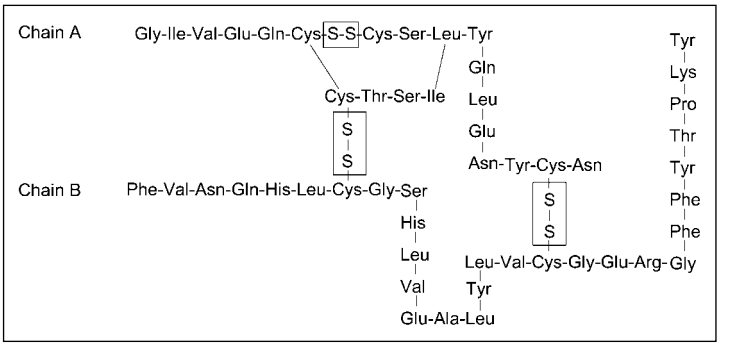
# *51. Insulin*

**CHEMICAL NAME** = insulin
**CAS NUMBER** = 9004–10–8 (human)
**MOLECULAR FORMULA** = $C_{257}H_{383}N_{65}O_{77}S_6$
**MOLAR MASS** = 5,807.6 g/mol
**COMPOSITION** = C(53.1%) H(6.7%) N(15.7%) O(21.2%) S(3.3%)
**MELTING POINT** = not reported
**BOILING POINT** = not reported
**DENSITY** = not reported




Insulin is a polypeptide hormone that consists of two peptide chains bonded by two disulfide bonds. The two chains are designated A and B. The A chain consists of 21 amino acids with a third internal disulfide bond, and the B chain contains the remaining 30 amino acids. All vertebrates produce insulin and the structure is similar in these species. For example, the insulin produced in humans and porcine species differs by only one amino acid, and humans and bovine insulin differ by three amino acids. Insulin plays a crucial role in several physiological processes. These include the regulation of sugar in the body, fatty acid synthesis, formation of triglycerides, and amino acid synthesis.

Insulin derives its name from the Latin word *insula* for island. Insulin is produced in the pancreas by β-cells in the islets of Langerhans (α-cells in the pancreas produce glucagon). Paul Langerhans (1847–1888) discovered the islets of Langerhans, which were subsequently shown to secrete insulin. Insulin binds to insulin receptors on cells and produces biochemical changes that allow the cells to take in glucose. Insulin also promotes the storage of glucose as glycogen in the liver. In this manner, insulin maintains glucose at a stable level in the bloodstream.

Insulin is most closely associated with diabetes. Diabetes results in excess blood glucose levels (hyperglycemia) and the inability of cells to absorb glucose, which in turn deprives them of energy. Instead of glucose providing energy, it is excreted excessively in the urine by diabetics. There are two main types of diabetes. Type 1 diabetes, called insulin-dependent diabetes mellitus, occurs when the body produces insufficient amount of insulin. This type of diabetes occurs in youth under age 20 and is the less prevalent form (about 10% of diabetics carry this form). Type 1 diabetes is controlled using insulin injections and regulating the diet. Type 2 diabetes, known as insulin-independent diabetes mellitus, is the most common form of diabetes and is more prevalent among older individuals (generally over 50) who are overweight. In this form of diabetes, individuals produce adequate supplies of insulin, but the cells do not recognize the insulin's signal and therefore do not capture glucose from the blood. This type of diabetes is regulated with drugs and a strictly controlled diet. It is estimated that 200 million people worldwide have diabetes, with about 16 million diabetics in the United States.

Diabetes has been prevalent in humans throughout history, but relief from the disease was not available until the 20th century. The term *diabetes* comes from the Greek words *dia bain-ein*, meaning to pass through or siphon. This denoted the condition of excessive urination in diabetics. Diabetes was traditionally diagnosed by a sweet taste in the patient's urine and the term *mellitus* comes from Latin meaning honey or sweet. In the late 1800s, it was known that diabetes was related to the pancreas, but it was not known exactly how. In 1901, Eugene Opie (1873–1971) determined that diabetes was related to the islets of Langerhans. During the early 20th century, knowledge was advanced on ductless glands and endocrine secretions that fed directly into the bloodstream. Diseases were treated with extracts obtained from glands. Within this framework, medical researchers attempted to treat diabetes with extracts obtained from the pancreas.

The discovery of insulin as a treatment for diabetes is primarily credited to several researchers from the University of Toronto. Frederick G. Banting (1891–1941) initiated the research in late 1920s after reading an article on diabetes and the islets of Langerhans in a medical journal. Banting had an idea on how to acquire secretions from the islets of Langerhans and wanted to attempt his method on treating diabetes. At the time, Banting had a medical practice in London, Ontario and was also assisting at the fledging medical school at Western University in London. Banting's medical practice was not very lucrative and he was searching for other areas in which to use his surgical and medical knowledge. Banting wanted to pursue research on diabetes, but the facilities at Western University did not have the necessary resources he needed. Using contacts at Western and the University of Toronto, where he received his medical degree, Banting approached John James Richard Macleod (1876–1935), who was Director of the Physiological Lab and Associate Dean of the faculty of medicine at the University of Toronto. Macleod's expertise was in glucose metabolism, but initially he was reluctant to support Banting's proposed work. Banting had little background knowledge on the research he was proposing, and Macleod was skeptical that Banting could add anything

to current research in the area. Macleod eventually agreed to provide Banting with laboratory space and dogs for the research, and assigned him a student research assistant named Charles Herbert Best (1899–1978). Macleod granted Banting use of his laboratory facilities during the summer break when there was less demand for their use and Macleod himself would be in Europe for several weeks.

Banting's idea was to litigate the pancreatic ducts of dogs to cut off external secretion. This would result in the degeneration of the gland's acini leaving the islets of Langerhans from which the internal secretion could be obtained. The secretion could then be used to treat diabetic dogs. Diabetic dogs were produced by removing the pancreas of individual dogs. The research Banting proposed used standard procedures of researchers who were studying the pancreas at the time. Banting began his surgeries on dogs in May 1921 and initially was unsuccessful. Seven of the first ten dogs he operated on died during the first two weeks of the experiment. As Banting acquired more experience, better results were obtained. At the start of July, Banting and Best began using degenerate dog pancreata to prepare an extract for injection into diabetic dogs. Throughout July and into August, Banting and Best prepared extract, which they called Isletin, injected diabetic dogs, and observed the results. Cats and rabbits were also used as test subjects. Although differing results were obtained from each individual, the researchers were encouraged by the extract's ability to lower blood sugar and alleviate the diabetes in several animals. Macleod returned to the laboratory in late summer and, based on the results obtained by Banting and Best, agreed to continue to support the research.

In November and December, Banting, encouraged by data reported in the scientific literature, decided to use bovine fetuses obtained from a slaughterhouse as a source of extract. Banting also acquired the help of James Bertram Collip (1892–1965), who was a first-rate biochemist spending his sabbatical at the University of Toronto. As the work generated more excitement, Macleod took a more active role in guiding the research. Collip was able to obtain more purified extracts than Banting and Best, although as work proceeded a rift divided the researchers. Macleod and Collip collaborated building on the original work of Banting and Best. The adversarial relationship between the two pairs of scientists grew as questions of priority and ownership surfaced. In January and February 1922, doctors used extracts prepared by Collip to successfully treat human patients. An article written in March of that year proposed the word insulin for Collip's extract, and the University of Toronto applied for a patent on the drug in the spring of 1922. The Toronto group was having difficulty meeting demand for insulin in clinical trials as word spread of its efficacy in treating diabetics. To increase production and commercialize insulin, the University of Toronto group licensed insulin production to the pharmaceutical company Eli Lily in May 1922, and that summer the company invested heavily in the mass production of insulin. The challenge faced by Eli Lily and others working on insulin was to find organisms capable of producing the greatest quantity of insulin.

Insulin obtained from animal sources was the primary source of insulin until the 1980s. Porcine (pork) insulin was the principal source of insulin, as it is almost identical to human insulin; it differs by only one amino acid. Although animal insulins are effective in treating diabetes, there are several related problems with its use. These include allergenic reactions to the insulin, developing immunity to the insulin so that it is ineffective, and slower response to treatment. In the 1980s, recombinant DNA was used to manufacture human insulin by inserting the gene sequence that codes for insulin production into yeast or bacteria. Today, most insulin is made using this technique, but there is current research on using plant

material to produce insulin drugs. Approximately 15 tons of insulin is produced annually worldwide.

Type 2 diabetes, also known as insulin-dependent diabetes, results from a lack of insulin. Type 2 diabetes, referred to as insulin-independent diabetes, occurs when insulin is low or cells cannot process the insulin. Diabetes impairs glucose uptake by cells, causing blood glucose levels to rise and producing a condition called hyperglycemia. This in turn results in frequent urination, dehydration, and hunger. Diabetes must be managed by monitoring blood sugar levels throughout the day, and using this information to adjust the diet and activities to keep blood glucose in an acceptable range; also, insulin must be taken for patients with Type 1 and some with Type 2. Insulin is usually administered through injections, but it can be delivered using other methods. Insulin pumps are small electronic devices that deliver insulin according to a programmed schedule throughout the day. Insulin pumps mimic the function of the pancreas to deliver a basal amount of insulin to the body. In recent years oral sprays have been developed to augment but not replace injected insulin. Another area of interest is delivery using dermal patches. Insulin cannot be delivered using conventional pills because stomach acidity denatures insulin. Although lack of insulin results in hyperglycemia, it is important when administering insulin to prevent hypoglycemia. In hypoglycemia blood sugar is too low. Hypoglycemia in diabetics can occur from too much insulin, lack of food, exercise, or lack of carbohydrates. Its symptoms include increased heart rate, nervousness, perspiration, and shakiness. When this condition is recognized, diabetics consume carbohydrates such as candy, fruit, or fruit juice to boost blood sugar levels. In extreme cases, a person can have a severe reaction and experience seizures or fall into a coma. Severe reaction to insulin is referred to as insulin shock.