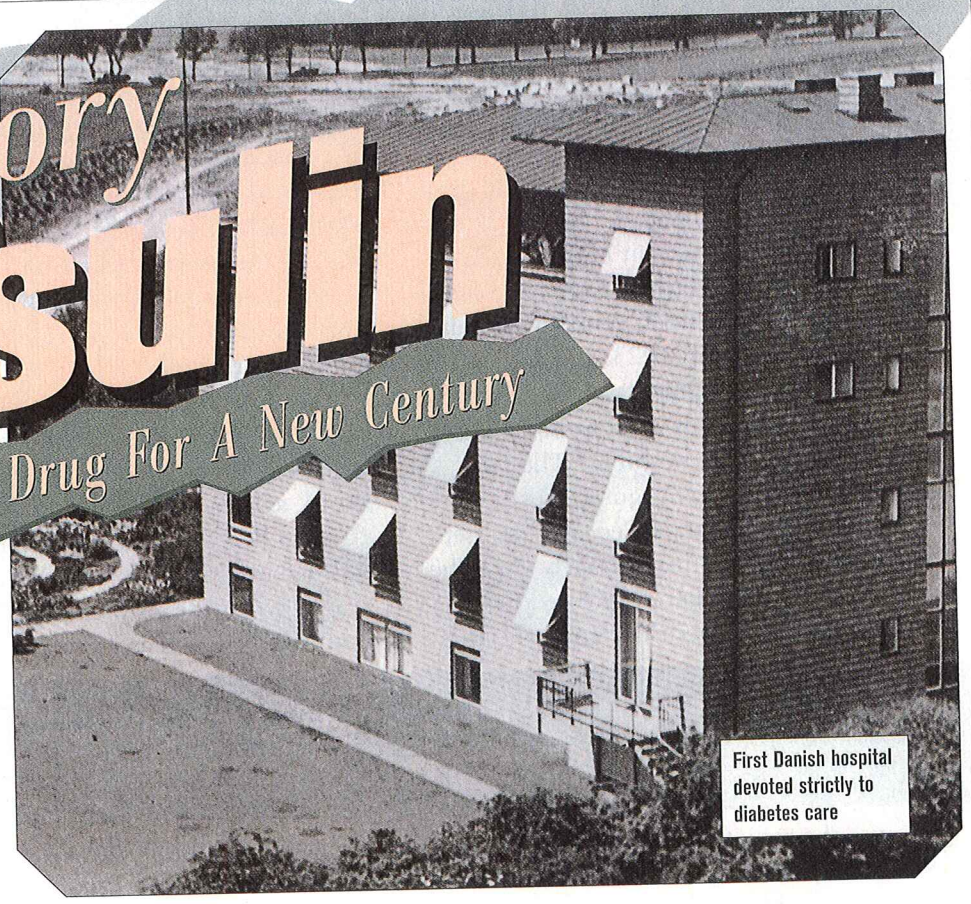
The History of Insulin

Life Saving Drug For A New Century

Part 2

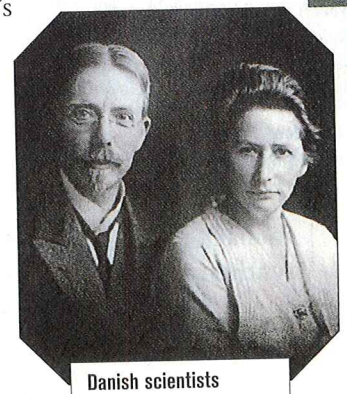
By Lisa Kingsley



First Danish hospital devoted strictly to diabetes care

The discovery of insulin, chronicled in the first part of this series, (DIABETES EXPLORER November/December 2006) was a drama composed of large successes in biomedicine and equally impressive advances in production. By 1925 diabetes had become, although still chronic, a manageable illness.

Development of insulin in the United States continued, primarily through research conducted by the Eli Lilly Corporation in Indianapolis. By this time, they had acquired the production rights to insulin from University of Toronto's Dr. Charles Banting. Another group, outside the U.S., was also gearing up for what would prove to be the next great advancement in insulin development, the introduction of NPH insulin.



Danish scientists August and Marie Krogh

European Development of The Lifesaving Drug

Nobel Prize winner August Krogh conceived Nordisk Insulinlaboratorium in Denmark after a visit to the U.S. Krogh had been invited to Yale to lecture on scientific discoveries in physiology with his wife Marie, also a physician, and a type 1 diabetic. After hearing of the extent of the insulin research in Toronto, he arranged to meet with Dr. John McCleod, chairman of the Physiology Department at the University of Toronto.

He was granted the opportunity to produce insulin, along with a license to use the methods the Toronto scientists had perfected. He returned to Denmark, determined to produce a commercially viable form of the drug for European distribution.

He contacted physician H.C. Hagedorn, who had previously treated his wife's diabetes, and the two set up a small company to purify and produce insulin in 1923.

"It was a real family affair," said Novo Nordisk Vice-President Alan Moses. "They basically started from nothing." The two brought in pharmacist August Kunstead and brothers Thor and Harald Pederson and set about producing insulin, primarily from the pancreas of the pigs that dominated the Danish economy, rather than from the cows that were the predominate pancreatic source in the U.S.

"In the beginning, they literally ground the pancreases using a meat grinder," explained Moses. Crude though they were, those early efforts were hardly being scrutinized for elegant preparation. "This was a lethal disease and it was really a matter of getting the stuff out," insisted Moses. "This was lifesaving therapy."

By 1925 the Pedersen Brothers, in a dispute with Hagedorn, broke away to start their own lab, Novo Terapeutisk Laboratorium. Novo, as it is now known, quickly showed itself to be a serious competitor to the Nordisk operation. It was this competitive spirit, says Moses, which propelled the development of insulin as a therapeutic agent.

Insulin Production Responds to Scientific Advances

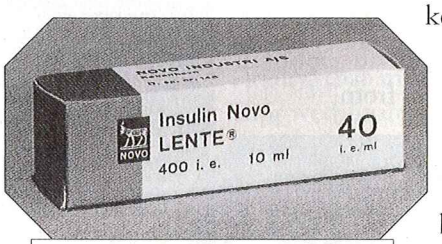
Because the early form of insulin was extremely acidic (the low ph factor was necessary to keep the pancreatic enzymes from destroying the insulin), injections were often painful, with a burning sensation. As scientists learned how to purify insulin, they began to get rid of the contaminants and reduce the painful, often allergic reactions to the drug.

Purity aside, the other significant problem with insulin was regulating the dosage. By 1925, most patients were injecting themselves anywhere from 4-6 times per day. Hagendorn theorized that, if he could make the insulin less soluble it would break down more slowly, meaning patients could cut down the frequency of injections.

In 1936 Hagedorn and Nordisk introduced protamine zinc insulin; adding zinc changed the structure of the insulin and acted as a neutralizing agent. This new form, NPH, lasted for up to 72 hours and was the first stable solution of insulin available. It was extremely convenient because it did not have to be mixed before being injected. Patients simply shook the vial of insulin before injecting it. Moses explained, "It was far from perfect, but a major advance from what they had before."

By the early 1950's Novo had countered this advance with the Lente family of insulins, which offered patients a wider choice to counter possible allergic reactions and also allowed more flexibility to their injection schedules.

By 1973, the mono component insulin technology offered the most pure concentration yet, and by 1982, Novo had introduced Human Monocomponent Insulin to the marketplace. This was pig insulin modified by enzymes to make it identical to human insulin.



Novo's Lente® insulin allowed patients greater flexibility of their insulin schedules

Photo Courtesy of Novo Nordisk Corporation

In 1989, in an effort to move away from animal-based insulins, Lilly countered by developing the first "human" insulin. Humulin® was the first diabetes therapy to make use of recombinant DNA technology, synthesized from a harmless strain of e-coli and inserted into a human gene. Also in 1989, after 74 years, Novo and Nordisk reunited to form Novo Nordisk.