# Almost famous: E. Clark Noble, the common thread in the discovery of insulin and vinblastine

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**Abstract**

CLARK NOBLE WAS ONE OF THE FIRST members of the University of Toronto insulin team and came within a coin toss of replacing Charles Best as Frederick Banting's assistant during the summer of 1921. Noble performed important early studies helping to characterize insulin's action, and he coauthored many of the original papers describing insulin. Because mass production of insulin from livestock pancreata had proved elusive throughout 1922, J.J.R. Macleod hired Noble during the summer of 1923 to help him test and develop a new method for producing commercial quantities of insulin that Macleod believed would revolutionize insulin production. However, commercial production of insulin from fish proved impractical and was dropped by 1924, as methods to produce large quantities of mammalian insulin had improved very rapidly. Noble later played a small but critical role in the most important Canadian contribution to cancer chemotherapy research: the discovery of vinca alkaloids by his brother Robert Laing Noble. Although one might expect that a physician involved in 2 of Canada's most important medical discoveries during the 20th century must be famous, such was not Clark Noble's fate. He died without so much as an obituary in *CMAJ*.

Insulin was discovered by Frederick Banting, Charles Best, J.B. Collip and J.J.R. Macleod in late 1921 and was successfully used to treat patients in January 1922.[1] The initial results were published in *CMAJ* 2 months later.[2] Much has been written about the discovery and the discoverers. As this year represents the 80th anniversary of insulin therapy, it seems an appropriate time to relate an interesting but little-known story, the sad saga of E. Clark Noble.

## The early years

Edward Clark Noble was born into a prominent Toronto medical family on Dec. 29, 1900. Clark's father, Robert Thomas Noble, worked as a general practitioner and was active in organized medicine in Toronto for almost 60 years. Over his career, Robert T. Noble served as president of the Ontario Medical Association, the Canadian Medical Association, the Toronto Academy of Medicine, the College of Physicians and Surgeons of Ontario and the Medical Council of Canada; he was also a recipient of an honorary LLD from Queen's University.[3,4]

Clark was the oldest of 3 sons. In 1918 he entered the University of Toronto, majoring in physiology and biochemistry. Throughout their undergraduate studies, Clark and Charley Best were classmates and best friends. They studied, travelled, double dated, held summer jobs and played semi-professional baseball together (Fig. 1). Clark and Charley were stellar students. In June 1921, they graduated as joint silver medallists with BA degrees in physiology and biochemistry. Both were accepted to work as summer students in J.J.R. Macleod's laboratory and to begin 1-year MA degrees that fall.[5]

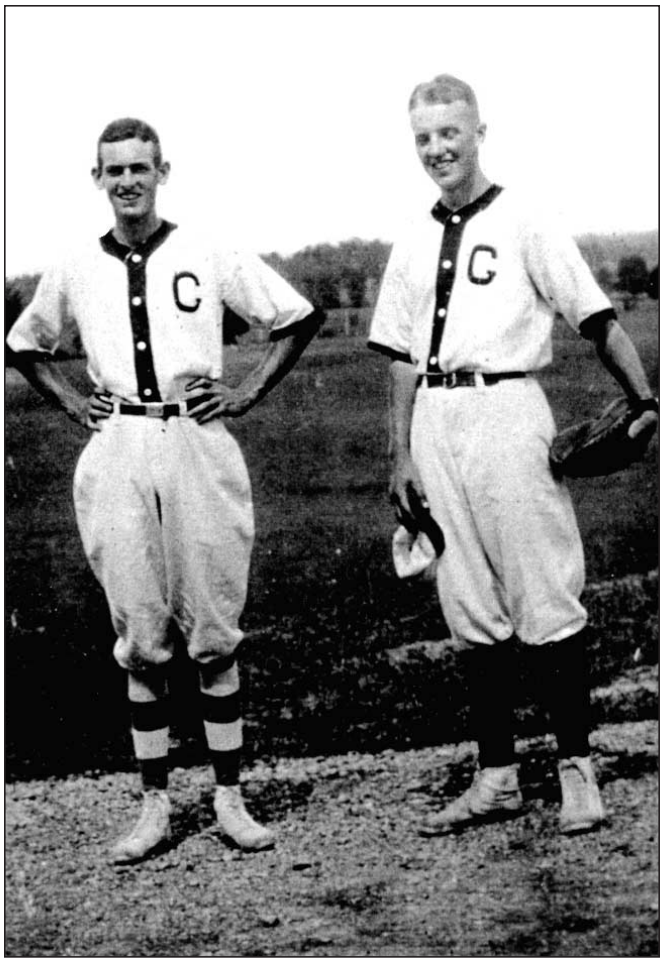
## The discovery of insulin

The discovery of insulin has been well documented.[1] Banting, a young surgeon with no research training, approached Macleod, a professor of physiology at the University of Toronto, with an idea. Macleod, although skeptical, provided Banting with the necessary facilities, research animals and technical assistance to test his hypothesis. Because Best and Noble had previously worked in his laboratory Macleod reckoned that they would provide the required biochemical expertise and that Banting would provide the surgical expertise. It was decided by a coin toss that Best would assist Banting for the first month and that Noble would assist him for the second month of the summer. However, the plan changed after it took Best his entire month to become a competent surgical assistant and it seemed unwise to switch.[1,6] Banting and Best performed canine pancreatectomies, made pancreatic extracts, injected the extracts into diabetic dogs and then measured blood glucose levels. When Macleod returned at the end of the summer, Banting presented their results. Macleod, considering the work promising, asked J.B. Collip to join the team. Collip was able to greatly purify the extracts, which permitted the first successful clinical application on Jan. 23–24, 1922. When Banting demanded that Collip share his methods, Collip refused, igniting Banting's fa-

mous temper. Noble dramatically documented this event by drawing a cartoon showing Banting sitting on Collip and choking him; he captioned the drawing "The discovery of insulin."[1]

Shortly after this incident, Banting curtailed most of his laboratory research and focused on treating diabetic patients. Collip returned to Alberta, and Best was put in charge of insulin production in Toronto. According to Noble, "at this point Macleod held a conference with Banting, Best and myself ... and outlined the essential work necessary to determine the various properties of the new substance; of this research I was awarded a substantial portion."[7]

Noble contributed considerably to the rapid increase in knowledge about insulin during the early months after the discovery. He studied the effects of insulin on blood glucose levels and hepatic glycogen content in normal and hyperglycemic animals and showed that hypoglycemia was responsible for the stupor or convulsions in rabbits that had been injected with insulin and that the symptoms could be reversed by injecting glucose.[7,8] Noble coauthored at least 10 early papers on insulin (3 in 1922, 5 in 1923, 1 in 1924 and 1 in 1925) and at least 6 abstracts.



Courtesy Henry Best

**Fig. 1: Before the discovery of insulin, Charles Best and Clark Noble were best friends and teammates on the Georgetown, Ont., baseball team, champions of the Peel–Halton Baseball League in 1920. Noble played first base and Best played catcher.**

On Oct. 25, 1923, Banting and Macleod were awarded the Nobel Prize in physiology and medicine. Banting, who had already concluded that Macleod was trying to steal credit due to himself and Best, was furious.[9,10]

## Fish insulin: Noble's second chance for glory

Throughout 1922, production of large quantities of insulin from livestock pancreata proved to be difficult, erratic and very expensive.[1] Macleod passionately pursued his belief that the solution was large-scale commercial production of insulin from fish.[11–14] He was aware that teleost (bony) fish have large discrete islet organs, whereas the islets are scattered throughout the exocrine pancreas in mammals; he believed that the anatomical separation of endocrine and exocrine pancreas in teleost fish might greatly facilitate extraction and purification. Macleod spent the summer of 1922 at the Biological Station in St. Andrews, New Brunswick, and demonstrated on a small scale that insulin could be easily produced from teleost fish islets.[11–13,14] Because of the urgent clinical need, scientists in the United States, Great Britain and continental Europe also evaluated piscine sources of insulin during 1923 and early 1924.[11]

In early 1923, Macleod focused on monkfish because they have very large islet organs. He arranged to have their islets collected and shipped to Toronto in acid alcohol for insulin extraction.[11] Gjert Mhyre, captain of the Halifax-based steam trawler *Venosta*, provided him with a steady supply, and Macleod demonstrated that insulin could be more easily and inexpensively produced from fish islets than from livestock pancreata. However, Macleod recognized that the main potential impediment was obtaining the raw material, fish islets.[11] Therefore, Macleod arranged for Noble, now a medical student, and N.A. McCormick (Fig. 2), one of Macleod's MA students[15] who would enter medical school in the fall, to spend the summer of 1923 at the Biological Station in St. Andrews and on *Venosta* critically evaluating the concept of using fish as a commercial source of insulin.

The students immediately ruled out monkfish, as there was no commercial fishery for this species; they decided to focus on cod.[11,16,17] They initially conducted small-scale studies at Grand Manan, New Brunswick. Because this was an inshore fishery, the cod were brought ashore for evisceration, at which point the islets were collected. The large, pink, triangular principal islets of the cod could be readily identified even by unskilled assistants. The students determined that insulin could be produced for as little as $0.0016 per unit.[11]

However, the inshore cod fishery was small, and most cod were caught by steam trawlers working a hundred or more miles offshore. The students realized that a mechanism to efficiently collect islets from the offshore fishery

would be necessary. Therefore, Noble and McCormick put out to sea in *Venosta*. From Sept. 21 to 26, the students collected islet tissue from about 1800 fish, which was sent to Toronto on ice, where 2400 units of insulin were extracted at a cost of $0.0037 per unit.[11] This insulin was tested in diabetic patients at the Toronto General Hospital by Walter R. Campbell, the head of the diabetes clinic. Unbeknownst to the patients, Campbell substituted cod insulin in 6 patients that he had been treating with beef insulin and concluded that the cod and beef insulin were equally effective.[17]

McCormick and Noble also tried producing insulin from cartilagenous fish, which do not have islet organs but rather have their islets scattered throughout the exocrine pancreas as in mammals. Nevertheless, Macleod believed that it would be easier to produce insulin from shark and skate pancreata than from mammalian pancreata on the basis of his studies during the summer of 1922,[14] and his belief precipitated similar, but very brief, research interests in centres on both sides of the Atlantic.[18,19] However, McCormick and Noble rapidly concluded "that fish of this class are not suitable as raw material for the manufacture of insulin."[17]

Although Noble and McCormick finished their summer jobs in full agreement about cartilagenous fish, they had very different opinions as to whether large-scale production of insulin from cod islets could ever be feasible. Noble was optimistic, whereas McCormick, for logistical reasons, was pessimistic. Because Noble and McCormick could not agree, they decided that further testing should be done and made arrangements for Jack Sugden, the wireless radio operator on *Venosta*, to continue their research. Sugden collected cod islets throughout the winter, and 7 more diabetic patients were successfully treated.[17]

Initially, Macleod agreed with Noble. Macleod's research in 1923 had been funded by the Carnegie Foundation. In his Carnegie annual report, he recounted McCormick and Noble's results and concluded that "there is not the slightest doubt as an outcome of their work that these fish will be a profitable source of insulin and that the material can be collected without great practical difficulty."[11] However, by mid-1924, Macleod recognized that mammalian insulin could be inexpensively mass-produced and that fish insulin could not.[11]

Two papers and a book chapter were published from this work. A paper by McCormick and Noble[17] described the studies performed and their results, but it did not conclude that commercial insulin production from fish was totally unrealistic, reflecting Noble's opinion. In contrast, the paper by McCormick[16] established conclusively that the logistics of collecting fish islets precluded the use of fish as a source of insulin. Macleod published a chapter entitled "The Islets in Fishes and Their Yield of Insulin," which summarized the literature on fish islets as well as Noble and McCormick's studies, in his 1926 textbook on carbohydrate metabolism.[20]

Undoubtedly, Best and Noble discussed their research activities with each other. These conversations must have become increasingly awkward as their research careers went in opposite directions. Noble continued to believe that commercial production of insulin from cod islets was very feasible, despite overwhelming evidence to the contrary. Best did not believe that fish insulin had any future. In the margins of his copy of Macleod's textbook,[20] he wrote "far more than cost from beef pancreas" next to Macleod's discussion of Noble and McCormick's research (Henry B.M. Best: personal communication, 2002).

## After graduation

Best graduated in 1925 at the top of his class. He continued his research training in 1925 and 1926 in the laboratory of Henry Hallet Dale at the National Institute for Medical Research in England. He had a long and distinguished career at the University of Toronto as a leading Canadian figure in medical research. He died in 1978.[21,22]

McCormick graduated with honours from medical school in 1926 and then did postgraduate training in Toronto, New York and Edinburgh, obtaining qualifications in surgery and in therapeutic radiology. He became a Canadian pioneer in the successful combination of surgery and radiotherapy. He died in 1967. *CMAJ* published almost 3 full pages of "appreciations" written by colleagues and trainees.[23]

Noble graduated with honours from medical school in 1925 possessing an MA degree, a very strong reference letter from a Nobel laureate[24] and 9 publications coauthored with 1 or 2 Nobel laureates. He undertook postgraduate training in England and obtained his MRCP (London) in 1927, after which he worked as a general practitioner in Toronto. He had a long career but one that was less distinguished than might have been expected considering its auspicious beginnings.

Clark Noble and Charley Best's close friendship survived the discovery of insulin, but not the turmoil that ensued. In the months after the discovery, Clark and his fiancée, Edith Constance, remained close to Charley and his fiancée, Margaret Mahon. Edith and Margaret spent time in Macleod's laboratory performing some volunteer secretarial services (Edith answered Banting's fan mail) while Clark and Charley continued their laboratory work. However, Clark and Charley's relationship became increasingly strained as their careers, and allegiances, diverged. Clark was an usher at Charley and Margaret's wedding on Sept. 3, 1924. Clark married Edith on June 16, 1926. Charley and Margaret did not attend their wedding, as they were living in London. Charley and Margaret's son Henry, who was born in 1934, remembers seeing the Nobles on only a few occasions during his childhood, and the Nobles were rarely mentioned in his mother's diaries after the late 1930s (Henry B.M. Best: personal communication, 2002).

## The discovery of vinca alkaloids

Clark Noble had one more brush with fame.[25] He maintained his interest in diabetes throughout his career, and this was known by his patients. In 1952, a patient visiting Jamaica sent him an envelope containing 25 leaves from the Madagascar periwinkle plant (*Vinca rosea*). She described how to make a tea widely used in Jamaica to treat diabetes and referred him to a McGill-trained Jamaican physician. Because Clark was no longer involved in research and had no facilities to test the material, he sent the envelope to his brother Robert Laing Noble, associate director of the Collip Medical Research Laboratory at the University of Western Ontario.[25] When tested by Robert Noble, leaf extracts had little effect on blood glucose levels but a profound effect on bone marrow and white blood cell counts. In 1954, Charles T. Beer, an organic chemist, joined Robert Noble's research team. Together they isolated and characterized a potent vinca alkaloid, vinblastine, which quickly became a mainstay in cancer chemotherapy and was one of the most important Canadian contributions to cancer research during the 20th century. The National Cancer Institute of Canada named its most prestigious award for excellence in cancer research the Robert L. Noble Prize in honour of this discovery.

## The bitter end

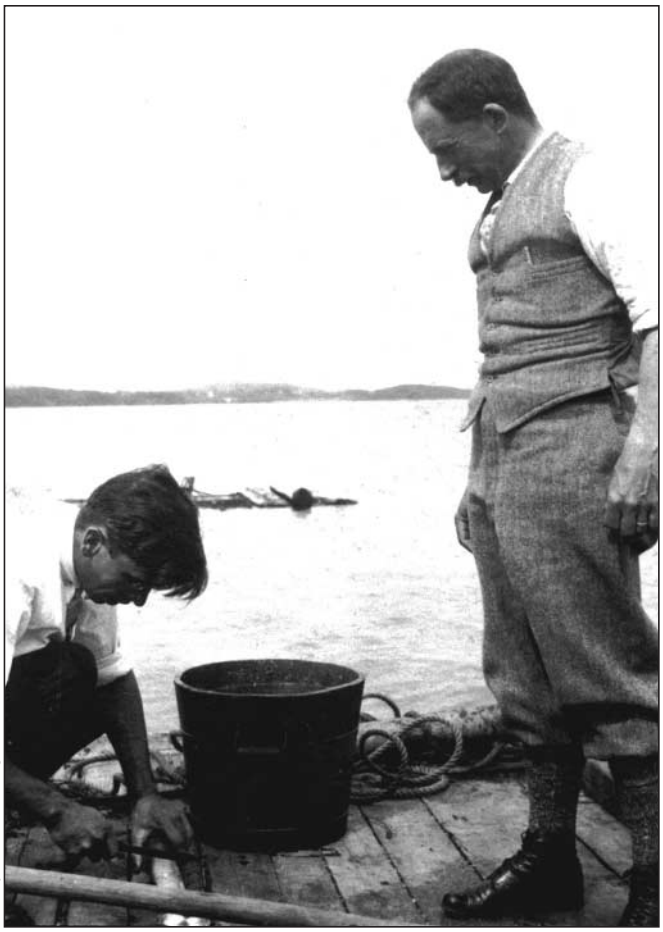
Not only did Clark Noble miss out on all of the glory and opportunities associated with the Nobel Prize that had been garnered by his close friend, Charley Best, he also let the envelope holding the Noble Prize for cancer research slip right through his fingers — unopened. Clark had other career-long crosses to bear. During Noble's lifetime, historians, when they did not ignore him entirely, unfairly impugned his character for not switching with Best. For example, Lloyd Stevenson, in his 1947 biography of Banting, stated the following:

> "Mr. Best and Noble," wrote Banting, "were appointed as assistants, each to give four weeks. They tossed a coin to decide who would give the first four weeks, and Mr. Best won the toss. At the end of four weeks, however, Mr. Noble did not return and Mr. Best stayed with me." Did ever Lady Luck provide an ambitious young man with such a singular opportunity! How Best converted this opportunity to use and glory Banting was always the first to relate.[26]

In this account, Stevenson stated in a footnote that "Drs. Best and Noble agree that the coin-tossing story is fiction, invented here by a newspaper reporter," that "Noble was not in the best of health at the time", and that "he left at once for a holiday."[26] Charles Best maintained that the story of the coin toss was made up by a reporter for the *Toronto Star* (Henry B.M. Best: personal communication, 2002). However, Clark Noble maintained that he had lost a coin toss,[6,7] and this version of the events is the one that historian Michael Bliss found to be most credible.[1,27] To make matters more confusing, Robert L. Noble, in a historical account of the discovery of vinblastine, flippantly stated that his brother "won the coin toss and chose to work with Professor Macleod because he had never heard of Banting."[25]

Neither Banting nor Best ever acknowledged Noble's contributions to insulin research. Having trained in the laboratory of a Nobel laureate is usually both career-enhancing and a source of pride. Perhaps most cruel of all, although Noble appeared to have held Macleod in very high esteem and to have been proud of his association with the professor, Banting had so successfully maligned Macleod that Noble's association with the professor would not have engendered much respect among his peers during his lifetime.

A letter written by Noble in response to a Macleod-bashing article by J.R. Henderson entitled "Who discovered insulin?" provides some insight into Noble's pain:



Courtesy St. Andrews Biological Station

**Fig. 2: N.A. McCormick working on the wharf in St. Andrews, NB, with J.J.R. Macleod watching. McCormick worked at the St. Andrews Biological Station with Clark Noble during the summer of 1923 and returned in 1924, when this photograph was taken.**

I ... feel that I should finally, in my own defence, present some facts regarding my identity and activities at that time — you see I happen to be the "E.C. Noble" referred to in Dr. J.R. Henderson's article. I have long since given up attempting to correct the mis-statements and misleading facts in the early authors' books and ... scientific papers. In these I have variously been referred to as "failing to appear," "being taken ill," "not returning" and "did not show up," etc. ... Best and myself were allocated to work with Banting for two months and to decide between ourselves in what manner we did so; to this end (contrary to most statements but corroborated by Banting in his Cameron Lecture in Edinburgh, 1928) we did toss a coin to see who would work first, and this happened to be Charles Best. It was also agreed that we should change over at the month's end; however, when this time arrived, Best had become proficient in assisting Dr. Banting in his surgical techniques so it was mutually agreed, in the best interest of the experiments, that Best should continue to work out the full time with him.[6]

Noble then maintains that he was a coauthor on "some ten to twelve" of the original insulin papers "found in any Medical Library" and that this was an "unlikely activity for the 'Man Who Never Was' — myself."[6] He continues his letter by recounting his and McCormick's fish insulin research and concludes that "no one ... has seen fit to seriously investigate this work further or to recognize its significance as a valuable source of Insulin scientifically, and now, perhaps, more important, as an additional source of income to the offshore fishermen."[6]

The Fisher Rare Book Library at the University of Toronto contains a small folder of Noble's papers, showing how he repeatedly attempted to resurrect interest in fish insulin. Of particular note are letters to and from J. Angus MacLean, the Canadian Minister of Fisheries, in 1961. On Apr. 13, Noble wrote the Minister briefly broaching the subject and volunteering to meet with him. The Minister replied on Apr. 20 expressing "a great deal of interest ... both from the viewpoint of diversification of the fisherman's occupation and of ensuring a good supply of this product which has become so important from a health standpoint."[28] On July 5, MacLean wrote to Noble again: "The reports which I now have before me have revealed many interesting facts, some of which may not be known or accepted by you."[28] MacLean noted that there was a "world surplus" of insulin. He also stated that the Fisheries Research Board of Canada and Connaught Medical Research Laboratories had conducted feasibility studies between 1947 and 1954:

The results were not much different from those obtained in the 1920's by Dr. N.A. McCormick. The yield was relatively high as compared with that from mammalian pancreas but the cost of dissecting out the tissue, and getting it to the laboratory appeared to be far in excess of that required for mammalian pancreas. In Denmark and Japan a similar assessment was made, and the fact that these countries are not now utilizing these sources would indicate similar discouraging results."[28]

MacLean concluded the letter by diplomatically stating that he had no further interest in the matter. He included a copy of written remarks from the Fisheries Research Board. Noble pencilled in and underlined comments such as "untrue" in the margins next to each negative statement in the minister's letter and the board's critique.

Noble's championing of fish insulin had one last hurrah. A front-page newspaper article in the *Toronto Star* on Oct. 28, 1974, described an impending shortage of insulin. In addition to describing more traditional approaches to improve insulin supplies, the paper interviewed Noble, now 73 years old. The reporter wrote that "perhaps the most interesting suggestion comes from Clark Noble, a retired Metro physician who tossed a coin with Best back in 1921 to see who would become Banting's research assistant. After Noble lost, he went to Nova Scotia with another graduate student to work on extracting insulin from the pancreas of codfish." Noble was quoted as saying, "We've done all the work on it and it's already to go, if anyone is interested in it. With all the current problems about pancreas supplies, I think it's not only an opportunity, it's a necessity."[29]

Clark Noble died on May 18, 1978; there was no obituary in *CMAJ*. He had come within a coin toss of the fame and fortune associated with the discovery of insulin and played a small but critical role in the discovery of vinca alkaloids. Although Clark Noble was not destined to become famous, he is a common thread in 2 of Canada's most important medical discoveries.

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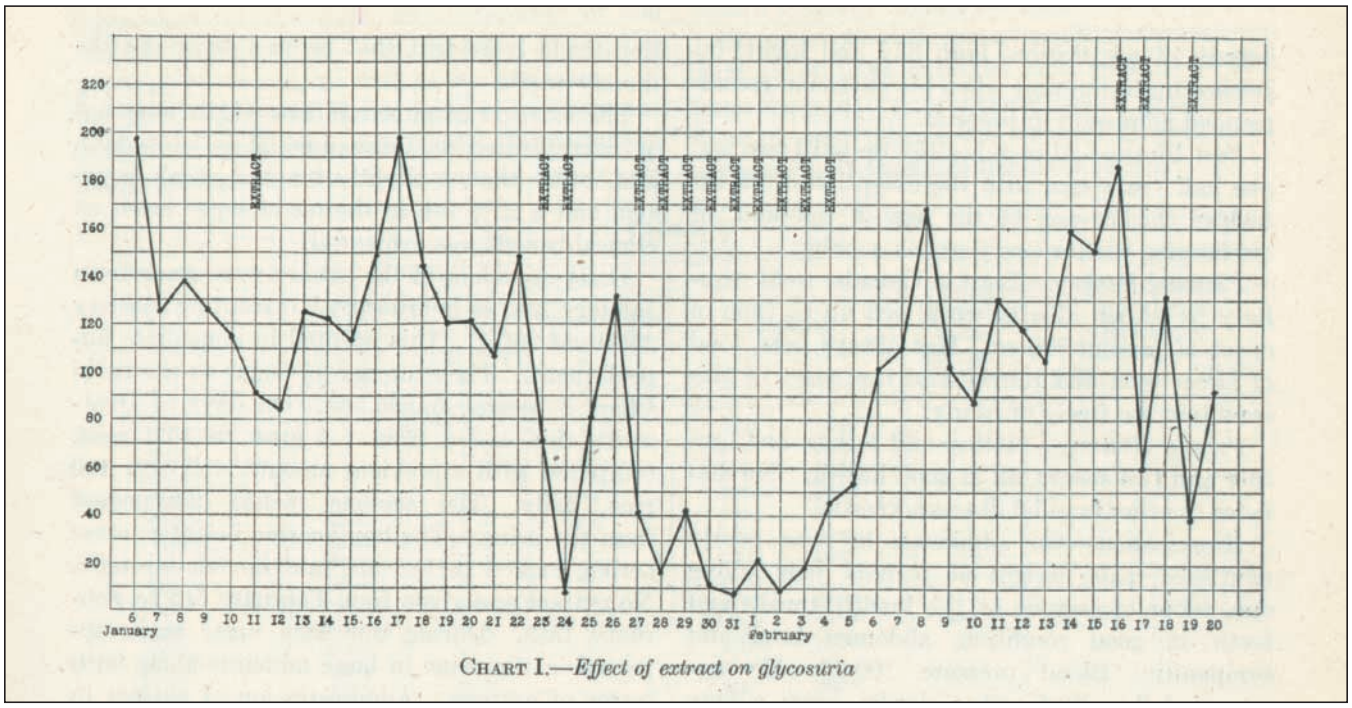


CHART I.—*Effect of extract on glycosuria*

Frederick Banting and his colleagues at the University of Toronto reported the discovery of insulin in the March 1922 issue of the *Canadian Medical Association Journal*. The first human subject to receive their pancreatic extract was a 14-year-old boy with severe juvenile diabetes mellitus and ketosis. Before receiving the extract, the boy "was poorly nourished, pale, weight 65 pounds, hair falling out, odour of acetone on the breath. … He appeared dull, talked rather slowly, quite willing to lie about all day." He received his first daily injection of the extract on Jan. 11, 1922. By Feb. 4, the boy was "brighter, more active, looked better and said he felt stronger." This graph shows the effect of injections of the extract on the boy's glycosuria. Seven patients received the extract in this initial study. The researchers commented that "all patients were improved clinically. It is difficult to put in words what is meant by clinical improvement. Those who have been treating diabetes will have recognized as early signs of improvement a certain change in the skin, the appearance of the eyes, the behaviour of the patient, his mental and psychic activity, and the physical evidences, as well as his testimony, of increased vigor and desire to use his muscles." (Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancreatic extracts in the treatment of diabetes mellitus. Preliminary report. *CMAJ* 1922;12:141-6.)