

The History of Insulin Therapy in Korea

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WHO WAS THE FIRST TO USE INSULIN IN KOREA?

The original groundbreaking research occurred in 1921, when Frederick Banting and Charles Best from Canada successfully isolated insulin from dogs [1]. The first insulin therapy was administered to Leonard Thompson in 1922, to treat juvenile diabetes. The year 2021 marks the 100th anniversary of the discovery of insulin [2]. It is not well known how and who introduced insulin to Korea. In Korea, who was the first physician to prescribe insulin, and who was the first person to receive it?

The history of medicine in Korea has been diverse and challenging due to internal and external circumstances, as with modern and contemporary Korean history. We could not find any official record of the first use of insulin or any information about early diabetes patients and the treatments they received. Even from the times earlier than the 1970s, there are no records of imports, exports, licenses, and sales of insulin for domestic use. It is assumed that insulin was introduced to Korea by missionaries at the time of insulin's initial discovery or by a Japanese doctor during the Japanese Colonial period. Herein, we investigated the early history of insulin use in Korea, by looking back at old news articles and by interviewing senior academics and early insulin product importers.

INSULIN INTRODUCTION IN KOREA

The country of Sweden shed some light on the origin of diabetes treatment in Korea in the form of breaking news from

Stockholm. The existence of insulin was reported first in Korea, on October 29, 1923, in an article published in the *Chosun Ilbo* daily newspaper [3]. Two Canadian doctors, John Macleod and Frederick Banting, were awarded the Nobel Prize for discovering insulin, a hormone used for diabetes treatment (Fig. 1). Three years later, a special article of the same newspaper dated December 11, 1926, announced insulin as a “new remedy for diabetes” [4]. Insulin therapy was described as a treatment that “can be easily injected by the patient himself or his family with little practice.” On April 15, 1930, the *Dong-A Ilbo* published another article titled “Advanced therapy for diabetes within the last decade,” which reported that insulin was discovered by Dr. Banting of Toronto, Canada, and his discovery had made great progress in diabetes treatment [5]. Another article that described insulin as a new treatment option for diabetes was published in *Choongwae Ilbo* in 1930 [6]. On May 17, 1933, the *Chosun Ilbo* reported that Dr. Mosenthal of the United States had announced to academia that the rate of death due to diabetic coma had decreased by 50% from 1900 to 1930. This decrease in mortality was due to the introduction of insulin therapy [7,8]. However, at that time in Korea, diabetes or insulin treatment did not gain much interest compared to treatment for more prevalent infectious and digestive diseases.

Among all academic records in Korea, Yuguchi Kasuga's review that was published in *The Journal of the Chosen Pharmaceutical Association* in January 1929, is thought to be the first official document on insulin in Korea. In 1959, a review article titled “Recent trends in diabetes treatment” published in *Korean Journal of Medicine* described insulin therapy in detail [9].

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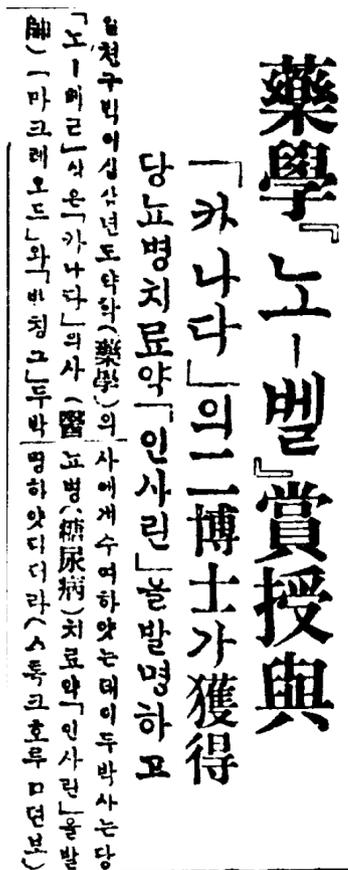


Fig. 1. The first news article reporting insulin in Korea. Adapted from *Chosun Ilbo* with permission [3].

The typical insulin used at that time was a short-acting regular insulin from animal. In that article, neutral protamine Hagedorn (NPH) insulin was introduced and “was recommended to be administered 30 minutes before breakfast for a negative urine glucose test in the afternoon.” Moreover, lente insulin, ultralente insulin, crystalline insulin, and globulin insulin were introduced. Of note, the purity of insulin was quite low at that time, and systemic allergic responses and anaphylaxis were mentioned as possible side effects. The author noted that hypersensitivity reactions could be particularly severe in patients who used protamine zinc insulin. In 1974, *Korean Diabetes Journal* reported that there was a selective hypersensitivity response to NPH or an immediate hypersensitivity response to all types of insulin [10,11]. Based on this, the low purity of insulin products was one of the major unmet clinical needs at that time.

The first case of type 1 diabetes mellitus was reported by *Journal of the Korean Pediatric Society* in 1959 [12]. The patient,

a 6-month-old boy, was treated with regular insulin and NPH (also known as isophane) insulin. In 1962, Professor Eung Jin Kim’s research team analyzed 182 patients who were diagnosed with diabetes between October 1956 and September 1961, at Seoul National University Hospital [13]. In total, they examined 62 of 182 patients who were on continued treatment; insulin was used in seven of 36 patients who had good control of their diabetes, 13 of 19 patients with fair control, and four of seven patients with poor control. Accordingly, we assume that a considerable proportion of diabetes patients was treated with insulin at a tertiary hospital during that period. Additionally, among 125 patients who received long-term treatment for more than 5 years (and up to 12 years) from 1955 to 1967, 49 (39.2%) reported that insulin had the lowest treatment failure rate compared to treatment with diet and oral drugs.

Unfortunately, insulin-related accidents also were reported in newspapers. For example, in 1969, an unlicensed pharmacist administered an overdose of insulin and was responsible for the death of a 12-year-old diabetes patient [14]. Consequently, the pharmacist reportedly attempted suicide. This was a clear indication that there was a dearth of awareness on diabetes, professional knowledge about insulin treatment, and the medical delivery system in general.

INSULIN USAGE FOR CONDITIONS OTHER THAN DIABETES MELLITUS

An article on diet and drug therapy for diabetes was published in 1939, by *Dong-A Ilbo* showed that the existence of diabetes was widely known in Korea in the 1930s [15]. However, considering the typical nutritional status and the lack of obesity at that time, type 2 diabetes mellitus was a rare disease compared to the present. Instead, thin or underweight individuals began using the anabolic action of insulin to gain weight. A professor at Gyeongseong Imperial University reported the use of insulin in a *Chosun Ilbo* article on February 1, 1935 [16] as follows.

“Recently, the effectiveness of insulin seems to be well known among clinicians. Even from my own experience, I found that insulin injection clearly resulted in weight gain objectively and subjectively in lean individuals.”

This information reflected the society’s preference for obesity rather than for skinny body types, and it could be said that insulin was used for gaining weight among thin or underweight individuals, which is in stark contrast to the present climate.

There was a time when hypoglycemia, one of the side effects of insulin, was an important part of psychiatric treatment. Insulin shock therapy was devised first in 1927, by a Polish neurophysiologist and neuropsychiatrist, Manfred J. Sakel. This therapy was used widely in psychiatry for 40 years until electroconvulsive therapy was introduced. According to Min et al. [17,18], during the Japanese Colonial era, Professor Kubo, a neuropsychiatrist at Gyeongseong Imperial University, performed insulin shock therapy on 21 patients with schizophrenia and five patients with psychoneurosis. He then presented these clinical experiences at conferences and published a paper on the subject in 1937. At that time, Professor Jou-Wan Myung, who had been working in the Department of Pharmacy since 1930, moved to the Department of Neuropsychiatry in 1934, and worked as Professor Kubo's assistant. In 1935, he was the first to introduce Sakel's insulin shock therapy into clinical practice, which is a well-known record that preceded Japan's adoption of this method [17-19]. An article published in *Dong-A Ilbo* on November 10, 1937, reported that insulin was used as the latest clinical treatment for schizophrenia, for which there was no specific treatment [20]. The article described detailed treatment methods, as follows.

"Insulin is a type of pancreatic hormone, a drug used for diabetes, which, when injected in large dosages, leads to coma. The doses vary with each patient (individual). If administered at 7:00 AM, the patient goes into a coma at 9:00 or 10:00 AM and wakes up immediately after the glucose infusion at 11:00 AM. If this sequence is repeated every day for 2 to 3 months, the patient is usually cured; however, shock therapy may become less meaningful several years after the onset of the disease. This stage of being in a coma is particularly dangerous, as the patient confronts between life or death. Thus, physical strength should be required and cases who were cured with this therapy were usually healthy individuals. The cost of the drug is approximately 3 Korean won per use. However, having a nurse is necessary for this treatment period; therefore, the total cost accounts for 5 Korean won per day, which includes the hospitalization cost."

This article demonstrates that insulin therapy was an expensive treatment at the time (after adjusting for inflation). In 1958, the *Chosun Ilbo* reported that a 38-year-old patient died due to hypoglycemic shock after receiving 60 g of insulin by an unlicensed doctor [21]. According to the report, the unlicensed doctor was 19 years old and had claimed to have the ability to cure mental illness. Subsequently, the unlicensed doctor was arrested and charged with involuntary manslaughter.

It was believed that the patient found the treatment at a hospital too costly and chose to visit an unlicensed private doctor instead.

On May 31, 1950, at the Korean Medical Association Conference, Dr. Sun-Bo Song gave a presentation titled "A modified insulin treatment of pulmonary tuberculosis" [22]. The content of his presentation was published in *Korean Journal of Medicine* in 1959, wherein insulin gained the spotlight as a state-of-the-art drug used not only as a hypoglycemic agent, but also to treat attrition caused by infectious diseases. At that time, insulin was administered at appropriate doses to avoid any potential shocks and treat anorexia, malnutrition, and neurotic symptoms in pulmonary tuberculosis patients. It was recorded that subcutaneous injections of insulin were administered for 1 to 2 months, starting with 20 units at 6:00 AM and then increasing the dosage by 5 to 10 units every day until reaching 50 to 60 units. The insulin units at that time might have differed from today's measurements, as there were no severe hypoglycemic events reported from the amounts used at that time.

INTRODUCTION OF HIGH-PURITY INSULIN PRODUCTS IN KOREA

According to Dr. Young Gil Yun, who was a professor at Kyungpook National University Hospital until 1981, the insulin used in Korea in the 1940s was produced by the Japanese company "Shionogi." It was highly likely that the insulin was imported by the Japanese to be used for diabetes treatment. During the 1960s, there was nowhere to distribute and produce insulin in Korea; therefore, doctors in Korea had to purchase and prescribe insulin privately produced in the United States for their patients.

By the 1970s, animal insulin (mostly bovine insulin) was common in Korea. The challenges in maintaining an adequate insulin supply during the 1970s were reported in the news article published in the *Dong-A Ilbo* on February 16, 1973 [23]. This article mentioned the high cost of insulin because it took dozens of cows to produce 10 cc of insulin at that time. Professor Eung Jin Kim argued for the necessity of a tax exemption for patients using insulin: "Korean patients suffer due to a shortage of insulin supply. Aside from the high cost, the bigger problem is that the quantity is not enough." This interview fully reflects the difficulties encountered in supplying insulin at that time.

Starting in the mid-1970s, domestic pharmaceutical compa-

nies began to import and distribute insulin. Green Cross Pharma (Yongin, Korea) and Dong Shin Pharmaceutical (Seoul, Korea) (1975) obtained insulin powder from a Canadian company (Connaught Laboratories, Toronto, ON, Canada) and a semi-finished insulin solution from an Australian company (Commonwealth Serum Laboratories, Melbourne, Australia). These pharmaceutical companies then reconstituted the ingredients to produce the finished products. Mr. Jongseob Jeong, the chief executive officer of Dalim Co., Ltd. (Seoul, Korea), who was in charge of importing and distributing insulin, recalls when he first joined Dong Shin Pharmaceutical in 1975. The company sold a product called “DS insulin,” which included NPH and covered most of the insulin market at that time. Domestic production technology was not sufficient to produce qualified insulin, and Mr. Jeong remembered that many professors complained about both the inconsistent pharmaceutical efficacy of insulin at that time and the shortage of supply.

In 1982, Eli Lilly announced a process to mass produce human insulin (Humulin, Eli Lilly, Indianapolis, IN, USA) using recombinant DNA techniques. Many members of the Korean Diabetes Association (KDA), including Professor Kim, welcomed this news but were disappointed that the official import of these products was limited due to domestic circumstances.

After liberation and the Korean War, the government strictly prohibited most import trade (including medicine) under the national policy for growth and protection of domestic companies. KDA members submitted a petition to the government for official import of insulin, but it was not accepted because of the protective trade policy. Meanwhile, Mr. Jeong, who had started the Dalim company in 1980, contacted the Nordisk company to buy the distribution rights for insulin in Denmark in 1983. However, Nordisk immediately rejected it because the company had already investigated the Korean market and knew that the trade of finished products was restricted by the national policy. Fortunately, the Minister of Health and Welfare, who had heard about the justification of for importation in terms of the need for rare drugs, ordered the permit promptly in 1984. The Dalim company requested an insulin import from Nordisk again, but Nordisk once more did not accept the request for the same reason. Nordisk was unaware that the trade policy had changed dramatically in Korea. The Dalim company and professors of the KDA collaborated to persuade the Nordisk employees who visited Korea to investigate the insulin market. Finally, on the day of the Nordisk employees' departure, it was decided to import insulin products with high

purity (chromatographically processed “monocomponent” insulin products) from Nordisk. The cooperative efforts between academia and the pharmaceutical industry provided great hope to people with diabetes at that time.

Since the approval to import insulin in January 1985, Dae-woong-Lilly, a joint venture, also introduced an intermediate product of Humulin [24]. The finished product was obtained through domestic production using imported raw materials [25]. Green Cross Pharma signed a technical cooperation contract with Novo-Nordisk (Bagsvaerd, Denmark) in February 1990, and began supplying human insulin and the NovoPen along with purified pure bovine and porcine insulin [26]. The insulin distributors were replaced by foreign or multinational companies in the mid-late 1990s. The list of insulin preparations available in Korea before 1992 is presented in Table 1 [27].

INSULIN USE: BEYOND MISCONCEPTION AND ACCUSATIONS

The prevalence of diabetes in Korea was <1% in the 1970s [28] but has increased remarkably since the early 1990s and now exceeds 10% of the general population [29]. In this context, insulin use in the past was a type of “drug repositioning” that was used with completely different intentions than it is now. Until the 1970s, malnutrition and infections were more prevalent than metabolic disorders caused by excessive energy intake in Korea. Therefore, the anabolic action of insulin, a side effect of modern insulin therapy, has also been used as a remedy for weight loss due to malnutrition.

It sounds quite strange that insulin-induced hypoglycemic shock was the standard therapy many decades ago for some psychiatric disorders because hypoglycemia is the most concerning side effect of contemporary insulin treatment. While hypoglycemia is recognized as a life-threatening side effect in diabetic people, this state was misused in the past due to limited clinical evidence and knowledge about insulin in the mid-20th century.

The insulin supply chain in Korea did not stabilize until the mid-1980s. The associated financial burden was another barrier that stood in the way of popularizing insulin use. When the issue of insulin purity was raised in the 1980s, advances in technology enabled adequate and qualified insulin production, and inconsistent efficacy and allergic reactions no longer occurred. The political conditions that existed in Korea until the early 1980s also explain why the delay in supply of imported

Table 1. Insulin preparations available in Korea before 1992

Brand name	Company	Units	Origin	Purity
Rapid insulin (onset: 0.5–1 hr; peak: 2–5 hr; duration: 6–8 hr)				
Insulin	Dongshin	u-40, u-80	Bovine+porcine	Conventional
Actrapid Beef	Green Cross	u-40, u-80, u-100	Bovine	High
Actrapid Pork	Green Cross	u-40, u-80, u-100	Porcine	High
Velosulin	Novo-Nordisk	u-40, u-80	Porcine	High
Velosulin HM	Novo-Nordisk	u-40, u-100	Human	High
Novolin R	Novo	u-40, u-100	Human	High
Novolin R penfill	Novo	u-100	Human	High
Novolet R	Novo	u-100	Human	High
Humulin-r	Lilly	u-100	Human	High
Intermediate insulin (onset: 1–4 hr; peak: 6–14 hr; duration: 16–34 hr)				
NPH	Dongshin	u-40, u-80, u-100	Bovine+porcine	Conventional
Protophane Beef	Green Cross	u-40, u-80, u-100	Bovine	High
Protophane Pork	Green Cross	u-40, u-80, u-100	Porcine	High
Insulatard	Novo-Nordisk	u-40, u-80	Porcine	High
Insularaed HM	Novo-Nordisk	u-40, u-100	Human	High
Novolin N	Novo	u-40, u-100	Human	High
Novolin N penfill	Novo	u-40, u-100	Human	High
Novolet N	Novo	u-40, u-100	Human	High
Humulin-N	Lilly	u-40, u-100	Human	High
Mixed type				
Insulin Mixtard HM	Novo-Nordisk	u-100	30% Velosulin+70% insulartard	
Novolet 30/70	Novo	u-100	Human	

Adapted from [27], with permission from The Diabetic Association of Korea.

insulin products. However, many members of the KDA, including Professor Eung Jin Kim, were dedicated to giving hope to diabetes patients who needed insulin treatment. Secret efforts and cooperation not only in the academic community, but also in the pharmaceutical industry were made to distribute high-quality insulin. These efforts helped to stabilize the supply of insulin and promote public health.

Progress in bioengineering technology aided in safer and convenient insulin delivery, and there was no supply or financial limit to anyone who required insulin in Korea. However, negative perceptions regarding insulin therapy arise in clinical practice every day. The real value of insulin treatment is being denigrated by an excessive fear of needles, which unfortunately has been prevalent since the discovery of insulin. In addition, there are many misconceptions about the use of insulin therapy in the terminal stage of diabetes and whether it exacerbates

diabetes-related complications. To overcome these obstacles, the government, academics, and healthcare providers will need to join forces to publicly promote the benefits and safety associated with proper insulin use that far outweigh any inconveniences.

Two passionate scientists with genuine curiosity brought hope to people with diabetes one century ago. Currently, issues remain, such as misunderstandings and pessimistic perceptions, that need to be overcome. A modern effort needs to be launched in memory of these insulin pioneers to work together to create a new era of hope for treating diabetes.

CONFLICTS OF INTEREST

We thank Lilly Korea, Novo-Nordisk Korea, Sanofi-Aventis Korea, Daewoong, and GC Pharma for providing information

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REFERENCES

- Banting FG, Best CH. The internal secretion of the pancreas. *J Lab Clin Med* 1922;7:251-66.
- Fralick M, Zinman B. The discovery of insulin in Toronto: beginning a 100 year journey of research and clinical achievement. *Diabetologia* 2021;64:947-53.
- Stockholm Telegram. Nobel Prize awarded. *Chosun Ilbo*. 1923 Oct 29:3.
- Ten nursing tips at home (1). *Chosun Ilbo*. 1926 Dec 11:3.
- Lim MJ. Advanced therapy for diabetes within the last decade. *Dong-A Ilbo*. 1930 Apr 15:5.
- How to cure diabetes: a new treatment invented recently. *Choongwae Ilbo*. 1930 Feb 24.
- Mosenthal HO. Diabetes mellitus: problems of present day treatment. *Bull N Y Acad Med* 1933;9:505-22.
- Shorter life expectancy of people with obese. *Chosun Ilbo*. 1933 May 17:3.
- Yoo BS. Review article: recent trends in diabetes treatment. *Korean J Med* 1959;2:35-8.
- Won DS, Kang MW, Kim DJ, Min BS. Selective hypersensitivity to NPH insulin. *Korean Diabetes J* 1974;2:64-5.
- Won DS, Park SH, Kim JH, Noh JC, Choi YK. A case of immediate hypersensitivity to all kinds of insulin. *Korean Diabetes J* 1974;2:61.
- Chin DS, Lim ES. Diabetes mellitus in infant. *J Korean Pediatr Soc* 1959;2:131-5.
- Kim SI, Kim EJ, Kim MW, Jun DS, Hahn SS, Chang CS, et al. Original articles: Clinical and experimental studies on diabetes mellitus in Korea-2. Clinical observation on Korean patients with diabetes mellitus. *Korean J Med* 1962;5:307-26.
- An unlicensed pharmacist who killed a child with insulin misuse tried to commit suicide. *Kyunghyang Shinmun*. 1969 Apr 16.
- Diet therapy for diabetes. *Dong-A Ilbo*. 1939 Mar 30:4.
- Lee JH. Recent update of weight control. *Chosun Ilbo*. 1935 Feb 1.
- Min SK, Lee C, Lee K. Research by psychiatrists of Chosun Chongdokbu Hospital and Keijo Imperial University in Korea during Japanese Colonial Rule. *J Korean Neuropsychiatr Assoc* 2015;54:142-71.
- Min SK, Lee CH. Research on psychiatric treatment by psychiatrists of Chosun-Governor Hospital and Keijo Imperial University Hospital in Korea during Japanese Colonial Rule. *J Korean Neuropsychiatr Assoc* 2016;55:143-57.
- Korean Academy of Medical Sciences: KAMS Hall of Fame. Available from: http://kams.or.kr/eng/fame/sub2.php?mode=view&sid=33&keyfield=all&sub_mode=public (cited 2021 Aug 23).
- Yoshimitsu T. New treatment of schizophrenia. *Dong-A Ilbo*. 1937 Nov 10.
- Unlicensed doctor killed patient. *Chosun Ilbo*. 1958 Sep 10:3.
- Song SB. A modified insulin treatment of pulmonary tuberculosis. *Korean J Med* 1959;2:51-4.
- Homedoctor. Diabetes: Dr. Kim's medical advice. *Dong-A Ilbo*. 1973 Feb 16:5.
- Daewoong Pharmaceutical established Daewoong Lilly Pharmaceutical joint venture contract with Mi Lilly. *Maeil Business News Korea*. 1982 May 4.
- Green Cross decided to supply high-purity purified insulin to Korea. *Maeil Business News Korea*. 1990 Feb 6.
- Foreign insulin companies such as U.S. Lilly are engaged in a proxy war to preoccupy the domestic market. *Maeil Business News Korea*. 1990 Feb 9.
- The Diabetic Association of Korea. Are your insulin choices right? *Mon Diabetes Mag* 1992;29:68-73.
- Kim KS, Choi CH, Lee DY, Kim EJ. Epidemiological study on diabetes mellitus among rural Korean. *Korean Diabetes J* 1972; 1:17-24.
- Kim BY, Won JC, Lee JH, Kim HS, Park JH, Ha KH, et al. Diabetes fact sheets in Korea, 2018: an appraisal of current status. *Diabetes Metab J* 2019;43:487-94.