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# The History of Insulin

## Discovery of Insulin

In 1921 the Canadian scientists Fredrick G. Banting, Charles H. Best, J.J.R. Macleod and James B. Collip discovered insulin, a peptide (small protein hormone) which lowers blood sugar. They extracted insulin from the islets of animal pancreases. Up to that time type 1 diabetes was a virtual death sentence for patients suffering from it. Now, it could for the first time be treated successfully. The researchers gave the patent rights to the University of Toronto so that diabetics worldwide could, through insulin, survive. The scientists refused financial gain in order to serve science, research and humankind – and to conquer diabetes.

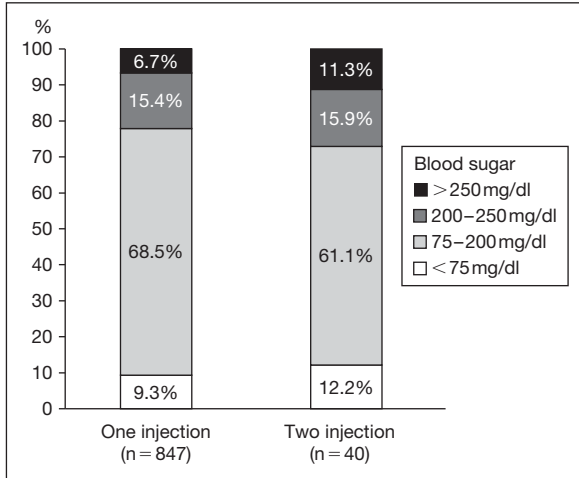
## First Diabetics on Insulin

A year later, in January 1922, bovine insulin was first given to humans by injection. It was still so impure that as a result of the first insulin injection Leonard Thompson had a 7.5 cm callus at the injection site on his left buttock. The co-discoverers, in particular James Collip, continued their work to purify the insulin extract to make it safer and more effective. Nevertheless, the quality of the insulin administered at that time was far from the quality of today's products. Each vial of insulin had a different effect because of differing purity. That is why Elizabeth Hughes, one of the first diabetics to be treated with insulin, often had hypoglycemic reactions. She also suffered pain and swelling at the injection site, especially when large quantities of insulin were injected [1].

## Evolution of Insulins

### *Animal Insulin*

Beginning in 1922, and in the face of great demand for the new medicine, several companies were granted licenses by the University of Toronto to manufacture insulin. In 1936, protamine, a low-weight protein, was used to develop a



**Fig. 1.** Percentage distribution of blood sugar levels in 887 cases with insulin zinc suspension (IZS) that were controlled during 1 week of hospitalization [2]. Reprinted with permission from Elsevier.

slow-release insulin. With the availability of protamine, as well as zinc, the first slow-acting insulin was produced. Protamine zinc insulin (PZI) was an insulin whose effect lasted for 24–36 h.

In 1950 yet another approach led to the presently available isophane NPH (neutral protamine Hagedorn) insulin, which is also bound to protamine. It has a maximal effect of 24 h and can be mixed with any proportion of fast-acting regular insulin.

In 1951 the amorphous ‘lente’ insulins (IZS) – semilente, lente and ultra-lente – were developed. Depending on the proportion of zinc – a natural component of the body’s insulin – used, variable kinetic and dynamic effects were obtained without the use of protamine. In a study conducted by Jersild [2], 1,000 patients with type 1 diabetes were switched from NPH isophane to lente and semilente, and of these, 936 patients were controlled satisfactorily with a single morning dose. The other patients needed an additional split dose with a second injection in the evening. Figure 1 shows the patients that were controlled in hospital, where blood glucose monitoring was available: 847 needed 1 injection and 40 needed 2 injections.

Using the same products, Spencer and Morgans [3] got similarly satisfactory results in 83% of 200 patients. Severe hypoglycemia in both studies was rare.

In 1956, the first antidiabetic oral drugs – sulfonamide (tolbutamide, carbutamide) and biguanide derivatives (metformin, phenformin) – came on the

market. Before the development of these new drugs, the only drug available for type 2 diabetics was insulin.

In 1974, chromatographic purification techniques allowed the production of highly purified animal insulin (less than 1 pmol/l of protein impurities). This product was called ‘monocomponent MC’ by Novo and ‘single peak’ insulin by Eli Lilly. Before this development, porcine and bovine insulin at times caused antibody allergies and lipoatrophy [4]. Today, however, there are no significant differences between the purity of animal and ‘human’ insulins. Indeed, insulin antibodies are formed at a very low level with both types [5, 6].

### ***‘Human’ Insulin and Analogues***

After several years of laboratory work during the years 1963–1966 human insulin was chemically synthesized in Germany by Meienhofer et al. [7], in China by Kung et al. [8] and in the United States by Katsoyannis et al. [9]. This work demonstrated that human insulin (and other proteins as well) could indeed be synthesized.

In 1975, fully synthetic insulin (CGP 12831) was synthesized in the laboratories of Ciba-Geigy in Basel. In a clinical trial, 6 patients with diabetes were treated with this insulin for up to 2 weeks [10]. It was not noted in the article that 2 patients experienced more sudden hypoglycemic events than with animal insulin, but apart from that, the synthetic insulin was well tolerated. Charles H. Best, one of the discoverers of insulin, personally commented this step in the evolution of insulin:

‘Dear Dr. Teuscher – I have received your letter and the enclosures. ... I congratulate your group on the first clinical use of synthetic human insulin. With regards, sincerely – Charles H. Best’ [personal letter, July 4th 1977]. For economic reasons, however, large-scale production and subsequent marketing were not undertaken.

In 1978, scientists from the biotechnology corporation Genentech in San Francisco, Calif., using a genetically manipulated plasmid of *E. coli* bacteria, succeeded in producing insulin with the same amino sequence as seen in humans.

In 1980, recombinant DNA ‘human’ insulin was first tested on 17 nondiabetic volunteers in England. The investigators concluded that ‘human’ insulin may be slightly more potent than porcine insulin at the low dose, and slightly less so at higher doses. They demanded ‘further and continuous careful observation of unexpected side effects’ [11]. The study predicted the problems with hypoglycemia unawareness seen later and which are discussed in the next chapter.

The race to mass produce ‘human’ insulin using gene technology was won by Eli Lilly in 1982 when the FDA approved Humulin R (rapid) and Humulin N (NPH) for the US market. This was followed by Novo’s semisynthetic insulins

Actrapid HM and Monotard HM. Eli Lilly and Novo both claimed that these products were identical to actual human insulin, and therefore were the best form of insulin therapy possible.

Since 1996, different insulin analogues have been introduced worldwide. These are characterized by various pharmacokinetics. Today, Humalog (Lilly), Lantus and Apidra (Aventis), Levemir and NovoRapid (Novo Nordisk) are available. A large number of additional analogue insulin formulas are currently being tested.

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