

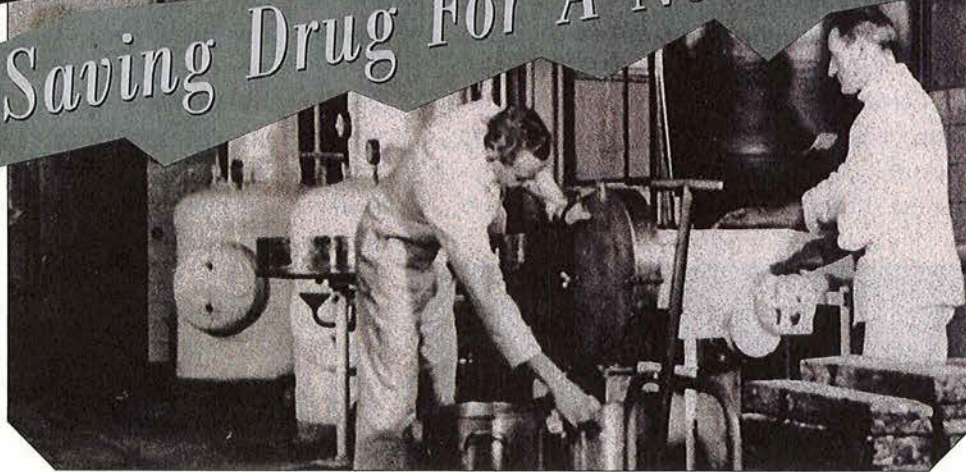
# The History of Insulin



Life Saving Drug For A New Century

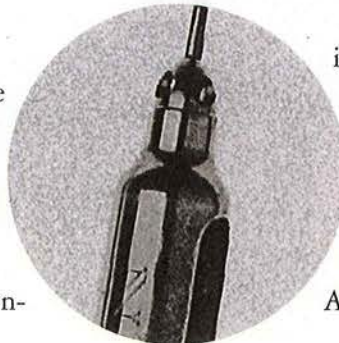
Part 1

By Lisa Kingsley



Jim Park uses a 21st century insulin pump to control his type 1 diabetes. It's simple and painless—and a lifetime removed from his first contact with managing his diabetes. Back in the 1940's the cutting edge technology of the day led five-year-old Park on a frantic race around the dining room table to avoid, “a needle that looked a foot long,” he recalled.

Such needles were then the only method of delivery available for insulin. Test strips, insulin pumps, portable pens, disposable syringes, and digital testing were the stuff of fiction, if imagined at all. Needles were large and needed frequent sharpen-



ing. Park recalls his father using an old-fashioned whetstone to sharpen their supply. Sterilization was effective, but basic. Needles were kept in glass vials, filled with alcohol, and stuck into a cotton swab. And, as large and ungainly as the

Photos Courtesy of Eli Lilly Corporation

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needles were, puncture sites were painful and often became infected.

Nevertheless, for insulin-dependent diabetics of the time, the time-consuming and painful delivery of the drug was literally worth their life. "Modern" medical treatment for diabetes at the beginning of the 20th century was almost non-existent. Other than its nearly-always fatal diagnosis, little was known about the disease or its treatment.

What treatment there was consisted almost wholly of a strict diet of almost starvation-level intake meant to control carbohydrates. This method, crude as it was, temporarily succeeded in controlling the amount of sugar in the blood. However, the patients, especially children (who comprised the majority of the disease's victims) all too often simply wasted away from lack of nourishment.

In less than 100 years, diabetes mellitus has become no longer a death sentence but a manageable condition. The reason, of course, is insulin. This single drug is one of the great success stories of modern medicine.

## Insulin Proves an Expensive Success

**A**lthough the presence of an internal pancreatic secretion (first termed "isletin") had been suspected since the turn of the century, it was not until 1921 that it was successfully extracted and proved to be a workable solution for diabetes.

A four-man team headed by the University of Toronto's Dr. Edward Banting was the first to publish news of the discov-

ery. By 1922, Banting and his partners Charles Best, J.B. Collip, and J.J.R. Macleod had successfully treated several patients. However, Banting's formula, while successful, was far from efficient as a long-term model for treating a great number of patients.

## How Much is Enough?

**E**li Lilly Corporation researcher Dr. John Holcombe explained that there were a number of issues that stood in the way of large-scale production. For one, the principals didn't always agree among themselves. For example, "Collip gave Banting his research, but wouldn't reveal his methods," he said. Such internal squabbling soon gave way to more pressing problems.

Purifying a drug derived from the pancreas of cows and pigs was proving difficult. Scientists also had a hard time extracting enough of the drug to provide a steady form of treatment, since diabetics seemed to need injections anywhere from 4-6 times per day.

Holcombe noted that in today's modern era of pure and precise dosages, one unit of insulin easily reaches an activity level of 100 units. However, in those early days each single unit of insulin yielded

only about 5 units of activity, so patients required injections of up to 20 cc's to achieve that same 100-unit activity level. Banting and his partners were constantly working to stockpile workable quantities. Help came in the form of an American company eager to spear-



Insulin developer F. G. Banting and student assistant C. H. Best shown with a canine subject on the roof of the Toronto University Medical Building

Photo Courtesy of Eli Lilly Corporation

head the development of a new product.

By the early 1920's Eli Lilly & Company was a well-respected Indianapolis establishment. Lilly's chief scientist, Dr. G.H.A. Clowes had heard intriguing information about the new drug a Canadian scientist had been developing to treat diabetes. After attending Banting's first lecture regarding his discovery, he was convinced of insulin's potential. Clowes immediately offered Lilly's services to market and mass-produce the drug.

Although initially rebuffed, he persisted, and the University of Toronto, Banting and the Lilly Corporation reached an agreement in 1923 to begin the first large-scale production of insulin.

According to Lilly historian Gene E. McCormick, it was none too soon. By that time Banting and others had opened private clinics, in an attempt to treat as many patients as possible. Once the public learned of insulin's possibilities, requests for treatment poured in to the University and the medical community. It was Banting's sad responsibility to determine who among them had the best chance of responding to the drug, as there was such a limited supply available.

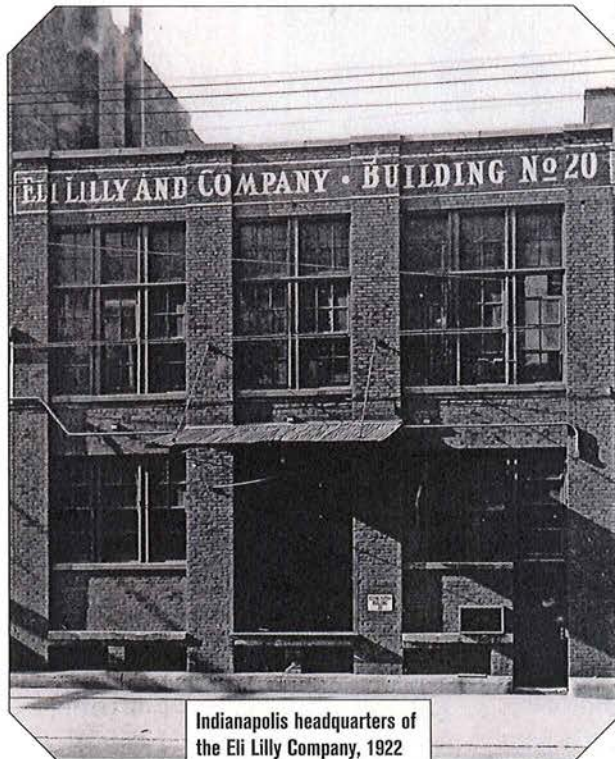
## Lack of Supplies— a New Threat

Undoubtedly, hundreds of diabetics had to be denied treatment, ironically just as production neared a breakthrough. Diabetic clinics were operating in the U.S. and Canada, but could address only a fraction of the patients seeking treatment. Banting himself was treating over 150 patients in the immediate vicinity.

Unfortunately, he was quickly overwhelmed. Patients were using up his supplies far faster than he could replenish them. He set out for Indianapolis hoping that Eli Lilly scientists had found some way to boost production.

"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," wrote Eli Lilly in 1922.

In addition to the question of supply, purity of the insulin was still an issue. "Some batches would work and some wouldn't," said Holcombe. By the beginning of 1923



Indianapolis headquarters of the Eli Lilly Company, 1922



Early Eli Lilly Company insulin production line, circa 1925

Photos Courtesy of Eli Lilly Corporation

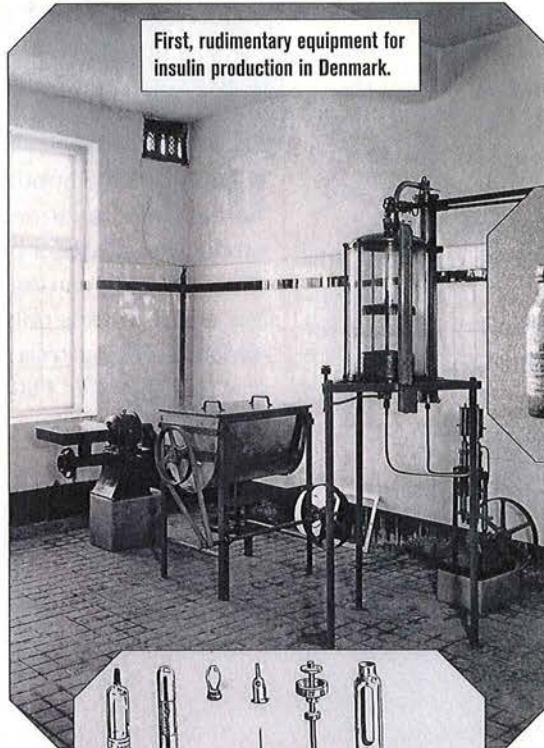
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though, the Lilly Corporation had solved most of the problems with purity and manufacturing, and was able to begin supplying clinics with the valuable drug. Although formal clinical trials had yet to be completed, says Holcombe, "in that first year, over 10,000 diabetic patients were treated with insulin." By year's end, over seven million units of insulin had been produced.

Production was far enough along by 1923 that the company could start distributing insulin overseas, with the first batch sent to the British Isles.

By the late 1930's the state of diabetes had stabilized. Banting had been awarded the Nobel Prize for his research, diabetics worldwide had some hope for the future, and the manufacture of insulin was so well established that doctors and researchers were able to begin refining the drug to allow for a more potent and longer lasting dose. Given the assuredly deadly future predicted for diabetic patients even 10 year earlier, it is astonishing that the drug could be mass-produced quickly and safely for so many patients.

Photos Courtesy of Novo Nordisk Corporation

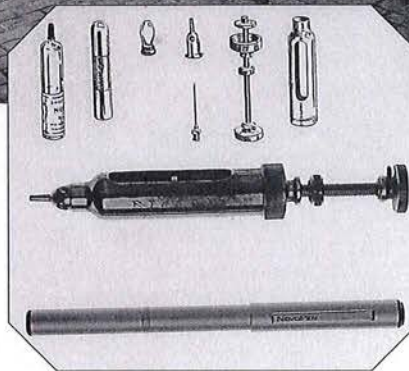


First, rudimentary equipment for insulin production in Denmark.

"My control got much better with this type," declared Park. For the first time he was able to check his



Vial of Iletin insulin. Commercial production of this animal-based synthetic insulin allowed patients around the world their first chance at a normal life-span



1925 syringe used for insulin injection, 1985 NovoPen®. As production techniques grew more sophisticated needles and syringes became progressively thinner and less painful

glucose readings several times each day, giving him a much better idea of his sugar levels. Park recalls that the later addition of zinc added to his protamine insulin then allowed him to skip a noon injection.

By this time insulin quality and production was assured. Now that diabetic patients had a far better chance at living a normal life,

attention could be paid to the numerous complications still inherent in living with diabetes. **DE**



Eli Lilly and Company's Humulin Regular Insulin

## NPH—The Next Step

The next breakthrough insulin advancement of the era occurred in 1946, with Danish corporation Nordisk's NPH, the first modified insulin. With the addition of protamine, this split-function insulin allowed for true 24-hour coverage.

**Next issue:** Insulin part 2—Complications, therapy and delivery systems.

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