



ADVANCES IN INSULIN TREATMENT OVER THE PAST CENTURY

Although insulin carries the same name it did 100 years ago, it is far from the same treatment. Three distinct eras— **animal insulins, synthetic human insulins and insulin analogs**—make up the rich history of insulin treatments.

Diabetes Treatment Approaches

Insulin is a naturally occurring hormone secreted by the pancreas that helps people properly absorb sugar. Patients with diabetes cannot make insulin (Type 1) or do not produce enough insulin and/or do not respond properly to insulin (Type 2).

In 1922, researchers discovered how to extract insulin from animal pancreases for safe use in humans. It took another 80 years for researchers to discover how to synthesize human insulins and alter them at the molecular level to resemble natural insulin release.

Insulin treatments generally fall into two categories:

- **Basal insulins** provide a long-acting background level of insulin in the body throughout the day and are often administered once a day.
- **Bolus insulins** are more rapid acting and are administered at meals or other instances where blood glucose may be high.

Insulin dependence varies widely, but patients requiring daily insulin injections often administer long-acting basal insulin for coverage throughout the day and supplement that with bolus insulins to regulate spikes.

THE RICH HISTORY OF **INSULIN ADVANCEMENTS**

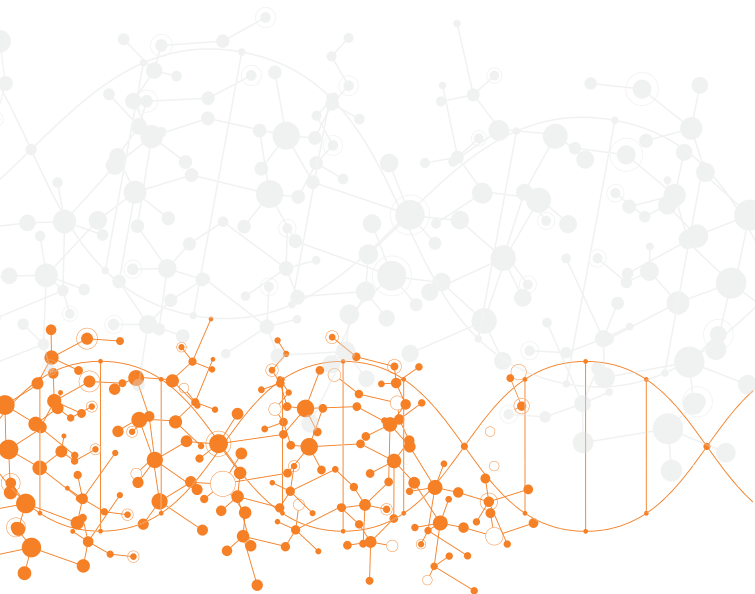
The Animal Insulin Era: 1922 to 1970s

With the discovery of a viable method of using animal insulin in humans in 1922, life expectancy for diabetes patients dramatically improved. But treatment was burdensome to administer and had to be injected every six hours—including at night.

BEFORE 1922: The only available treatment is a “starvation diet” and patients with diabetes usually die within two years.

1922: Banting and colleagues discover a viable method of extracting insulin from animal pancreases for use in humans.

In the 1930s through the 1950s, researchers discovered versions of insulin that lasted longer in the body. The range of insulin formulations with varying durations of action laid the foundation for treatment protocols commonly used by patients today.



1923: Insulins derived from pigs and cows become commercially available. Life expectancy dramatically improves, but is still 25 years shorter than those without diabetes.

1946: The long-acting neutral protamine Hagedorn (NPH) animal insulin is introduced and can be combined with short-acting insulins to allow for more flexible disease management.

1960s: The first disposable syringes are introduced, greatly improving the convenience of delivery.

1936: The first long-acting animal insulin, protamine zinc insulin (PZI) is introduced. PZI allows for less frequent injections and enables patients to sleep through the night.

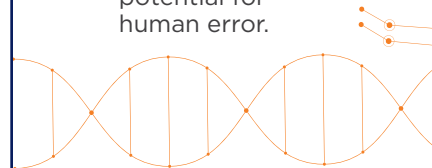
1956: The lente series of insulins are introduced, offering patients long-acting, rapid-acting and intermediate-acting forms of insulin.

The Synthetic Human Insulins Era: 1980s to Mid-1990s

With the development of synthetic human insulins in 1983, new basal insulin formulations provided more consistent and stable levels of insulin delivery throughout the day and new bolus insulins more closely resembled natural insulin secretion from the human pancreas at meal times. Because these insulins were created by genetically modifying bacteria to construct DNA sequences of human insulin, they reduced injection site and allergic reactions that were characteristic of animal insulins. This time period also saw advances in treatment convenience, portability and flexibility with the introduction of insulin pens. These pens reduced human error by simplifying administration through dials, or clicks, and allowed patients to set more accurate dosing.

1983: The first synthetic human insulins are produced with recombinant DNA technology, reducing the frequency of injection site and allergic reactions.

1985-1989: The first insulin pens are introduced, making every day diabetes management more portable, convenient, simpler and less painful, and reducing the potential for human error.



The Insulin Analog Era: Mid-1990s to Today

As diabetes patients began to live longer, complications such as heart disease, blindness, kidney disease and lower-extremity amputations became more common. By 1993, research emerged documenting the clear association between the degree of glycemic control and the development of disease complications. As a result, researchers developed insulins that more closely mimicked insulin release naturally occurring in the body and improved management of blood glucose levels. The ability to synthesize human insulin and advances in molecular biology enabled researchers to alter the human insulin molecule at the amino acid level, resulting in the first insulin analog in 1996.

The number of rapid- and long-acting insulin analogs continued to grow in the decade that followed, offering patients better control over the management of their disease, including greater flexibility of dosing, decreased weight gain and reduced incidence of dangerous blood sugar drops (hypoglycemia) and associated inpatient hospitalization visits. Important delivery advancements also occurred during this period, including the first-ever injection-free, inhaled form of insulin and a “junior” pen for use in pediatric populations that require more precise dosing adjustments. The recent development of “ultra-long-acting insulins” also represents a critical advance for patients by providing a more stable and consistent level of insulin delivery for 24 hours or longer.

Advances over the last two decades allow for better disease management more closely aligned to natural insulin release in the body. And the variety of insulin choices and convenient delivery options help patients better manage their condition, enabling them to live long, healthy and productive lives.

1996: The first rapid-acting insulin analog, insulin lispro, more closely resembles the natural physiological release of insulin and provides greater flexibility by allowing for closer administration to meals.

2000-2005: Rapid-acting insulin aspart and insulin glisine and long-acting insulin levemir expand the insulin analog choices available to patients.

2014: A more portable inhaled rapid-acting insulin allows for greater flexibility of mealtime administration.

2015-2018: More concentrated high dose options of various insulin analogs enable fewer injections for some patients.

2018: An improved formulation of insulin aspart provides quicker onset, allowing for greater patient flexibility to administer insulin before, during, or even after meals.

2000: The first long-acting insulin analog, insulin glargine, mimics the characteristics of healthy pancreas release, allowing for a more stable effect and less frequent, once-a-day dosing.

2015: Two ultra-long-acting insulin analogs offer patients 24-hour (or sometimes even longer) coverage and greater flexibility in dosing for patients with shifting schedules.

2017: A pre-filled “junior” pen for children offers more precise dosing adjustments due to low-insulin requirements, greater accuracy, reduced injection force and torque and a memory function for prior dosing.