The Discovery of Insulin: The Rochester, New York, Connection

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The discovery of insulin in Toronto by Dr. Frederick G. Banting and colleagues has been well chronicled. The story of how insulin therapy was introduced into the United States has been less detailed. The first patient to be treated with insulin in the United States resided in Rochester, New York, a city with a then newly developed medical school that had also tried to recruit Dr. Banting. A series of letters from that period provides a description of the course of a juvenile patient with diabetes before and after the use of insulin as a therapeutic agent.

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The story of insulin's discovery, which revolutionized the treatment of diabetes mellitus, has been dramatically described by Bliss (1). Dr. Frederick G. Banting, a surgeon-turned-physiologist at the University of Toronto, has been the subject of a biography by the same author (2). Across Lake Ontario, about 90 miles from Toronto, in Rochester, New York, the first treatment of diabetes mellitus with insulin in the United States took place, illustrating the dramatic effect of insulin on the treatment and outcome of juvenile diabetes.

In 1915, James "Jim" Dexter Havens (**Figure 1**), age 15 years, received a diagnosis of diabetes from Dr. John Ralston Williams (**Figure 2**, *left*) in Rochester (4, 5). Jim was treated soon thereafter at the Rockefeller Institute of New York by Dr. F.H. Allen with an extremely low-calorie diet devoid of any glucose. Each patient had their total caloric intake scrutinized by counting calories, weighing food, and sometimes fasting. Although seemingly cruel, there was no better way to keep patients with diabetes alive. Such treatments prevented rapid death from diabetic ketoacidosis, allowing patients with diabetes to live many years before they generally died of starvation. Between 1915 and 1916, Jim's diabetes was not severe and he tolerated a diet of 1900 calories (1.9 kcal or 7.9 kJ) of food without severe hyperglycemia. His diabetes progressed, however, and to avoid severe ketosis, his maximum caloric intake was drastically reduced. In 1918 and 1919, his diet approximated 1000 calories or less ($\leq$1 kcal or $\leq$4.2 kJ), at which time his blood sugar level ranged from 0.13% to 0.20% (7.2 to 11.1 mmol/L) with occasional traces of sugar in the urine. By 1920, his diabetes became very severe, requiring a maximum caloric intake of 800 calories (0.8 kcal or 3.3 kJ). Despite this reduction, Jim's blood sugar was almost constantly more than 0.20% ($>$11.1 mmol/L), with the urine containing 2% to 6% of sugar or more ($\geq$111.0 to 333.1 mmol/L) and evidence of acidosis with a total urinary ammonia level ranging from 2 g to 5 g daily. By spring 1922, Jim's condition had continued to deteriorate, causing him to lose all tolerance for food (4, 5).

On 3 May 1920, the patient's father, James S. Havens (**Figure 3**), an executive at Eastman Kodak and a lifelong friend of George Eastman (president of Eastman Kodak Company), wrote to a friend, E.C. Gale, about the treatment of his son (4):

> When Jim was first taken [to the Rockefeller Institute] for treatment, he seemed to have a tolerance of something like 2300 calories [2.3 kcal or 9.6 kJ] and his trouble was said to be slight. Keeping him sugar free as far as the test with Benedict's solution went, he gradually lost tolerance. For a long time he was able to take 1500 calories [1.5 kcal or 6.3 kJ] a day and keep sugar free as far as the tests that we made were concerned, and then the sugar began to appear without the increase of food. Last fall I was very much discouraged and took him to New York and left him four or five weeks with Dr. Allen who sent him home assuring me that his blood sugar could be kept normal on 800 calories, but we haven't been able to get that result. For three weeks now he has been on a diet of 200 calories [0.2 kcal or 0.8 kJ] per day, consisting of 50 grams of protein per day, which is pretty near starvation, and last weeks [*sic*] his blood sugar was [0].15 [8.3 mmol/L], while the normal is [0].10 to [0].13 [5.6 to 7.2 mmol/L] during digestion. . . . He is a mere shadow, weighing about eighty-five pounds [38.6 kg] stripped, and is my height (5' 8″). . . .

The first evidence of James S. Havens' knowledge of Dr. Banting and colleagues' work appears in a letter written to his brother less than 3 months after the first clinical use of pancreatic extract to treat juvenile diabetes. In that letter (6), dated 5 April 1922, appears a short paragraph:

> Jim is not very well and gets rather discouraged. Some Toronto doctors have made some progress toward developing a pancreatic extract and Dr. Allen is working along the same lines in New York and has told me that the prospect was encouraging.

According to David O. Woodbury, in an article in *Liberty* in June 1962 (7), Havens asked George Snowball, the manager of a Kodak store in Toronto, whether he knew of anyone in Canada who was working on the treatment of diabetes. Snowball put the question to a golfing partner, Dr. John J.R. Macleod, who indicated that he had been working on the problem, but that it was premature to report success. Snowball persisted in his inquiry and eventually met with Dr. Banting (3) (**Figure 2**, *right*), who related that experimental doses had been administered to

Figure 1. **James Dexter Havens.**

As a teenager with diabetes mellitus (*left*) and as a highly notable artist and master of the woodcut in his later years (*right*).

some patients and that the preliminary results were encouraging. When Snowball conveyed the information to Havens, Havens, in turn, immediately sent Dr. Williams, the physician in charge of his son's medical care, to Toronto on 9 to 11 April to try to get some of the preparation.

A follow-up letter (8) from Havens to Stephen B. Cornell, at Canadian Kodak Co. Ltd., on 11 April 1922 stated:

> He [Williams] found the people he wanted to see very willing to co-operate and he had a long conference with them on Sunday. They are just now at a stand still in making the preparation, something having gone wrong so that temporarily they are unable to produce it, but they promised Dr. Williams he should have some of the first that was produced when they get past their present difficulties. . . .

During the next month, James S. Havens watched his son's medical condition rapidly deteriorate as manifested by severe neuropathy and near coma. Little did he know that a successful response had already been achieved. Leonard Thompson had received the medication in Toronto on 23 January 1922 after a failed initial attempt (1).

Subsequent to the report of the success achieved with insulin, which was announced publicly on 3 May 1922 at the American Association of Physiology in Washington, DC, Havens arranged to have the insulin shipped from Toronto to Rochester. On Monday, 22 May 1922, James Dexter Havens became the first patient with diabetes in the United States to receive the newly purified insulin. Unfortunately, the administration by Dr. Williams did not lower Jim's blood sugar level, which remained in excess of 22.2 mmol/L (400 mg/dL). Jim was given a subsequent dose on 23 May and another on 24 May, both to no avail.

Two letters written by Havens on 24 May 1922 document the first administration of pancreatic extract to James Dexter Havens in Rochester. A letter to George Snowball (9) stated:

> You will think, I am afraid, that I am dilatory in letting you know something about the result of giving Jim the extract which you took so much pains and trouble to get to me last week, but it is not so simple a matter as I thought it would be and I cannot tell you anything very definite even now. The doctor [Dr. Williams] has gone out of town and it was impossible to get him back, so that the first dose was not given [to] Jim until Monday afternoon [22 May]. We have no report and won't have until some time late today of the effect of any dose except the first. That, however, was apparently negative. There was no change in the blood sugar. The second dose was given [to] him yesterday morning and a third this morning. Each of the first two doses was 1 cc and the third dose was 2 cc. A sample of blood was taken this morning and we shall get a report on that, as I have said, late this afternoon. The first dose resulted in a great deal of pain and soreness, the

> latter lasting for a day or more. The second dose was not followed by these symptoms and we hope the third will not be. I have asked Dr. Williams after he gets the report on the blood taken today to talk with Professor Macleod by telephone this afternoon. What the final result will be, of course, we cannot tell. . . . Jim suffers terribly from pain in his feet and general discomfort from lack of food, but he is very brave and stands the treatment well, better than I should think he could. . . .

The news of the failed injections quickly reached the attention of Drs. Macleod and Banting. As a consequence of this failure and with the great amount of pressure from Dr. Williams and Havens, Dr. Banting traveled to Rochester to personally administer the insulin. Jim's morning blood and urinary sugar levels were 22.2 mmol/L (400 mg/dL) and 1170 μmol/L (21 mg/dL), respectively. At 10:30 a.m., Dr. Banting arrived with Dr. Williams, and he administered 2 cc of insulin that decreased both levels to 15.0 mmol/L (270 mg/dL) and 480 μmol/L (8.6 mg/dL), respectively. Subsequently, Jim received another 4 cc of insulin, causing the serum glucose level to decrease to 11.1 mmol (200 mg/dL) and the urinary glucose level to decrease to 0. Dr. Banting declared his treatment a success and stated that this was "simply just the need for more insulin."

Bliss (10) credits James Dexter Havens as the first person to receive insulin in the United States. This was specifically affirmed by Eliot P. Joslin, the distinguished Boston diabetologist, who wrote to James Dexter Havens on 3 July 1957: "I think it is probable that you were the first in the United States to receive insulin" (11).

Dr. Banting also recorded the case in his notes (12) as follows:

> On May 17/22 evidences of acidosis were marked. The blood bicarbonate had dropped to 23 cc volumes per cent [10.3 mEq/L] an almost fatal level. All other clinical tests showed practically complete metabolic failure. The patient was anxious to die and end his misery. The administration of the extract was begun, at first in small doses then increased to 8 cc daily. The laboratory data since the use of extract was begun affords no index of the clinical improvement which has since taken place. The transformation has really been miraculous. In ____ days has been given ____ cc. Body wt has increased from ____ lbs to ____ lbs [*sic*]. He is now able to be about the house and takes a daily auto drive. The pain has disappeared from the legs. Opiates are no longer necessary. The mental picture has changed from one of despair to hope and tranquility.

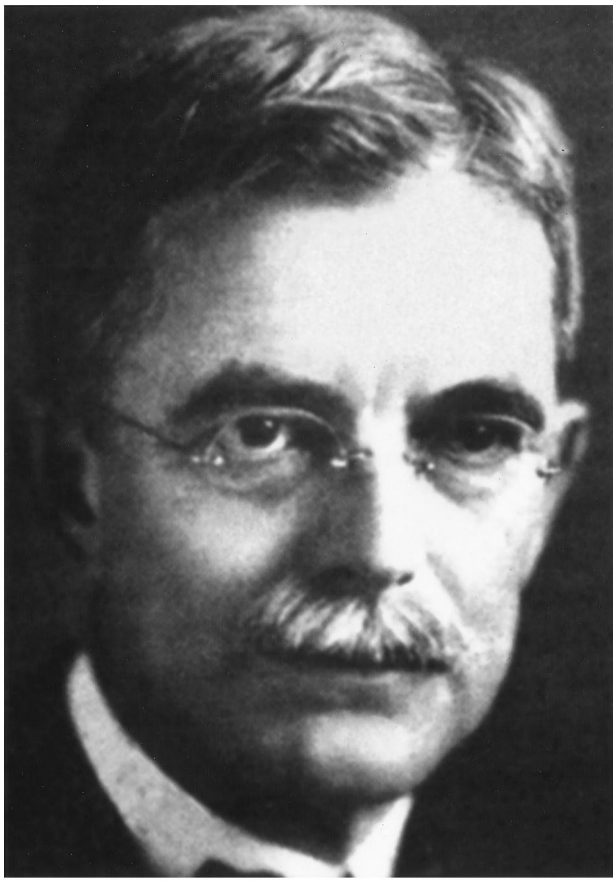
Continued arrangements were made for the porter of a Pullman car that left Toronto at 5:00 p.m. and arrived in Rochester at 11:00 p.m. to carry the insulin over the border daily. Dr. Williams would then administer the insulin daily to Jim. Dr. Williams continued to report Jim's progress and wrote to Dr. Banting (13):

> I shall send you today the last notes on the case. The patient is very much better. His appearance indicates much greater improvement than the laboratory studies suggest. . . . Jim now is up and about. The pain

Figure 2. **John Ralston Williams in his later years (*left*) and chalk drawing of Fredrick Banting (*right*).**

The chalk drawing of Dr. Banting was sketched by Dr. Williams on the cover of *The Bulletin* in 1946 (3).

Figure 3. **James S. Havens in his later years.**



Lawyer, congressman, legal counselor for Mr. George Eastman of the Eastman Kodak Company, and a loyal and caring father to a son who was gravely ill from diabetes mellitus.

> in his legs has diminished somewhat. The greatest advance noted is in his state of mind. . . .

At the height of good news of a successful recovery, Dr. Banting wrote to Havens and asked to see Jim and about the possibility of meeting George Eastman to gain support for his future endeavors. In a letter to Havens on 11 June 1922 (14), Dr. Banting indicated that the work was being hampered by a lack of funds and that he would like to meet with Eastman. Havens responded that "Mr. Eastman has never, I think, contributed to institutions to promote the general health. He has done a great deal for Rochester in that respect but I understand that his charities are confined to Rochester as far as health promotion goes . . ." (15). Dr. Banting took the ferry to Rochester on 15 June 1922 (16) and met with Eastman. After Dr. Banting left Rochester, Eastman indicated that he would like him to return to meet with George Hoyt Whipple, dean of the newly formed University of Rochester Medical School (17), so that Whipple could offer him a position at the institution. Dr. Banting politely declined. He wrote: ". . . the University here are giving me a good offer and . . . they are providing, in so far as they can, facilities for the further research" (18).

In a letter dated 22 November 1957 to Dr. Joslin (19), Jim Havens, then having received insulin for 35 years, wrote:

> I remember so vividly that when Dr. Williams reported to Dr. Banting that the first treatment seemed to have little effect, Dr. Banting came right over with some insulin in his pocket and stayed overnight—and he had me sugar-free in 24 hours, for the first time in many years! And of course I remember too how I sat in a chair and read in comfort for the first time, the pain that had been so incessant in my feet having gone. . . . My parents arranged a dinner for Fred with George Eastman, who was anxious to persuade Fred to come to Rochester and work at the new medical school here. When Banting told Eastman his first loyalty was to Canada, Eastman turned to my father and said 'here's a young man I admire, he has a backbone'. . . .

On 27 June 1922, slightly more than 1 month after insulin therapy was initiated for James Dexter Havens, Dr. Williams summarized Jim's progress in a letter to Dr. Macleod (20):

> I know you are interested in the use of the pancreatic extract on Mr. Havens' son. If one were to judge by the laboratory tests, he would say that very little were being accomplished. There is, however, very great clinical improvement. The patient feels much stronger and many of the disagreeable symptoms which he formerly had have disappeared. The blood sugar, before we began the use of the extract, ranged around 0.45 per cent [25.0 mmol/L]; the daily urinary ammonia exceeded 5 grams; the daily urine sugar, on a diet of approximately 900 calories [0.9 kcal or 3.8 kJ], ranged from 200 to 300 or more grams daily which means that he must have been making sugar out of his tissues.
>
> At the present time on a diet of approximately 900 calories [0.9 kcal or 3.8 kJ], carbohydrate 14 [grams]; protein 45 [grams]; fat 75 [grams], he excretes a little over 200 grams of sugar daily; the urinary ammonia averages 4½ grams per day; the plasma bicarbonate ranges from 33 to 38 volume per cent [15 mEq/L to 17 mEq/L]. The blood sugar averages about 0.36 per cent [20.0 mmol/L] and the patient eliminates an average of 4 liters of urine daily with a specific gravity of 1.035. . . .

By mid-July, Jim was receiving 8 cc of insulin daily. Shipping arrangements were changed once storing insulin became possible. Instead of daily shipments, the Toronto laboratory prepared 14 vials of insulin on Thursday afternoon and shipped the insulin on the train, car 553, per routine. Intense pain with the injections was the main side effect, which was usually accompanied by a transient rash.

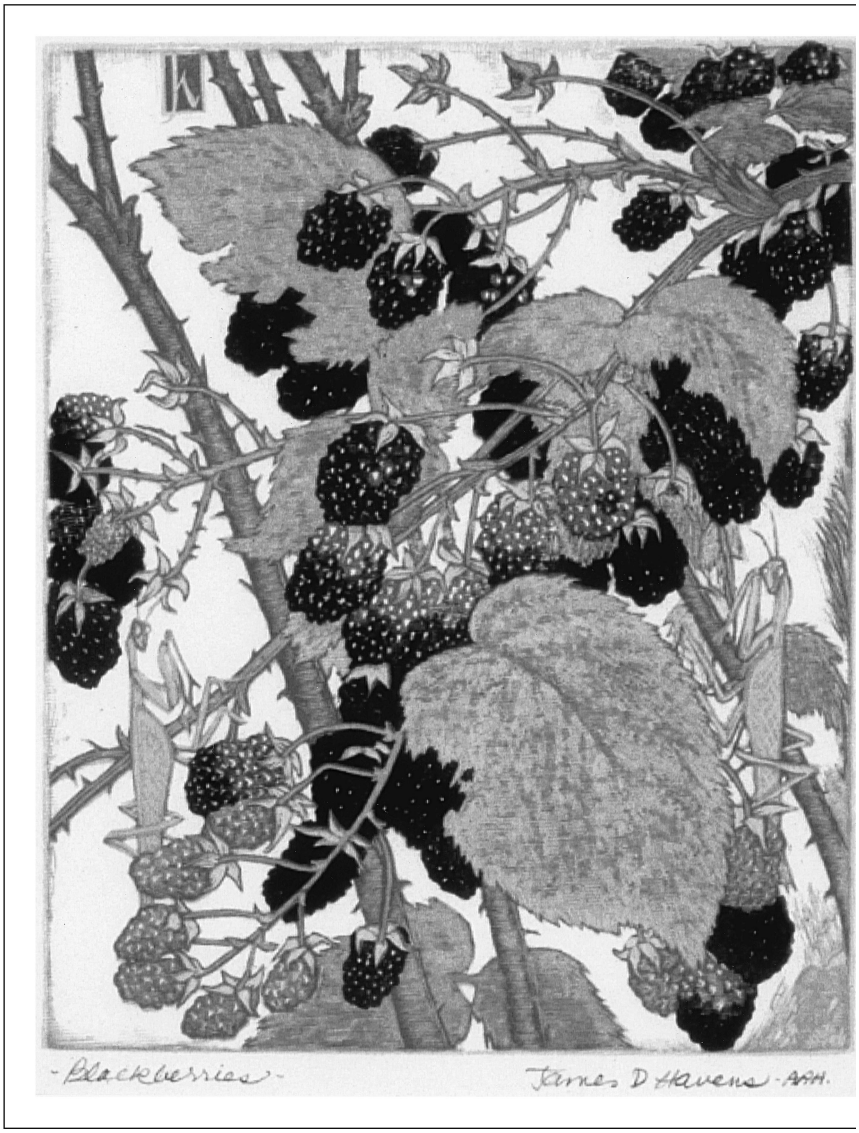
Occasionally, the injections would have to be discontinued for a couple of days for Jim to recuperate. During this period, his weight decreased to its original level when insulin therapy was initiated. On 11 July 1922, however, Jim had an intense reaction after an injection, which brought him to near coma and death. Dr. Williams wrote to Dr. Banting about the event (21):

> We have had a lot of trouble with Jim Havens. The injections became so painful that I had to discontinue them for a few days. Yesterday I thought that he would die on me. He appeared to be heading for coma. To avert it I injected 8 cc of the extract into the buttocks. He immediately complained of a sensation all over his body as though he had been poisoned, and of a profound burning in the stomach. I at once gave him by mouth a dram of soda bicarb in 12 ounces of water. This did not relieve the burning or apparently ease the symptoms, but in a few minutes he vomited more than 2 quarts of undigested food and fluid. Shortly after that intensely itching wheels [*sic*] broke out on his body. I thought he would die but he came out of it all right.

The correspondence from the files of the Havens family from the remainder of 1922 chronicles the patient's improvement and weight gain. He continued to have skin reactions, and on one occasion, he required an incision and drainage of an abscess. By the end of the year, Jim's weight had increased by 20 pounds.

On 14 April 1923, Dr. Williams wrote to Dr. Banting, summarizing his personal experience with insulin (22):

Figure 4. **Woodcut entitled "Blackberries" by James Dexter Havens.**



Exhibited in the Memorial Art Gallery of the Rochester Museum.

> You will be greatly pleased to hear about Jim Havens. When you saw him he weighed 74 pounds [34 kg]. He now weighs 110 pounds [50 kg], and he is the picture of health. One would never suspect that he is ill. There has been one very unfortunate result however from the use of the extract in his case. He apparently has an intense desire to get married. I wonder if you have observed that phenomenon in any of your cases. . . .

Jim Havens returned to his studies at the Mechanics Institute, now the Rochester Institute of Technology. He also went on to marry, father 2 children, and have a successful career as an artist. He became an acknowledged 20th-century master of the woodcut (**Figure 4**). His works are represented in the Metropolitan Museum of Art in New York City, The Library of Congress, The New York Public Library, The Brooklyn Museum, and other institutions. He received the American Artists Group award in 1955 and was a member of the National Academy of the Arts. At age 60 years, he received a diagnosis of colon cancer, and he died of its complications on 30 November 1960. In 2000, the Memorial Art Gallery of the Rochester Museum presented an exhibition of his works entitled "Woodblock Prints by James Havens: A Centennial Celebration."

From the University of Rochester Medical Center, Rochester, New York.

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