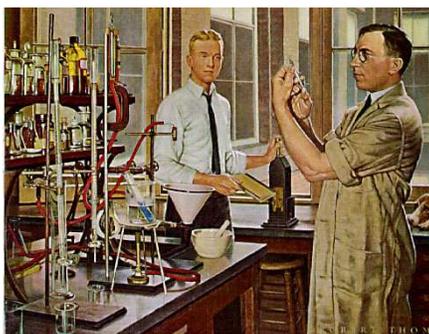


Protein of the 20th century

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Insulin should have been named protein of the 20th century. It was one of the first proteins to be crystallised in pure form, in 1926. It was the first protein to be fully sequenced in 1955, the first protein to be chemically synthesized in 1958 – though in insufficient quantities to be produced commercially – and the first human protein to be manufactured by way of biotechnology in 1979. Indeed, insulin has been on the forefront of Science for more than half a century. And why? Because of diabetes.



Banting and Best in the laboratory where insulin was discovered

Courtesy of Dr Brenda J. Andrews
Banting & Best of Medical Research

Diabetes is a disorder caused by the presence of too much glucose in the blood. A first depiction of this “sugar disease” was described in the “Ebers Papyrus” – a papyrus sold to the German Egyptologist Georg Moritz Ebers in 1872. It is said to have been found close to a mummy in the tomb of Thebes and appears to have been written between 3000 and 1500 BC. The Ebers Papyrus is a compilation of medical texts featuring anything from diseases of the tongue to those of the toes. Right up until the beginning of the 20th century, opium and various diets were given to diabetics. Though the opium dulled the patients’ anguish and the diets helped the glucose level in the blood, most would not survive for more than a year. Today, there are over 15 million diabetics in the world. And many of them survive thanks to the daily injection of insulin.

Insulin is produced by pancreatic β cells, in response to glucose and amino acids. It regulates the level of glucose in the blood both by suppressing its production by the liver and by directing it towards muscle and adipose tissue. There, the glucose is converted into complex carbohydrates, protein and fat and subsequently stored. Insulin does this via insulin receptors located on the plasma membrane of most cells. If the insulin is deficient – or cannot reach the blood – then the level of glucose in the blood rises. And if it rises, it is not being distributed to hungry cells that need the fuel to function. In the long run, an untreated diabetic can fall into a coma because of an uncharged – literally – body.

A Canadian surgeon, Frederick Banting, was the first to isolate insulin in 1922. However, research on the understanding of diabetes had been going on since the 1880s. Two German physiologists and pathologists, Oskar Minkowski and Joseph von Mering, removed the pancreatic glands from dogs that subsequently showed all the signs of being diabetic and died soon after. Further research narrowed down the origin of diabetes to the Islets of Langerhans, which are clusters of specialised cells within the pancreas. In 1910, an English physiologist, Sir Edward Albert Sharpey-Schafer, suggested that a single chemical component was missing from the pancreas of diabetics and called it “insulin”.

In 1920, Frederick Banting managed to isolate the fluid extract (that he called “isletin”) from the Islets of Langerhans and injected it into diabetic dogs. The dogs’ abnormally high sugar level in the blood lowered and they survived for

as long as they received the extract. The same extract was then given to a diabetic teenager whose condition improved daily. The news spread round the world like a house on fire and by 1923 already, large laboratories were extracting insulin.

There are two main forms of diabetes: insulin-dependent diabetes and insulin-independent diabetes. Patients suffering from insulin-dependent diabetes used to be given bovine or pig insulin, which differs very little from the human hormone. However, complications such as rashes frequently arise and today – thanks to recombinant technology – patients are given human insulin. As always, recombinant human insulin is expensive and many third world countries have to settle for bovine and pig insulin. Sadly, Banting died in a plane crash in 1941 and his house is now the Banting Museum and Education Centre, where a flame of hope burns from a huge five ton granite ball. The day a cure for diabetes is found, the flame will be extinguished.

Once it had been established that insulin was indeed a protein, it was only in 1955 that Frederick Sanger, a British biochemist, actually managed to sequence it. It is an important date with regard to bioinformatics and in particular protein sequence databanks. Now, it seems so obvious for biologists that a protein is a sequence of amino acids. However, when Sanger undertook to disentangle the insulin molecule, he did not know how the amino acids were involved and wrote in his Nobel Prize lecture given in 1958: “The results [...] showed that proteins are definite chemical

substances possessing a unique structure in which each position in the chain is occupied by one, and only one, amino acid residue.” Not only did he sequence the insulin molecule but he also established that one amino-acid residue followed another. Sanger then went on to develop DNA sequencing methods and collected a second Nobel Prize in 1980. “The concern with the basic problem of ‘sequencing’ remained the same”, he wrote “this theme has been at the centre of all my research since 1943, both because of its intrinsic fascination and my conviction that a knowledge of sequences could contribute much to our understanding of living matter.” The well-known Sanger Centre based in England – a research centre for the mapping and sequencing of genomes amongst which the human genome – was named after the British biochemist.

So, the sequencing of insulin was the very beginning of automated protein sequencing and of what would soon be the growing need for protein sequence databanks. The first protein sequence databank was edited in book form in 1965 by the late Margaret O. Dayhoff and published as the ‘Atlas of Protein Sequence and Structure’. From there evolved the well-known Protein Information Resource (PIR) established in 1984 by the National Biomedical Research Foundation. Swiss-Prot is also an offshoot of this very first protein sequence... Indeed, if it hadn't been for insulin, Banting and Sanger, the biomedical sciences – like bioinformatics – may not be where they are now.

Cross-references to Swiss-Prot

Insulin, *Bos taurus* (Bovine) : P01317
Insulin, *Homo sapiens* (Human) : P01308
Insulin, *Sus scrofa* (Pig): P01315

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