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What Was Known About Childhood Diabetes Mellitus Before the Discovery of Insulin?

James R. Wright Jr.

Abstract

It has been widely reported by historians that physicians were aware of two distinct types of diabetes mellitus by the 1880s, and that these were both similar to and the direct forerunners of type 1, juvenile-onset and type 2, adult-onset diabetes. The writings of prominent specialist physicians practicing just prior to the discovery of insulin in 1921–1922 were reviewed and there is little evidence that experts believed that adult and childhood diabetes were different. In fact, more than a decade passed after the discovery of insulin before diabetes in children and adults even began to be distinguished. Childhood diabetes was exceedingly rare in the early 20th century and diabetes was believed to be primarily a chronic disease of adults. It is interesting to speculate about what might have happened if the first pancreatic extract tests had been performed on adult-onset diabetics with insulin-resistant diabetes mellitus. Clearly, the results would have been disappointing and the discovery of insulin delayed. This essay explores how the test subject decision was made. It is fortuitous that a 14 year old boy with what was unequivocally type 1 diabetes was selected to be the first insulin recipient, and the rest is history.

Keywords

medical history, discovery of insulin, diabetes mellitus, classification, incidence, type 1 juvenile-onset diabetes, Leonard Thompson, Elliott P. Joslin, William Osler, Luther Emmett Holt

As we near the 100th anniversary of the discovery of insulin by Frederick Banting (1891–1941), Charles Best (1899–1978), J. Bertrand Collip (1892–1965), and JJR Macleod (1876–1935) in 1921–1922, we are reminded of the world-wide sensational reports from Toronto after 14 year old Leonard Thompson (1908–1935), emaciated, skeletonized, ketotic and near death, responded miraculously to the injection of pancreatic extracts (Figure 1).[1] How was it that the insulin research team in Toronto chose a youth suffering from what we unequivocally know now as type 1, juvenile-onset diabetes mellitus (DM) to test their pancreatic extracts? This specific question has never been addressed by any historical account. One might assume that there was a compelling medical reason and that the choice was intentional; this premise would seem to be supported by extensive literature stating that physicians were aware of two distinct types of diabetes mellitus (DM) by the 1880s, and that these were the direct forerunners of type 1, juvenile-onset and type 2, adult-onset diabetes. For instance, a recent chapter on the classification of DM in an important reference textbook matter-of-factly states:

> In the late 19th century, two categories were recognized, one category was described as occurring in young people with a short time course before ketoacidosis occurred and the second one was described as common in older and obese people.[2p23]

Departments of Pathology & Laboratory Medicine and Pediatrics and the Julia McFarlane Diabetes Research Centre, Cumming School of Medicine, University of Calgary, Alberta Children's Hospital, Calgary, Alberta

Corresponding Author:
James R. Wright Jr., Departments of Pathology & Laboratory Medicine and Pediatrics and the Julia McFarlane Diabetes Research Centre, Cumming School of Medicine, University of Calgary, Alberta Children's Hospital, 28 Oki Drive NW, Calgary, Alberta, Canada T3B 6A8.
Email: jim.wright@albertaprecisionlabs.ca

Figure 1. Leonard Thompson, the first patient to receive insulin, was photographed as a young man (shown here). While some sources have published before and after photos purported to be Thompson showing transformation from an emaciated, skeletonised child to a healthy child, these are not actually photos of Thompson but rather are photographs of 3 year old patient "J.L." (not shown here) Apparently, no one photographed Thompson's transformation, perhaps because it was so rapid and unexpected.

In more detailed historical accounts, this seminal insight is attributed to the French physician Étienne Lancereaux (1829–1910). who classified diabetes either as *diabète maigre* (thin diabetes) or *diabète gras* (fat diabetes) circa 1880.[3–6] However, extensive reading of the North American diabetes literature, from either before or even shortly after the discovery of insulin, suggests that there is little evidence that diabetologists recognized a DM specific to children or, in general, subscribed to the beliefs of Lancereaux, which, although these were correctly understood at the time of the discovery of insulin, have since been misinterpreted over the past 60 years. Having reviewed Lancereaux's original papers about *diabète maigre*,[7,8] it was surprising to find that all of his patients were 35–61 years of age and none had clinical histories resembling what we now recognize as type 1, juvenile-onset DM. In fact, all clearly had type 2, adult-onset DM, although some subsequently became emaciated. Lancereaux attributed *diabète maigre* to pancreatic calculi resulting in pancreatic atrophy, and there is no evidence that he was even aware of DM in children.[9] It should also be noted that Lancereaux's writings on *diabète maigre* predated interest in the islets of Langerhans as a potential source of the internal secretion of the pancreas; such theories began in the 1890s.[10–12] His autopsy studies make no mention of islets.[9]

As I will demonstrate in this essay, Thompson's choice was simply fortuitous and opportunistic, because at the time DM was considered to be primarily a chronic disease in adults. As we now know, many adult-onset diabetics are insulin-resistant. It is interesting to speculate about what might have happened if the first tests were performed on adult-onset diabetics with insulin-resistant DM. Clearly, the world-wide reports of a miracle cure in Toronto would not have happened and, considering the famously acrimonious relations between important members of the team,[1,13] the research might even have been abandoned.

So, What Was Known About the Classification of DM at the Time of the Discovery of Insulin?

While prominent physicians of the day sometimes wrote about DM in children, they did not distinguish the condition from that seen in adults. For example, Elliott P. Joslin (1869–1962), unequivocally one of the two most eminent diabetologists in North America at the time of the discovery of insulin, wrote a popular book *A Diabetic Manual for the Mutual Use of Doctor and Patient* in 1918. Joslin's book does not describe two distinct types of diabetes based on age of onset or presence or absence of obesity. Quoting the "thoroughly revised" second edition published in 1919: "The development of the disease may be gradual or acute, and with or without symptoms."[14] Joslin notes that about 60% of diabetics are obese and includes a table entitled "Overweight Usually Precedes Diabetes," which compares age ranges at the onset of DM (12–24; 25–29; 30–39; >39) and "average number of pounds overweight" at onset in each patient age group. While he does not include an age group of <12 years old, he considers adolescents and young adults in the 12–24 age group to be an average of 3 lbs overweight and those in the 25–30 age group to be an average of 54 lbs overweight. He concludes that "lack of exercise is, of course, a factor in producing the condition of overweight, and thus is an indirect cause of diabetes."[14] Joslin focuses on the importance of diet, mental relaxation, and physical exercise for treatment of the disease, and highlights the contributions of Frederick M. Allen (see below) to establishing proper dietary therapy. He appears to see diabetes as a single chronic disease entity but existing as continuums related to increasing age and body weight at onset.[14]

A review article Joslin published, which was directed at physicians, in the *Canadian Medical Association*

Journal in 1916 describes his extensive experience with treating DM. Joslin notes that when children die, it has been his experience that they always die of diabetic coma. However, he also notes:

> Next to children in the frequency of death from coma, strange as it may appear, were those of my cases who succumbed during the first year of the disease. The cause of death in 87 per cent of them was coma. But diabetes is a chronic disease and the first year of its course should be mild rather than severe, and in mild diabetes coma should find no place.[15p674]

Despite these observations, nowhere in this review does Joslin suggest that he believes that childhood DM is distinct.

Frederick Madison Allen (1879–1964), the other contemporary preeminent North American diabetologist, discounted Lancereaux's ideas in his 1919 textbook *Total Dietary Regulation in the Treatment of Diabetes*, which was considered the" bible" for the treatment of DM before the discovery of insulin.[16] Allen's thoughts on Lancereaux are summarized elsewhere.[9] Like Joslin, Allen did not believe there was a distinct childhood DM.

Allen and Joslin each treated many hundreds of diabetic patients before the discovery of insulin. Maybe, even if they had an inkling that there might be two distinct types of diabetic patients, each saw enough exceptions (ie, crossover patterns) so as not to be able to draw firm conclusions. Undoubtedly, most "adult-onset" cases remained sub-clinical for many years and the patients were not diagnosed until they became symptomatic, had long-term complications such as renal disease or blindness, or were hospitalized for another reason that acutely exacerbated DM. At this point, these "adult-onset" patients might be referred to a specialist such as Allen or Joslin – sometimes in a condition that was as severe as seen with "juvenile-onset" cases, and in these instances, could present with ketoacidosis. Another confounding factor might have been cases of maturity-onset diabetes of the young (MODY).

The matter was likely further compromised by the absence of routine laboratory testing in the decades prior to the discovery of insulin. During the early 20th century, laboratory testing was in its infancy. Routine laboratory testing was not an element of normal medical care until after World War I. In both the United States and in Canada, laboratory support became a requirement for hospital accreditation in the 1920s.[17,18] However, these events occurred during or shortly after the discovery of insulin. Suffice it to say, diabetic patients prior to the discovery of insulin were often referred from generalists to specialists without much clinical history or laboratory data.

Joslin, in his above-mentioned discussion of the high mortality rate due to coma in the first year of treatment, basically confirms this:

> Reference has just been made to a mortality rate of 87 per cent from coma among diabetics who die during the first year of the disease. Is the term "first year of the disease" quite accurate? It is meant to be accurate. I have most conscientiously tried to fix a definite date for onset of diabetes in all of my cases. But honestly would it not be more truthful to say the first year of the recognition of the disease? And herein lies a vast difference which gives rise to serious reflection, for it is in the first year of *recognition* of the disease that treatment is begun, and the highest mortality occurs.[15p674]

JJR Macleod, who a decade later would receive the Nobel Prize as co-discoverer of insulin, published a 1913 textbook *Diabetes: Its Pathological Physiology* which makes no suggestion that diabetes in children differs from that in adults. He does not mention Lancereaux or his two types of DM. He viewed the etiology of DM to be much more complex.[19]

William Osler (1849–1919), considered by many to have been one of the greatest physicians of all time,[20,21] published the first edition of his 1079 page long classic textbook *Principles and Practice of Medicine* in 1892. Osler, in his 11 page long chapter on DM, alludes to Lancereaux indirectly when discussing emaciation:

> In spite of the enormous amount of food consumed a patient may become rapidly emaciated. … Many, diabetics, however, do not show marked emaciation. Patients past the middle period of life may have the disease for years without much disturbance of health, and may remain well nourished. These are the cases of the *diabète gras* in contradistinction to *diabète maigre*.[22p300]

Osler also noted under a subtitle "Diabetes in Children": "The course of the disease, as a rule, is much more rapid than in adults."[22p300] Elsewhere he notes rapid onset in adults "after sudden emotion, an injury, or after a severe chill.[22p298] Later editions of Osler's *Principles and Practice of Medicine* do not really show additional insight. For instance, in his 14 page long chapter on DM in his 8th edition published in 1912 (and the last edition published while Osler was alive), Osler notes when describing DM symptoms: "Acute and chronic forms are recognized, but there is no essential difference between them, except that in the former the patients are younger, the course is more rapid, and the emaciation more marked [NB, This exact sentence also appears in the first edition.[22p298] but is now followed by:] I have twice seen acute diabetes

in the aged."[23p432] Under the heading "Diabetes in Children," Osler notes that it is uncommon and repeats the sentence "the course of the disease is, as a rule, much more rapid than in adults."[23p430]

In the 14 page long DM chapter in the 9th edition, the first edition after Osler's death [which was co-authored by Thomas McCrae (1870–1935)] and the last edition before the discovery of insulin, the above-mentioned sentence about rapidity in children is repeated again but this time is immediately followed by "While the disease is usually severe there are not infrequent cases of a mild type."[24p426] Clearly, Osler, although he used Lancereaux's terminology in the context of emaciation, did not recognize two distinct types of DM.

Luther Emmett Holt (1855–1924) was one of the first pediatricians in North America (Figure 2).[25] In the first edition of his classic 1,200 page long textbook *The Diseases of Infancy and Childhood*, published in 1897, Holt includes a 1 1/2 page long chapter on DM and cites European literature stating that DM is exceedingly rare in children under 10 years of age – representing between 0.14% and 0.59% of all cases of DM.[26] In fact, in Holt's first edition, there is no evidence that he had ever seen a case. By the second edition published in 1904, Holt has treated some patients, but not enough for him to have formed any of his own opinions on the frequency of DM in children.[27] His text is identical except that he adds these new sentences on prognosis:

> The cases which I have seen have all terminated unfavorably. In a given case the prognosis, as to the duration of the disease, is rendered much worse by the presence in the urine of diacetic and oxybutyric acids. This condition is even more serious than is a high percentage of sugar; that the patient will then live more than three months is highly improbable.[27p1136]

In the 6th edition published in 1911, he notes:

> Among the etiological factors, heredity is one of the most important.... Inherited gout, insanity, and nervous diseases generally may be looked upon as factors in the production of diabetes. Several of the cases reported in children have been preceded by injuries received upon the head. In a number of my own cases the disease has followed the consumption of large quantities of sugar for a long time. Often no adequate cause can be found.[28p1091]

By the time of his 1920 edition, Holt includes an almost three page long chapter on DM. Holt notes that "it is a rather infrequent disease in children,"[29p1155] but also suggests that most 19th century sources have likely somewhat underestimated its frequency, and that he had personally seen 26 cases during his busy 32 year career in New York City. He indicates that the course of the disease is more rapid in children and that wasting is common. He notes that "the indications for treatment in children are the same as in adults,"[29p1157] and he advocates dietary therapy. Holt does not suggest that childhood DM is a distinct form of DM in any of five pre-discovery of insulin textbook editions reviewed. In fact, the wording in these early texts changed only minimally indicating that the knowledge base on childhood DM was not increasing.

In the 8th edition published just as insulin was being discovered in 1922, Holt and his co-author, John Howland (1873–1926), pediatrician-in-chief at Johns Hopkins Hospital, include a 3 1/4 page long chapter on DM.[30] Together, they have seen 50 cases. The identical text citing European studies suggesting that childhood DM represents between 0.14% and 0.59% of all cases of DM is followed by:

> More recent statistics have shown that the proportion of children under ten among diabetics is not so small as would be indicated by these figures. Joslin has reported 58 cases in children under 10 years among the diabetics under his care, or 4.9 per cent of the total number... Joslin believes that the increase in the number of diabetics in children is not the result of an increased

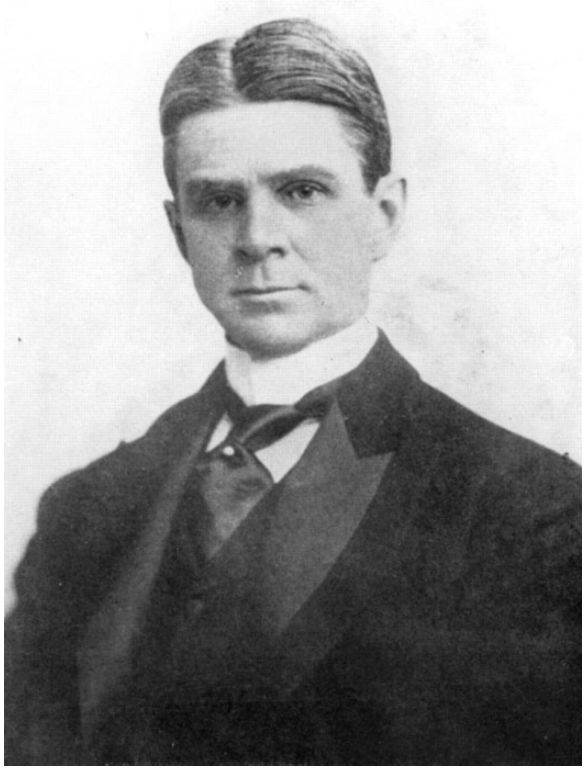

Figure 2. Luther Emmett Holt (1855–1924). https://fn.bmj.com/content/83/3/F221

> incidence of the disease but is due to better methods of diagnosis.[30p1107]

The 9th edition in 1926, the first after the discovery of insulin, now includes instructions on the treatment of children using insulin but is still only 3 1/4 pages in length.[31] Clearly, the progression of the DM chapter through nine editions suggests that childhood DM is sufficiently uncommon that a detailed chapter is not warranted, even after the discovery of insulin. Pediatricians Holt and Howland considered DM to be primarily a chronic disease of adults.

Similar to internists and pediatricians, pathologists who studied the pancreas extensively in the decades before and after the discovery of insulin did not believe there were two types of DM.[12,32] The rare autopsy studies on pancreata of diabetic children were highly valued simply because these provided "the best examples of pure, uncomplicated [DM]... since their organs are free from the various degenerative changes so often encountered in adults."[32p99] Such studies were "not... motivated by a hypothesis that the disease in children could constitute a separate disease entity"[33p132] It should be noted that lymphocytic infiltration specific to islets, later named insulitis, was not recognized as being associated with DM onset in young people until after the discovery of insulin.[33]

Francis Carter Wood (1869–1951), a clinical pathologist at Columbia University in New York, describes three clinical types of diabetes: the mild, the intermediate, and the severe forms in his 1905 textbook. His classification was based on severity of symptoms and results of urine testing for biochemical abnormalities. Age of onset and presence or absence of obesity played no roles in his classification scheme.[34]

At this point, it is also appropriate to specifically debunk a myth. Banting has often been depicted by the media, and even in some historical accounts, as having begun his research because he wanted to find a cure for childhood DM; this is not true. Prior to beginning his research in 1921, Banting had little knowledge of or even interest in DM. He openly admitted this in 1940, stating: "I heard of people mostly well on in life dying in a coma and believed there was nothing one could do ... There was no such thing as a diabetic in any ward in my surgical experience."[1p48] While Banting had worked as a surgical resident for over six months at Toronto's Hospital for Sick Children (1919–1920), there is no evidence that Banting was even aware of childhood DM when he began his research.

In summary, there is little evidence that physicians believed that there were two distinct age of onset-based types of DM. Even after the discovery of insulin, enhanced classification of DM was not immediately possible. The concept of type I (juvenile-onset, or insulin-dependent) and type II (maturity-onset, or non-insulin-dependent) DM evolved over a matter of many decades. In 1931, Wilhelm Falta (1875–1950) in Vienna observed that some diabetics were more sensitive to the glucostatic effects of insulin than others.[35] By 1936, Harold Himsworth (1905–1993) in London further characterized insulin-sensitive and insulin-resistant DM.[36] This was further reinforced in the mid 1950s when it became clear that the newly developed oral hypoglycemic agent tolbutamide "had no efficacy in the diabetes of young children... Orinase seemed to work best in older, overweight patients."[37p90] In 1964, the World Health Organization (WHO) Expert Committee formally classified DM based upon its age of onset (ie, juvenile-onset vs maturity-onset). From 1974 to 1976, the etiological heterogeneity of ideopathic DM became clear, and type 1 DM was recognized as an autoimmune disease.[38] Currently, the American Diabetes Association classifies DM as type 1, type 2, other specific types (with at least 8 sub-categories), and gestational DM.[2]

How Is It Possible That Nothing Was Known About Childhood DM Before the Discovery of Insulin?

The foregoing has demonstrated that almost nothing was known about what we now call type 1 DM until a decade after the discovery of insulin and that there is no compelling evidence that pre-insulin era internists, pediatricians, diabetologists, or laboratory physicians considered childhood DM to be distinctly different. So, how is it possible that almost nothing was known about childhood DM at the time of the discovery of insulin, since from a present day perspective, the disease is so distinctly different?

First of all, it was exceedingly rare. Eminent British diabetologist Edwin Gale, using highly credible European and North American historical sources, has demonstrated convincingly that childhood DM was rare well into the 20th century; its incidence/prevalence began to rise steeply only in the latter half of the 20th century.[39] So the next obvious question is whether childhood DM was really less common a 100+ years ago or was the diagnosis missed?

In some instances, the diagnosis would have been missed. Prior to the 1840s, DM could only be diagnosed by tasting a patient's urine; undoubtedly, the threshold for invoking this test was high. In specialized centers, "reducing agents such as glucose" could be biochemically detected in the urine by the 1840s and blood glucose could be estimated by the onset of World War I.[12] However, routine laboratory testing was not an element of normal medical care until after WWI. In both the United States and in Canada, laboratory support became a requirement for hospital accreditation in the 1920s and laboratory medicine flourished after that.[17,18]

In fact, Babies Hospital in New York City, where Holt was pediatrician-in-chief and Martha Wollstein was the pediatric pathologist,[40,41] was the only children's hospital in North American with an in-house pathology department before the discovery of insulin, with its bacteriology laboratory opening in 1896 and other laboratory services coming on line over the next few years. Holt's private office used the hospital's laboratory for testing pediatric patients.[40] So after 1900, Holt was perhaps best positioned to diagnose DM in children, and, hence, his first personally diagnosed cases occurred between the first and second editions of his book. Since DM was believed to be exceedingly rare in children, most physicians were unlikely to even consider the diagnosis.

While it is possible that, as Joslin suggested, underdiagnosis was the primary reason childhood DM was perceived to be rare before the discovery of insulin, this cannot easily explain 19th century European data that the percentage of childhood cases (< 10 years old) relative to total cases was between 0.14% and 0.59%. Even if many childhood cases were missed because pediatric patients died quickly, DM in adults would also have been vastly under-diagnosed in the absence of routine laboratory testing.

The alternative is that DM in children really was exceedingly rare prior to the discovery of insulin. It is widely recognized that the incidence of type 1 DM, an autoimmune disease directed at insulin-producing beta cells in the pancreatic islets, has been rapidly increasing since the latter third of the 20th century;[39] its global incidence is currently increasing about 3% a year.[42,43] This has been linked to decreased exposure to a variety of infectious agents during childhood (ie, the hygiene hypothesis) similar to the "dirt hypothesis" for the increasing incidence of asthma; other theories for the spiking incidence of type 1 DM include the viral hypothesis (ie, exposure to a variety of viruses may initiate or accelerate beta cell autoimmunity), the vitamin D deficiency hypothesis, the breast-feeding vs cow's milk hypothesis, and hypotheses related to other environmental triggers as well as reduced natural selection.[43,44] Extrapolating backwards from the 1920s which was the baseline for many of Gale's historical sources, maybe the combination of genetic factors and environmental triggers before the turn of the last century resulted in the incidence and prevalence of childhood DM being significantly and substantially lower than the low levels Gale documented for the early 20th century. There is simply little available data.

In addition to the true incidence/prevalence of childhood DM being very low, many cases were never diagnosed. In the early 20th century and before, medical care for children was limited and many were expected to die during childhood, usually of infections but also of other causes, including unintentional injuries. Parents often compensated by having many children. Since a significant percentage of children were expected to die, relatively little effort was exerted to determine why. Autopsies were rarely done, especially since most deaths were outside of hospitals. Even those dying in children's hospitals would not normally have autopsies as 19th century children's hospitals were very small and did not have staff pathologists. Pediatric specialists were also rare and so most children, if treated by a physician at all, were treated by generalists. Since DM was rare in children, physicians were unlikely to see sufficient cases to make repetitive observations from which generalizations could be made. As noted earlier, even Emmett Holt, who had personally seen 26 cases during his 32 year career, had not speculated that DM in children was fundamentally different than DM in adults. For all of these reasons, little was known about DM in children.

Discovering That Insulin Works in the Absence of Knowing of Childhood DM: Why Was Leonard Thompson Selected as the First Test Subject?

Since childhood DM was both rare and not recognized to be different than adult DM, how was it that the insulin research team in Toronto chose a youth to test their pancreatic extracts? Was this just good luck? DM was believed to be primarily a chronic disease of adults and since its incidence in children was low (and its prevalence, because of its rapid mortality, even lower), why did they not choose an adult with DM? Walter Campbell, the clinician at Toronto General Hospital (TGH) who treated Thompson, explained 40 years later. Thompson was chosen, not because of his age, but because he was available, ketotic, and near death. Thompson had been recently referred to Campbell by a colleague and he told the colleague "if the boy was 14 years I thought I had pull enough to get him into the General Hospital"[45p1057] [ie, where he had privileges and ran Ward H, the diabetes clinic, as opposed to Hospital for Sick Children, which did not have a diabetes clinic[46]]. He was admitted to the diabetic ward about a month before insulin testing was begun, and so he was available. According to Campbell, the rational for his selection was:

> We thought it should be tried on the most severe case we could find, for two reasons. If nothing of value happened, their number was up anyway and, more important, if effective in such patients, the results could not be gainsaid.[45p1057]

There were perhaps other considerations which Campbell did not disclose. Unlike very sick adults with

chronic diabetes, Thompson would not have had multiple other co-morbidities to confound their results. Perhaps, practicality played a role as well; this 14 year old boy had been on a "starvation diet" for over two years as was typical before the discovery of insulin; such diets lowered blood sugar levels and delayed ketosis and diabetic coma, which usually combined as a terminal event. Thompson was emaciated and weighed only 65 lbs. The Toronto investigators, when developing their pancreatic extracts, had only extremely small quantities available; in fact, except for perhaps some covert self-experimentation by Banting and Best, they had never injected any preparation into an animal larger than a dog [NB, on December 20, 1921, Banting gave an oral dose of an extract to his diabetic former medical school classmate Joe Gilchrist (1893–1951) with "no beneficial result."[1p102]]. Likely, Thompson's small size played a role in the choice. Regardless, the history of the discovery of insulin would have been very different if they had tested their extracts on a very sick type 2, insulin-independent, adult-onset diabetic patient.

The choice was not intuitive in the absence of knowing there are differences in childhood and adult-onset DM. Michael Bliss' *The Discovery of Insulin* opens with an extensive discussion of some of the many investigators who had previously made pancreatic extracts in an attempt to cure DM. While the vast majority worked exclusively with animals, there were rare publications of small trials involving human patients. Bliss highlights two.[1] John Rennie and Thomas Fraser at the University of Aberdeen in Scotland performed a clinical trial from 1902 to 1904[47]; their extracts were made from teleost fish islets (NB, teleost fish have anatomical separation of their exocrine and endocrine pancreata and 20 years later their islets were shown by JJR Macleod and two medical students to be a source of highly pure insulin[48,49]). Their first patient was an 18 year old who, after a two year downward course, was close to death. These investigators had just made their islet extract, and he was the only patient available. According to Rennie and Fraser: "This was a hopelessly bad case, in which all methods of diabetic treatment had effected no result. Little was expected of islet treatment in such a case, but it was the only case available at the time."[47p10] Unfortunately, they fed, rather than injected, their islet extracts into this patient. The treatment was unsuccessful and the patient died a little over 4 months into the treatment. The mean age of their other four preferred (less severe) patients was 49.5 years.[47]

Georg Ludwig Zuelzer (1870–1949), a German internist, treated patients in Berlin with pancreatic extracts which he named "acomatol" beginning in 1906.[1] His first patient was 50 years old, and only one of his next five patients was under 27 years old (the mean age of his adult patients was 48). He had mixed results that were promising enough to obtain a patent and a pharmaceutical partner.[1] Clearly, his patient selection could have adversely affected his results and his pharmaceutical support eventually evaporated. Of note to our profession, Zuelzer was the father of Wolfgang (Wolf) Wilhelm Zuelzer (1909–1987), a Detroit pediatric pathologist trained by Sidney Farber and who trained Bill Newton.[50]

These examples demonstrate that it was not intuitive to pick a pediatric patient or even a very sick patient. Furthermore, the prevalence of what we now recognize as type I, juvenile-onset DM was so low that most extremely sick patients were, as Banting so distinctly recalled, poorly-controlled adult-onset patients. Clearly there was a huge element of luck that the first patient picked was as susceptible to the glucostatic effects of insulin as the depancreatized dogs that Banting and Best has been experimenting on just months earlier.

Leonard Thompson's life was extended 13 years; during this period, he had good and bad intervals and was treated for several episodes of ketoacidosis and hypoglycemia. While it has often been reported that Thompson had a "normal life" and that he died of injuries sustained from a motorcycle accident, this is not true, as he was hospitalized for ketoacidosis and died as an inpatient at TGH.[46] His autopsy showed that he died of bronchopneumonia with some longer term complications of DM.[51]

Happily, by mid-1922, other diabetic youths were being treated in Toronto, with children of two wealthy and powerful Americans at the front of the queue.[1,52,53] By August of 1922, Eli Lily was providing limited insulin samples for research purposes and shortly thereafter, diabetes researcher H. Rawle Geyelin (1883–1946) and colleagues from Presbyterian Hospital in New York City, published a study on nine diabetic children, 2 to 16 years of age, showing astonishingly good results with before and after photographs.[54] The rest is history. The efficacy of insulin in childhood DM had been firmly established in less than one year.

In retrospect, it is likely that the hype around the initial exceedingly well-publicized and dramatic success stories which focused on pediatric diabetic patients, which was further subconsciously colored by the understanding of the nature of childhood DM that evolved in the mid 20th century, has led medical historians to the incorrect notion that clinicians at the time of the discovery believed that childhood DM was distinct, and that insulin should be tested on a pediatric patient. However, as demonstrated in this essay, none of this was obvious 100 years ago when the Toronto insulin team selected its first patient.

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ORCID iD

James R. Wright https://orcid.org/0000-0003-1497-5741

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