanly possible to do so. Yet your generous words have tended to make us more satisfied with that phase. (26)
Dr. Frederick Grant Banting and Charles Herbert Best first reported their findings to the Physiological Journal Club of the medical faculty at the University of Toronto, November 14, 1921, and the paper was first published in The Journal of Laboratory and Clinical Medicine, Vol. 111, No. 5, February 1922. The paper delivered at New Haven was considered a summary by Banting and Best and, consequently, its publication in the American Journal of Physiology, Vol. 59, No. 1, February 1922, was not regarded by them as their first report. Nonetheless, the Nobel Prize for the discovery was based on this article, and since Professor James J.R. Macleod was listed as co-author (because he was the head of the department of physiology at the university under whom Banting had carried out his work), he was recognized as the co-discoverer and not Best. Banting was much distressed by this and said so many times.

A Canadian farm boy in origin and a graduate of the University of Toronto, Banting was an orthopedic surgeon and part-time instructor in physiology at Western Ontario University, London, where he was in the practice of medicine. It was in preparation of a lecture that he had read the now famous article on pancreatic lithiasis by the obstetrician, Moses Barron, that prompted his search for insulin. This was in the fall of 1920, and by May of the following year he had convinced Macleod to provide him with laboratory facilities. Within a few years after his discovery of insulin, Banting forsook studies of diabetes and concentrated on other fields, such as the adrenal cortex, cancer, and silicosis. He also did important work on the Franks antigravity suit for the Canadian Air Force at the outbreak of World War II. On February 21, 1941, Banting was killed in an airplane crash in Newfoundland while in the service of his country. He had recently turned 49.

Born in West Pembroke, Maine, in 1899, Best was working on his master's degree in physiology at the University of Toronto at the time he and another student were assigned by Macleod to assist Banting. By a toss of a coin, Best won the chance to first work with him. In 1925, he obtained his medical degree from the university, and, two years later, his doctor of science degree from the University of London. Upon his return to Toronto in 1927, he was appointed professor of physiology at the medical school (later to head the department) and became director of Connaught Laboratories, director of the Banting and Best Department of Medical Research, and head of the Banting and Best Institute. He retired from those duties in 1967. In addition to devoting his career to diabetes, he made significant contributions to studies of choline and liver damage, heparin, and thrombosis. He also was the discoverer of the enzyme histaminase. Best died in 1978.

As a part of their studies on fat digestion with depancreatized dogs, these German investigators discovered that the urine of the animals possessed an excessively high sugar content. Thus, they had demonstrated the relation of pancreatic function to diabetes, and Oskar Minkowski went so far as to conduct preliminary experiments as further confirmation, but, for reasons unknown, he abandoned these very promising leads. The history of diabetes is replete with such ironies.

Professor J.J.R. Macleod to Dr. G.H.A. Clowes, May 15, 1922. Copy in the files of the Insulin Committee, University of Toronto.


“Today’s Problems in Light of Nine Hundred and Thirty Fatal Cases,” The Journal of the American
Medical Association, Vol. 78, No. 20, May 20, 1922. In another article of the time, Dr. Elliott P. Joslin referred to the co-discoverers as “the young Lochinvars of Toronto.”

(7) Dr. Charles H. Best, interview with author, September 24, 1968.

(8) J.J.R. Macleod, “Insulin and the Steps Taken to Secure an Effective Preparation,” The Canadian Medical Association Journal, Vol. 12, No. 12, December 1922. Years later, Best recalled, “It was his (Clowes) scientific training, his great interest, and his ability which were in part responsible for the selection of Eli Lilly and Company as the first company in the United States to collaborate with the University of Toronto in the production of Iletin. . . . Of course, he was interested in large-scale production, it was so much easier for the Lilly company than for us here because we'd had no experience in the use of large stills or other apparatus for concentrating large volumes of material.” Transcript of interview with author, September 24, 1968. Copy in the Lilly Archives.

(9) The agreement, dated May 30, 1922, was signed June 28 by representatives of the Board of Governors of the university and on July 7 by J.K. Lilly, Sr., and General Manager and Secretary Charles J. Lynn on behalf of the company. Copy in the Lilly Archives.

(10) Jasper P. Scott, a graduate of Franklin College, Franklin, Indiana, joined the company in 1920 as a research chemist upon the recommendation of George B. Walden. He held various positions in research until 1946, when he was appointed a director in Industrial Engineering and Facilities Planning. Scott died in 1953.

(11) Information about early insulin production at Lilly was obtained from a six-volume series of laboratory data entitled “Insulin Research” for the years 1922 to 1925. The entries, mostly recorded by Mrs. George B. Walden, who was an employee at the time, noted the date of each lot, the number assigned it, the extraction procedure, and assay results. The volumes are in the Lilly Archives.

(12) Clowes, undated reports on distribution of R-4320-D to clinical investigators for the periods June 19 to September 1 and July to September 25, 1922. The first report states that 3,085 units had been sent to Banting by September 1, but the second report gives the amount as 2,985. Reports in the files of the Insulin Committee. R-4320-D was the first successful lot of insulin Lilly made, and four house samples of this lot have been preserved in the Lilly Archives.

(13) July 26, 1922. Letter in the Lilly Archives.

(14) Clowes to Macleod, October 20, 1922. Letter in the files of the Insulin Committee. This seven-page summary of events was written to explain the reasons for production setbacks and product deterioration.


(17) General Letter No. 13, February 20, 1923. Copy in the Lilly Archives. The company had established a clinic to carry out its own investigation of insulin. The unit was organized in July 1922 at Methodist Hospital, Indianapolis, and headed by Dr. John A. MacDonald, professor of medicine at Indiana University and personal physician to the Lilly family. His staff consisted of Dr. Cecil L. Rudesill; Dr. John H. Warvel, head of the hospital’s pathology laboratory; and Miss Ruth Michaels, a nurse whom Warvel later married. Michaels received training under Dr. Rollin T. Woodyatt for the care and training of the clinic’s patients. The first therapeutic dose given at the clinic was on August 12 to Mrs. Nellie Underwood, the hospital's
housekeeper. Joslin was the first American physician to use Lilly’s insulin when, on August 7, it was administered to one of his regular, long-time patients, Miss Elizabeth Mudge. Mudge and J.K. Lilly, Sr., struck up a friendship and corresponded many years until her death in 1947.

(18) Vol. 2, Nos. 5 and 6, November-December 1922.

(19) Samuel E. Bassett to Joslin, November 30, 1922. Letter in the Lilly Archives. Joslin sent the letter to J.K. Lilly, Sr., with the notation that it was a nice Christmas present for the company and Banting.


(21) In the summer of 1923, F. Lorne Hutchison was appointed Executive Secretary of the Insulin Committee, a position that was created when Macleod asked to be relieved of his Insulin Committee duties in order to give full attention to his responsibilities as head of the department of physiology. Some years later, he was appointed Regius Professor of Physiology at his alma mater, the University of Aberdeen, a post he held until his death in 1935. Hutchison served as Executive Secretary until his death in 1952.

(22) General Letter No. 88, October 9, 1923. Copy in the Lilly Archives. With the adoption of unit potency specified by Toronto, unit designation was changed from “H” used in the clinical trials (presumably standing for human) to that of “U”, which began with commercial introduction. The “U” was 40 percent greater in potency than the “H” and thus resulted in fractional calculation in converting dosage from the latter to the former. For example, one unit of “H” = 0.7 of “U,” 10 = 7, 20 = 14.5, 30 = 21.5. For derivation of unitage and establishment of an international standard, see Albert H. Lacey, “The Unit of Insulin,” Diabetes, Vol. 16, No. 3, March 1967, and “International Insulin Standards,” Diabetes, Vol. 17, No. 11, November 1968. Lacey was Chief Chemist of the Insulin Committee from 1931 until his retirement in 1969.

(23) Records of the Insulin Committee.

(24) From the outset of commercial distribution, Lilly offered specifically calibrated syringes, a urinary test kit, plain agar, saccharin tablets and the “Ever Aseptic Iletin Syringe Outfit,” designed and patented by Mr. Eli Lilly. In time, supply houses began to carry diabetic accessories and the company eventually discontinued them.


(26) J.K. Lilly, Sr., to Joslin, February 6, 1931. Copy in the Lilly Archives. The company anonymously contributed $50,000 to the Banting Research Foundation in 1925, which was created to advance further work by private means. Lilly also provided unrestricted grants to Best, which were paid periodically for several years. After the expiration of the patent on amorphous insulin and royalty payments in 1941, it made annual grants to the Banting and Best Department of Medical Research. All royalty payments on sales of later insulin preparations ended in 1969, when the Food and Drug Administration assumed full authority for safety and potency determination.