

The Indianapolis Literary Club 2014-2015: 139th Year

“From Thebes to Indianapolis: The Sweet Taste of Success.”

Essayist: Stephen J. Jay M.D. Read on Tuesday, 8:00 P.M., 20 January 2015, at the regular meeting of the Indianapolis Literary Club, Park Tudor School, Indianapolis

“When Nature has work to be done she creates a genius to do it.”

---Emerson

“In all things sought to see the Whole, Brooked no disguise; And set his heart upon the goal, Not on the prize.”

---William Watson, In Laleham Churchyard, Aug 18, 1890, stanza 11.

“Knowing is not enough; we must apply.

Willing is not enough; we must do.”

---Johann Wolfgang von Goethe (1749-1832). *Wilhelm Meisters*, 1830

“Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine...”

---Aretaeus, the Cappodocian, London: Sydenham Society, 1865, p238

“Three horses draw the diabetic chariot and their names are diet, exercise and insulin.”

---EP Joslin, *A Diabetic Manual*, 1917

“In insulin there is glory enough for all.”

---Lewellys Barker, Johns Hopkins. At Toronto’s 1923 Nobel Prize dinner. *Toronto Star*, 1923.

Acknowledgments

Kevin Armstrong, President, Methodist Health Foundation, Indiana University Health, shared the excellent history of Methodist Hospital by Kenneth E. Reed, editor and Edward A. Leary, author: History of Methodist Hospital of Indiana Inc. 1984. This book includes Methodist's general role in the research and development of insulin.

Paul Boyce M.D., (1939-2014) Dr. Boyce, a prominent endocrinologist in Indianapolis, practiced at Methodist Hospital and contributed to the Methodist Hospital Joslin Diabetes Center. In a conversation on June 25, 2013, Dr. Boyce shared stories with me regarding his remembrance of John Henry "Jack" Warvel Sr., MD (1893-1967) and Dr. Warvel's relationships with George Henry Alexander Clowes. Dr. Warvel Sr. played tennis in the mornings with Dr. GHA Clowes. Dr. Warvel's wife, a nurse at Methodist, gave the first dose of insulin to a patient there. When the new 'wonder drug' was available, family physicians from around Indiana would send their patients to Dr. Warvel, a pathologist, who would arrange for them to receive insulin. Dr. Boyce reflected on the remarkable contributions that Drs. Warvel, father and son, to the care of countless persons with diabetes mellitus when the knowledge of how to use insulin was in its infancy. Dr. Warvel's son, John Henry "Jack" Warvel, Jr. (1930-2009) practiced at Methodist Hospital and founded the Indianapolis Diabetes Association.

Kathy Clark, Indiana Historical Society, processed the Clowes Family Collection (Finding Aid: <http://www.indianahistory.org/our-collections/collection-guides/clowes-family-collection.pdf>) Ms. Clark introduced me to this Clowes Collection (1842-1998); she and Dr. Alexander Whitehill Clowes (grandson of GHAC) are organizing the Clowes papers that were recently given to the Historical Society by the Clowes family; they are researching these papers for a book they are publishing.

Alexander (Alec) Whitehill Clowes and companion Susan E. Detweiler MD, Clinical Pathologist at University of Washington Medical Center offered insights into George Henry Alexander Clowes, Sr. They were pleased to receive from me a written exchange deposited in the Lilly Archives between George Henry Alexander Clowes, Sr. and JK Lilly from 1945 that reveals the depth of their respect and friendship with one another.

Randy Couch, IU Health, Indianapolis, IN. Coordinator of Supply Chain Office Services kindly provided access (December 2014) to about 200 boxes of Methodist Hospital archived records of the medical staff at Methodist and Board of Trustees Minutes; these records are being reviewed to search for evidence of Methodist-Lilly-Toronto interaction during the insulin trials circa 1922-23. These materials are to be organized, cataloged and deposited at the Indiana Historical Society.

Justin Davis, Indiana Division Librarian, Indiana State Library, did extensive searching in newspaper archives, the Indianapolis Medical Society Bulletins and other holdings for information regarding Frederick Banting's meeting with the Indianapolis Medical Society in 1921. The internationally known hypertension researcher, Irvine Page MD, who was born in Indianapolis and worked at City Hospital and Eli Lilly, mentions this meeting in his 1988 Memoir—a 15 line piece in an Indianapolis newspaper describing Banting's et al. discovery of insulin. We have yet to find the clipping Dr. Page referenced in his Memoir.

Nancy L. Eckerman, Indiana University School of Medicine, Ruth Lilly Medical Library, Special Collections Librarian, History of Medicine and Nursing, (recently retired) provided invaluable assistance in researching archives for details regarding Methodist Hospital's role in the insulin story.

Dan Evans, President and CEO Indiana University Health and past Chairman of the Board and CEO of Methodist Hospital, provided access to Methodist Hospital Archives. Although incomplete for the period 1920-1924, both Trustee and Medical Staff Minutes provided useful information regarding Methodist's role in the University of Toronto and Eli Lilly and Company interactions during the insulin clinical trials at Methodist.

John Lechleiter, President and CEO Eli Lilly and Company kindly provided access to the Lilly Archives and Archivist Michael Jarrell.

Ray Gnat, former Director, Indianapolis-Marion County Library and member Indianapolis Literary Club, brought to my attention the paper: "The Story of Insulin" by George H.A. Clowes, read before the Indianapolis Literary Club, Dec 1, 1924 (Editor's error, it was 1923); the paper was previously read before the Association of Life Insurance Presidents, NY City circa November 20, 1923. This paper was previously unknown to our Indianapolis Literary Club and was found by Mr. Gnat in another section of the IHS Archives. This paper was unknown to historians of the insulin story.

Mike Jarrell, archivist, Eli Lilly, kindly provided access to documents relating to George Henry Alexander Clowes, not otherwise accessible in the Indiana Historical Society Clowes Family Collection (1842-1998). He shared keen insights into Dr. H.A. Clowes and the early years of Eli Lilly's response to the urgent need in 1922 for a safe and efficient production facility to meet escalating U.S. and global demand for the 'miracle' drug, Insulin.

Kristi Osborn, formerly with Methodist Hospital (Indianapolis) House Staff Alumni Office provided access to historical records, the History of Methodist Hospital Graduate Medical Center (Volume 1: 1908 -1953 and Volume 2: 1954 - 1971. Ms. Osborn was intimately involved in the preservation of historical documents from the 1920s that relate to the role Methodist Hospital played in early clinical trials of insulin.

Matt Rohweder, University of Toronto Library, directed me to the special collections that hold minutes of meetings of the Insulin Committee that monitored the University of Toronto's management of the discovery, production, and clinical use of insulin for treating diabetes mellitus. These documents are difficult to access; some are not available for review.

Edward Shorter PhD, University of Toronto, a classmate from Wabash College, and medical historian who has written a text (Partnership for Excellence, Medicine at the University of Toronto and Academic Hospitals, 2013 University of Toronto Press) that includes history of the discovery of insulin at University of Toronto, offered excellent advice regarding research in this area and suggested I talk with his associate, Dr. Bliss, author of the definitive history of the discovery. I shared with Dr. Shorter a rare article, *The Story of Insulin* by George H.A. Clowes, read Dr. Clowes before the Indianapolis Literary Club, Dec 1, 2003; this article and essay had escaped attention of historians.

Joyce M. Hammon, Executive Assistant, IU Health graciously provided help in securing Methodist Hospital Board of Trustees minutes in the 1920s—an enormous effort taking months because these documents were held off campus in storage for many years.

Stephen Towne, Indiana University Purdue University Indianapolis (IUPUI Library Archivist kindly and successfully searched the IUPUI digital archives for images of John A. MacDonald and other physicians involved in the Methodist insulin trials in the early 1920s.

Title: *From Thebes to Indianapolis: The Sweet Taste of Success.*

Introduction

Marcus Aurelius (121-161 CE) in his Stoic tome said, “Time is a river, the resistless flow of all created things. One thing no sooner comes in sight than it is hurried past and another is borne along, only to be swept away in its turn.” This is an apt metaphor for the flow of knowledge from ancient times to the period October 31, 1920 to December 10, 1923, the focus of tonight’s essay.

History

Near Thebes on the Nile, in 1872, Georg Ebers acquired a papyrus from the First Dynasty, 5,000 years ago, that offered remedies, “to eliminate urine which is too plentiful.” (74; 75; 87; 105; 122; 135) Aretaeus of Cappodocia (130-200 CE), the Greek physician of the 1st century, named the condition *diabetes* and said, “Patients never stop making water ... as if from the opening of aqueducts.” (74; 107; 109; 134) Remedies then included purges, poultices, and juice of acacia.

Mellitus was added to the word *diabetes* by Willis in England in 1674 after rediscovering the sweetness of urine, observed by ancient Hindu physicians who found insects attracted to the *honey urine* of sufferers. (94; 104) In 1776, Dobson heated two quarts of urine, found sugar residue, and presented his findings to the medical society of London. (93; 128) By 1817, in London, treatment with bloodletting was recommended. (138)

In the 19th c., a person dying of diabetes was often found to have a damaged pancreas. (61; 134) In Berlin, at Virchow’s institute of pathology, the student, Langerhans, described (1869) clusters of unique cells in the pancreas, called ‘islets’. Their function was unknown. German physiologist, Oskar Minkowski, (1864-1909) in 1889 produced diabetes in dogs by removing their pancreas. (115; 116; 117; 119) But, tying off the ducts through which pancreatic enzymes flowed to the gut caused minor digestive problems—not diabetes. The pancreas must have at least two functions: promote digestion and regulate glucose.

Schafer in Britain (1850-1935) proposed that the islets of Langerhans secreted a substance that affected metabolism of carbohydrates—he called it *insuline* from Latin, *insula* or *island*. (131) In 1906, Dr. Zuelzer (1870-1949) in Berlin injected pancreatic extract into human diabetics; their urine sugar decreased but toxicity of extract limited its use. (3:28-32, 177; 97; 134)

By 1920, the ‘summit’ of a cure for diabetes was within reach. (124; 130) But daunting tasks remained at base camp: prove extract works, purify it, and produce and distribute the drug to diabetics.

Aims

My aims this evening are threefold:

1. To suggest that the successful search for a cure for diabetes depended on the novel collaboration of a university, industry, and clinical research centers that shared values, including commitment to science-based change and a tenacious pledge to relieve suffering.
2. To submit that the confluence of unique leaders in Toronto and Indianapolis, including Dr. George Henry Alexander Clowes Sr., J.K. Lilly, and Eli Lilly, Jr. was central to the successful, if often contentious, negotiations among participants.
3. To propose that today's leaders might apply lessons learned from the historic events in the 1920s to address our 21st c diabetes pandemic.

Discovery

The proverb, "Necessity is the mother of invention" fit the often fatal diabetes problem in 1920. (3; 78; 113)

The challenge fell to an unlikely foursome in Canada, Frederick G. Banting (1891-1941), 29, a jobless surgeon, who was a decorated soldier, wounded at Cambrai in 1918; Charles H. Best (1899-1978), a 22 year old Canadian-American student who had served in the Canadian Army Tank Battalion; James B. Collip (1892-1965), 27, a biochemist on a Rockefeller Scholarship to work at the University of Toronto with Professor Macleod; and John R. Macleod (1876-1935), 44, a Scottish Professor of Physiology. (4: 52-58; 6:11-117; 72; 73: 49-56; 77; 78; 81: 87; 110; 124)

Banting, an aspiring artist, lit the fire of innovation. He read of a patient with a pancreatic duct stone obstruction that destroyed the digestive enzyme cells but not the islet cells. (6:56-63; 79; 85) After reading the paper and retiring, Banting awoke at 2 AM on October 31, 1920, and wrote in his journal: "Diabetes. Ligate pancreatic ducts of dog. Keep dogs alive till acini (enzyme cells) degenerate leaving islets. Try to isolate the internal secretion of these to relieve glycosuria (sugar in the urine.)" (6: 61-2; 108)

Banting proposed experiments to Dr. Macleod who reluctantly offered him a small laboratory, ten dogs, and medical assistants. Two students applied and Charles Best and Clark Nobel flipped a coin for the position; Best won the toss.

From April 14 to December 1921, Banting and Best injected pancreas extracts into diabetic dogs; their blood sugars decreased. After seven months of research, they prepared extract for humans and injected themselves, suffering minor side effects. (61)The first diabetic patient to receive extract was Leonard Thompson, a pale 14 year- old boy weighing 65 lbs.; he didn't respond and there were side effects. (3: 112-3; 6: 138-9; 51) Purer extract was needed to save Leonard and Dr. Collip prepared it. Injections January 23, 1922, were effective, the first successful test of pancreatic extract in humans. (3: 121; 10; 72: Jan 23, 1928)

Banting and Best published favorable results. (51; 72: Feb 27 1922; 77; 78) The news spread quickly. (53; 54; 55; 72: Mar 22 1922) Dr. Macleod, supervisor of the lab, turned full- time to this promising research (February 1922) and diabetes clinics were established at three Toronto hospitals (3: 12; 65; 72: April-May 1922)

On May 3, 1922, in Washington D.C., Macleod, announced to the world they had discovered insulin. (3: 127-8) He received a standing ovation. Banting and Best boycotted the meeting, saying the trip was too expensive.

Demands for insulin increased dramatically. Toronto needed a partner in insulin production. What led to Toronto's collaboration with Lilly?

Toronto and Lilly Collaborate

On Christmas Day, 1921, Dr. Clowes attended a meeting of diabetes experts, at Yale University. (3: 104; 39; 136) Clowes seemed to have no reason to attend as an Englishman with interests in cancer and working for industry. (6:124-136) Banting presented his findings but seemed "paralyzed" with fear before this prestigious group; he failed to convince researchers that his dog studies proved the internal secretion of the pancreas. Dr. Clowes, however, told Dr. Macleod that Banting's evidence was convincing and asked Macleod to consider Lilly as a partner in producing the extract. (6:133-34; 112: 56-57) Macleod was suspicious of commercial interests but with tensions rising, he agreed to collaborate. (3: 106,137, 171; 72: April 3 1922) On May 25, 1922, Dr. Clowes and Eli Lilly, Jr, met with the University for three days in the King Edward Hotel in Toronto and wrote an agreement to produce insulin. (3: 137-139; 112, 56-57; 72: May 30 1922) Toronto gave Lilly a one-year exclusive license, a head- start that would reshape corporate Lilly. (3: 178-81) On June 2, 1922, Toronto researchers, Collip and Best came to Indianapolis and informed Lilly chemists how to make insulin. (3: 140) Lilly prepared to scale up to supply researchers and clinicians with the drug. (9; 72: July 1922; 113)

Clowes reflected on the Yale meeting 25 years later and said that though Banting's research presentation was modest, "anyone who was at all cognizant with the subject must have realized that a great discovery had been made." (3: 106) A consummate scientist, Clowes had quickly recognized the sentinel discovery and hastened the agreement to produce insulin. (37; 39) Clowes and Banting developed a close relationship during these turbulent times of bitter disagreement over who discovered insulin, a friendship that would benefit all. (3: 193; 124)

The challenge was to assemble a team to organize large scale insulin production and develop research sites to prove its safety and effectiveness. (3: 137,149-50)

The Team

The team consisted of the Toronto group, Lilly, and a core of prominent diabetes specialists. Toronto, called a "beastly place" by American poet John Dos Passos was, in 1922, anything but 'beastly.' The University and teaching hospitals were excellent. (132: 8-53) But, Toronto lacked experience and capacity to mass produce pharmaceuticals. (3: 132)

Lilly, had been making pharmaceuticals for 46 years. (3: 128) To strengthen its ties with the scientific community, J.K. Lilly, Sr., in 1919, established a department of Experimental Medicine to help Lilly collaborate with universities to bring new drugs to international markets. (112)

The final members of the team were prominent diabetes specialists. A small number of leading institutions were chosen to study insulin in patients. Toronto and Lilly designated Methodist Hospital as one of the first research sites, with Dr. John A. MacDonald, Director. (LA; 6: 170)

Many leaders on this team were vital to success; but Dr. Clowes, Sr. is recognized as one of the catalysts for translating the science of insulin to production and distribution to clinicians. (3; 4; 6:118-127; 37-41; 111-113; 142) Who was Dr. Clowes?

The Person: George Henry Alexander Clowes

Clowes was born in August 1877, Ipswich, Suffolk, England, the year of our Literary Club's founding. (21; 101; 133)

The Clowes family, listed in Burke's "Landed Gentry," included Sir William Clowes, surgeon to "Good Queen Bess." Dr. Clowes' father operated a chemical plant, piquing young George's interest in chemistry. (89) His early education was rich in science and religious controversies of Darwin, Pasteur and Huxley. (106) Educated at the Royal College of Science in London, Clowes received a doctorate in chemistry in 1899 from the University of Göttingen. During his oral examination in German, Clowes translated several pages of Latin from Cicero. (89) Clowes also studied in Paris and Berlin, but, concerned about the stifling effects of the hierarchy in England, he accepted his first job in 1901, in Buffalo, at the Institute for the Study of Malignant Disease. (6:121) There he married his wife Edith Whitehill Hinkel, a "beautiful and sensitive lady of 25." (89) In eighteen years in Buffalo, Clowes became one of the pioneers in cancer research.

In 1917, he left to serve in the Chemical Warfare Service in Washington, D.C.; as an alien, he was a Major without uniform. (6:121-124; 112: 53) At 41, Clowes made a daring career move to Indianapolis in 1918, recruited by J.K. Lilly, Sr. and son Eli. They dined at the Indianapolis Athletic Club, where Clowes learned of Indianapolis' traditions in automobiles—a hobby of his. (6: 121-23) But the heart of their discussion focused on how to decrease the time from discovery to production of medicines. Clowes, drawn to the opportunity of translating discoveries into products to benefit humanity, joined Lilly and was appointed Director of Research. (89: 46) Lilly funded a research lab at Woods Hole, Massachusetts, where Clowes could continue his research interests in marine biology and cancer. (LA; 38; 40; 106; 114) In 1921, Clowes became a citizen of the U.S. (89: 204)

Clowes' secretary, Miss Clark wrote *Biography of a Boss*, the persona of Dr. Clowes: "... with gray, touched with dark hair... blue eyes, under thick, overhanging brows... a good natured aggressiveness, and a British accent, of course..." (89) She said: "I never saw him lose his temper... He never used the elevator...always walked up three flights to his office—even the day before his cerebral hemorrhage..." And he loved detective stories and cars. (LA; 6: 122; 114) Eli Lilly, Jr. said of Clowes, "He lived more hours per day than any man I ever knew." (112: 55)

His laboratory assistant of 30 years, Mrs. Anna Hickson, said: "He always included people working in the lab on papers even if they didn't have a degree. (114) He said; 'I can put their names on the paper and it doesn't hurt mine, but it may, some day, do them some good.'" (LA; 37; 114)

Dr. Clowes' son, George Clowes, Jr. wrote in his masterful biography of his Dad: "Clowes ignored tables of organization and abominated the committee system." (89) He had a sense of humor; when his friends asked him "how many girls in Buffalo are in love with you? The reply was "My dear fellow, how many girls are there in Buffalo?"

Clowes' Indianapolis home was Spring Hollow Road, Golden Hill, where he kept his treasured art collection. A neighbor recounted being invited by Dr. Clowes to see the paintings. They went into a room completely dark except for a ceiling light on a Rembrandt portrait. Clowes said, 'Let us sit here for a while,' and they sat for 15 min, without saying a word." (LA; 37; 99; 114)

Such was the character of one of the leaders of the collaborators in Canada and the United States who brought insulin to sufferers of diabetes, first to researchers in Toronto, July 1922, then leading researchers in the United States a month later. 3:146-49)

Early Use of Insulin in Toronto and U.S.

The Toronto researchers and University of Toronto clinicians carried out the first use of insulin in patients. (72: Jan 11,1922, Jan 14, Jan 23, April-May) From the time Leonard Thompson received the first successful injection of insulin in Jan 1922, it was just four months till Toronto and Lilly reached their historic agreement to produce insulin. Four months later in August 1922, Lilly insulin was administered in the United States. Dr. Clowes and J.K. Lilly sensed the importance of their accomplishments. Clowes, who had befriended Banting, offered Lilly's support to publish a key paper of Banting's results so Banting would receive credit for his work and secure the Nobel Prize. (3: 147-149) J.K. Lilly said to Clowes, "I am ... overwhelmed with this tremendous situation...and experience ... difficulty in keeping my feet on the ground and my brain in normal operation..." Dr. MacDonald, at Methodist said that it looked like this was "the biggest thing that ever happened in medicine." (3: 149)

But optimism of the moment was overshadowed by the enormous need for insulin by researchers, physicians and patients. Clinicians were making heart-wrenching decisions to save one child's life, knowing their action was committing another child to certain death. (3: 144-9;6: 175-83)

The early use of Lilly insulin was begun by Drs. Joslin in Boston and MacDonald at Indianapolis Methodist. At the direction of J.K. Lilly, Dr. Joslin received the honor of supervising administration of insulin to the first patient on August 6/7, 1922; the second patient treated was a housekeeper at Methodist Hospital. (LA)

Early Use of Insulin at Methodist Hospital, Indianapolis

Methodist was among the prominent North American research sites for Lilly Insulin. (24; 32; 33; 113) Opened for patients in 1908, the hospital had traditions of excellence in patient care, education, and hospital services with close ties with IU School of Medicine. (25; 26) The Hon Charles Warren Fairbanks, former Senator from Indiana and the 26th Vice President of the U.S. was President of Methodist Board of Trustees. (24; 33) Dr. Charles S. Woods, a national hospital leader was Superintendent of Methodist

(1915-22) during the creation of the insulin clinic and the novel Clinical Research Society of the medical staff. (27; 28; 33: 181-2; 35)

Dr. MacDonald, Lilly's diabetes research director at Methodist, served on the Executive Committee of the Clinical Research Society; he was the personal physician of the Lilly family. (LA; 33; 113; 143-146) Other prominent diabetes specialists at Methodist included, John H. Warvel MD and Dr. Rudesill MD. (LA; 13; 15; 34; 121) An Indianapolis native and medical student, Irvine Heinly Page (1901-1991) did chemical testing on the Methodist diabetic patients and later became a preeminent researcher making basic discoveries in hypertension at Lilly's Research unit at City Hospital. (LA; 15; 96) Page was on the cover of *Time Magazine*, October 1955.

On August 12, 1922, Drs. MacDonald, Rudesill, and Warvel looked on as nurse Michael gave one unit of insulin at a time to Mrs. Underwood. Treatment was successful. (LA, 13; 15) Methodist was soon flooded with inquiries about admittance to the clinic. (LA, 14) J.K. Lilly replied that the MacDonald clinic could receive patients from across the country, and more than 130 diabetics were treated during the research phase; Methodist was among the first centers to caution about the risks of insulin. (3: 173).

Establishing Clinical Research Sites in America

It was soon apparent to the early researchers that insulin was effective in treating diabetes. (6:147-53, 206) But larger clinical trials were needed. The challenge: to scale up production of insulin, conduct this research, and develop a system for distributing insulin widely.

Leaders of the Toronto Insulin Committee and Dr. Clowes met in November 1922 to select experts to study the safety and effectiveness of insulin. (3:141, 149; 6:170; 81:87; 72: Aug 17 1922, Nov 25 1922; 113) Clowes served as a vital bridge in these discussions. He had extensive connections with university scientists. (112: 76) Clinicians respected his science credentials and trusted his judgment. Seven physicians representing their institutions attended the meeting. Dr. Elliott Joslin, (1869-1962) Boston; Dr. Frederick Madison Allen (1879-1964), Physiatric Institute (for diabetes 1921), Morristown NJ; Dr. John Ralston Williams, (1874-1965) Rochester, NY; Dr. Rollin Turner Woodyatt, (1873 -1953) Chicago; Dr. Russell Morse Wilder, (1885-1959) Mayo Clinic; Dr. Henry Rawle Geyelin (1884 -1942) Columbia University, NY; and Dr. MacDonald, Indianapolis, Methodist. (LA; 6: 170, 222; 57)

Perhaps the best advertisement for insulin trials was Dr. Banting's favorite patient, Elizabeth Hughes, daughter of the statesman, Governor of New York, and a Justice of the Supreme Court, Charles Evans Hughes. (6:13-19,195-201) Elizabeth, who found insulin "unspeakably wonderful", was saved by it. On August 16, 1922, Banting started insulin two days before her 15th birthday. (72: Aug16 1922) She was 5 ft. and weighed 45 pounds; just three months later, at the November meeting of diabetes experts, Banting introduced the men, including Dr. MacDonald from Methodist, to Elizabeth Hughes; she looked remarkably well. (6:222) By five months she had bloomed in health to 105 pounds.

In North America, insulin use increased rapidly. (3:173; 52) The New York Times reported June 20, 1923, that the Rockefellers gave \$150,000 to fifteen hospitals in North America to promote the new treatment and help the poor. (57) The Carnegie Corporation gave money to support diabetes research. (52)

Toronto University, Lilly and major diabetes centers educated their staff on the proper use of insulin. (3: 173; 72: Mar 28 1923; 52) The original ten clinical research sites were expanded to sixty by February 1923, as research proved insulin's effectiveness. (3:156, 162; 56; 72: May 1923; 113)

Dr. Clowes summarized the progress of the clinical trials at the Indianapolis Literary Club December 1, 1923, "... in April 1921, there were ... 10 patients receiving pancreatic extract, in December 1922 there were about five hundred and in December 1923, there were no less than sixty thousand... forty thousand were in the U.S." (6: 227; 19; 21; 32) The Toronto Daily Star said (May 19, 1923) "Dr. Banting's discovery has a direct and vital meaning to one percent of mankind (that) suffers from diabetes."

Lilly distributed insulin free to researchers then began limited sales at cost to physicians through retail pharmacists. In a note of irony, insulin was still under clinical trial in North America and Lilly was unable to export it. Burroughs- Wellcome, using Lilly insulin, began to establish their company in Mexico, Cuba and other Latin American countries. Lilly insulin was similarly used in Great Britain. (3: 173-4)

Lilly's optimism over the future of insulin was soaring. J.K. Lilly celebrated the discovery during an around the world cruise on the S.S. Samaria from January to May 1923. (LA; ISa; 12; 92) The Indianapolis Star reported "Clowes' presentation on the subject of insulin excited the greatest possible interest among the passengers". (ISa) A close friend of J.K. Lilly and Lilly Director, William Fortune, kept a log of this famous trip of prominent Hoosiers; Lara Fortune Balter, the great- great granddaughter of Mr. Fortune, found the log in a safe at the Fortune Trust Office in the Indiana Chamber of Commerce Building in the late 1980s; it is now archived at Indiana Historical Society. (12)

In October 1923, *Iletin*, Lilly's Trade name for insulin, was released with a physician's prescription. (6:227) October 9, Lilly announced to its employees: "Now gentleman, we place in your hands for development The Greatest Advance in Medicine in fifty years." (LA: GL#88; 3:157, 187,191; 72: Oct 10 1923) This celebratory proclamation came just 21 months after Dr. Clowes' first contact with leaders in Toronto, December 1921.

As one of the original research sites designated by the University of Toronto Insulin Committee, Methodist Hospital provides a unique glimpse into clinical research in America in the 1920s. Snippets of this history may found in dusty archives (Toronto, Lilly and Methodist). Remarkably, the Indianapolis Literary Club has a link to this story.

Indianapolis Literary Club

In 1920, our Club (ILC) was in its fifth decade, a forum for serious and convivial conversation. (21-23) The Methodist Hospital Trustee, Charles Fairbanks, was a member and Vice President of the Club. The Lilly family physician, Dr. MacDonald was a member, as were J.K. Lilly and Dr. Clowes who became President in 1936. (19; 20)

It's likely that the keen interest of leaders, medical and administrative, in advancing medicine was shaped by interactions among these talented researchers, and clinicians. Dr. Clowes' arrival in Indianapolis in 1919 and his link to the Literary Club may have influenced the creation of the novel

Methodist Clinical Research Society, whose Chairman, Murray N. Hadley, and other leaders interacted at the Club with Dr. Clowes and JK Lilly. (21; 33) We know from Dr. Clowes' Literary Club presentation of the *Story of Insulin* that discussion in Club meetings included diabetes. We can only wonder what questions Club members posed of this famous scientist in December 1923. Clowes would present other Club essays on science but not diabetes. J.K. Lilly, essay in 1922 was entitled "A Speculation Upon the Mysteries of our Endoconic Control"—not about diabetes, I think. (20; 21)

Successes

The successes of collaborators in the insulin story have been recorded; the achievements have had lasting impacts on science, medicine, industry, and society. Notable successes include, in addition to the discovery of insulin (3: 209):

- Stimulation of research into diet and exercise in diabetes.
- Breakthroughs by Lilly in the science of mass production and purification of insulin and later, liver extract and penicillin. (72: Sept 14 1925) In 1926, J.K. Lilly's wife, Lilly Ridgely suffered from pernicious anemia; the family brought Harvard physician George Minot to treat her with liver extract. She improved and Lilly partnered with Minot and Murphy to produce Liver Extract #343 in 1928. (88; 112: 66-67; 100; 118) Methodist Hospital was also involved in the clinical testing of liver extract. (112:106-110) *Arthur N Jay MD, U.S. Army, WWII, received penicillin at Fort Lewis Washington where he was medical director of the German Officer prisoner of war camp, circa 1943. Jay was President, Methodist Hospital (Indianapolis) Medical Staff in 1955.
- Novel intellectual property agreements in ethical patenting: protecting corporations' rights to market and discoverer's rights to ensure quality and fair pricing. (72: Nov 1922, Dec, Jan 1923; 91)
- Demonstrating feasibility of the large -scale distribution of insulin.
- Creation of a model for university-industry collaboration. (3:173) After the Nobel Prize award J.K. Lilly wrote: "we are now flooded by propositions from scientists both in this country and abroad to cooperate with them to develop their new item." "The days of the Creek Indian remedies were gone." (112: 76)
- And the most notable success: improving the span and quality of life in diabetics. Childhood mortality from Type 1 diabetes in 1900 was 98% (Naunyn period, 1898-1914), in 1920, 69% with starvation diets (Allen period, 1914-22) but only 11% after 1922 (Banting period, 1922-26) with diet and insulin. (102)

To what do we attribute these successes? Team members embraced science and change. As Marcus Aurelius put it: "Natures highest happiness lies in changing things that are, and forming new things..." (36) Scholars have identified conditions that foster discovery. Toronto, Lilly and diabetes clinicians created the ecology of discovering, production, and translation of research to benefit public health. (123)

- Sponsoring institutions had traditions of excellence in education, research, and clinical care.

- Researchers were “Truth Seekers,” searching for the “unity in hidden likenesses” of Jacob Bronowski. (*Science and Human Values*, 1956)
- Collaborators were motivated to serve the greater good.
- They were risk takers, sometimes impulsive, but usually purposeful.
- The team had visionary leaders with a moral compass.
- All raised and invested money and resources to advance discovery and health.

Of course, the quest for fame and fortune was a powerful motivator. Today original discoveries are costly, but in 1920, a small investment in a few months in Toronto produced incalculable human and financial rewards. In Robert Root-Bernstein’s classic book on “Discovering,” he notes that when Banting and Best isolated insulin each had no more than \$200 in the bank, no steady salary, and no position; both were living with friends. (123: 198, 396)

Nobel Prize

The reward for their discovery came quickly and not without controversy. (124)

Banting and Macleod were awarded the Nobel Prize December 10, 1923. (3:212-233; 10; 58; 60; 61; 63; 65; 66) The insulin patents credited Banting, Collip and Best; (72) the Nobel Committee added Macleod. (3) To many observers, exclusion of Best and Collip was a failure of the selection process. (59; 67) One scientist put it recently, “The Nobel Medallion is etched with human Frailties.” (62).

Banting was near apoplectic that Macleod received the prize; in protest Banting gave half of his share of the award to Dr. Best. (58) Later Macleod shared half with Dr. Collip. (3: 231,233; 136) The feud would last. In 1936, a photo of Drs. Collip, Banting, and Best was taken, the only photo in existence of more than two of the discoverers of insulin together. (3: 128-9; 118) Lewellys Barker, a University of Toronto graduate familiar with the bitter disagreements among the discoverers, said, “There is in insulin glory enough for all.”

Nobel Prizes beget Nobel Prizes. Banting’s work sired three for insulin research in 1958, (129) 1969, and 1977. One additional Prize attributed to the Insulin award is that of George Minot. The discovery of insulin arrived just in time to keep Dr. Minot, a severe diabetic, from dying. He lived to discover liver extract and was co-recipient of the Nobel Prize in 1934. (3: 237; 64; 98; 100: 16; 118) Lilly produced the liver extract for Harvard and savored the glory of a second Nobel Prize. Methodist also participated in the liver extract clinical trials. (88; 112: 66-67)

Rest of the Story

Amid glory, there were dark sides to the discovery. (3:133,176-77; 97; 124)

The Toronto group was on the verge of a milestone in medical history; but they were concerned that competitors might beat them to the summit. In February 1922, Dr. Collip announced he would apply for a patent for his purified insulin. A fight erupted between Banting and Collip. Dr. Best broke it up. Clark Nobel, the student who had lost the coin toss to Best, drew a cartoon of Banting sitting on Collip choking him; the caption: “The Discovery of Insulin.” (3: 118)

Toronto supported patents to prevent anyone from “securing a profitable monopoly.” Researchers were bound by medical ethics to not profit from discovery that benefitted humanity. To resolve this problem, researchers who discovered insulin assigned their patent rights for a dollar each to the University of Toronto. (3: 178; 72: Nov 1922; Dec; Jan 1923) Unknown to the Toronto group, the first patent had already been awarded in 1912, to Berlin physician, Zuelzer. His extracts, however, were considered impure and dismissed. (3: 177, 210)

In the end, an American-Canadian patent compromise was reached January 23, 1923. An American patent on insulin and Toronto’s method of making it were awarded to the discoverers. (3:177) The skirmishes over naming and licensing died out. (3:181)

The lives of all protagonists in the insulin story were changed forever.

Sir Frederick Banting, an accomplished painter, stopped research in diabetes. (95; 98; 147) He conducted physiological research in pilots of high-altitude aircraft for the Royal Canadian Air Force. In February 1941, his Lockheed Hudson bomber crashed in Newfoundland; he died of wounds and exposure. (68; 69) At Sir Fredrick Banting Square in London, Ontario, a perpetual flame of hope was lit in 1989, a tribute to Banting and all who have lost their lives to diabetes. (2)

Charles Best succeeded Macleod at the University of Toronto and had a productive research career. After Banting’s death, Best and friends spread Banting’s account of the discovery of insulin to write out Macleod from history books. Macleod’s image suffered, but in 1950, the first independent review of events was made and gave credit to the four discoverers. When Best died in 1978, the University of Toronto released details of the bitter feuds. (124) The preeminent historian from the University of Toronto, Dr. Michael Bliss, published the definitive history of the insulin discovery in 1982.

James Collip had a distinguished career in biochemistry at McGill University. (3:237) He died in 1965.

John James Macleod stopped research in insulin and left the Toronto in 1928 amid the hostile environment created by Banting’s hatred of him. As Macleod walked to the train, a friend asked him why he was shuffling his feet. Macleod said: “I’m wiping away the dirt of this city.” (3: 234) Macleod and Banting never spoke to each other again. Macleod returned to Scotland, had distinguished career in academia. He died at 59, in 1935.

George Clowes, Sr., retired as Director Emeritus at Lilly in 1945. (40; 41; 140; 141) He had failed to convince Lilly to keep basic research independent of the clinical branch. (9: 63, 65) He received many accolades and awards, including the prestigious Banting Medal of the American Diabetes Association in 1947. (43; 142)

Clowes, his family, and descendants have enriched Indianapolis for almost one hundred years, from the arts and humanities to education, science, medicine, and social services. (LA; 38-41; 86; 89; 106; ISb; ITC) Landmarks include Clowes Hall, the Clowes Pavilion at the Indianapolis Museum of Art, Trinity Church, Orchard and Park Tudor Schools, the Indianapolis Symphony, and Herron Art Institute. (48; 139) With El Greco’s, Rembrandts, and paintings by Titian, Rubens and Holbein, Dr. Clowes was recognized by Anton

Scherer, then president of the Herron Art Institute, who said: “with the possible exception of Booth Tarkington, Dr. Clowes and his wife were the most avid and ardent collectors of paintings in the history of Indianapolis.” (LA).

Active in civic affairs, Dr. Clowes and family gave their time, energy and wealth through the Clowes Fund. (1952) (5; 86). George Clowes, Sr. chaired the Indianapolis Committee on Foreign Relations, was a founder of the Indianapolis Council on World Affairs, and a member Indianapolis Literary Club (ILC), perhaps drawn to the Club’s roots in the England of Samuel Johnson and Sir Joshua Reynolds--seen in the image behind me-‘A Literary Party at Sir Joshua Reynolds’. (101)

Dr. Clowes died August 25, 1958, two days before his 81st birthday at Woods Hole in Massachusetts, where he is buried. (4; 37-39; 139) The inscription on his tombstone reads: Servant of God, Benefactor of Mankind, and Seeker after Truth and Beauty. (18; 38; ITC; 106; 133) The Indiana Academy of Science said of Clowes: “The world owes much to those who have left their native lands and sought careers in America where the pioneering spirit still prevails and success and recognition, in general, depend on health, hard work and innate ability.” (39)

Leonard Thompson, whose life was saved at 14 by insulin, had a relatively normal, yet short life; he had a steady job but was not a well-controlled diabetic; he died at 27 of influenza and pneumonia. (3: 242)

Elizabeth Hughes’ life was remarkably productive; she died unexpectedly in 1981, after receiving 42,000 insulin injections over 58 years. (6: 244) Elizabeth guarded the secret of her diabetes or any link between Elizabeth Hughes Gossett of married life and the frail desperately ill Elizabeth of her youth. (6: 223-24) Among many accomplishments, Elizabeth was founder of the Supreme Court Historical Society. (6: 241)

Almost one hundred years since Elizabeth Hughes’ life was saved with insulin, there remain barriers to treating diabetics with insulin, diet, and newer drugs.

21st c Challenges

“Time is a river, the resistless flow of all created things” and today despite a century of progress, we have failed to translate discoveries into improved public health for millions of persons. Within 20 years, if the global pandemic is unchecked there will be half a billion diabetics. (8) Today, 29 million Americans have diabetes; another 79 million have pre-diabetes. (76; 137)

The optimism in 1923 for treating Type 1 diabetes has not been realized in many parts of the world. (82; 83; 91; 103) Life expectancy for a child in rural Mozambique is less than that of a child in Boston before the discovery of Insulin. (80; 82) Lack of access to insulin is the most common cause of death in these children and a similar threat to children in many urban communities in the U.S. (82; 91)

Diabetes specialists, humanitarians, and public health organizations advocate for elimination of the barriers to access to insulin by 2022, the centenary of the first person, Leonard Thompson, to be treated successfully with insulin. (82; 7; 8)

Conclusions

In conclusion, the discovery, production and distribution of insulin resulted from a collaboration of visionary leaders. Toronto University and clinical research sites in North America clearly benefitted from having the Lilly's at the helm with Dr. Clowes 'trimming the main'. (16, 58) The relationship these men had was personal, professional and history suggests, unique.

Let me end by sharing a touching exchange between Dr. Clowes and J.K Lilly, written three years before Mr. Lilly's death.

Mr. Clowes to Mr. J.K. Lilly Sr: July 7, 1945, Woods Hole: from a 4-page letter single-spaced:

"I appreciate very greatly your recognition of my efforts...the confidence in me and courage which you and Eli have always exhibited in giving me a real opportunity to push fundamental research, on which in the last analysis all our practical developments ultimately depend. "

Mr. J.K. Lilly Sr. to Dr. Clowes: July 26, 1945.

"Dear Dr. Clowes, Your kind letter of July 7 'warmed up the cockles' of the old man's heart like a pound of 'Diglugin'. (11) The job of Cheer Leader on the Sidelines is now mine, with the duty of cheering on you men of science from whom comes every good and perfect gift; to cheer the men of production whose efforts during these trying times will go down in history as something superb. Then come the men of sales creation, carrying the Gospel of Lilly Products and Policy to the far reaches of the earth. Then we must cheer the general management that is trying to build up the self-respecting character of everyone both major and minor. It really requires some cheering to cover all these eggs! And you, my dear Sir Alexander Clowes, are never to doubt or forget this at your peril! Years may come and years may go but your and our welfare are one and the same."

SJJ end Essay

January 20, 2015

Title: From Thebes to Indianapolis: The Sweet Taste of Success.

Selected Sources, references, citations, images

To the reader: A complete list of citations for this essay is available from the author and numbers 147, including peer-reviewed research papers, news clippings, images, personal communications, and popular press and internet sources.

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Images

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SJay Personal Notes:

Association with Methodist Hospital Indianapolis:

My Uncle Harry L. Foreman MD, an internist at Methodist Hospital and Superintendent of Indianapolis City Hospital in 1919-1921, became a member of the Clinical Research Society of Methodist Hospital February 3, 1922, and President of the Indianapolis Medical Society in 1944. (30; 31; 33) He and my father, Arthur N. Jay MD, became Presidents of Methodist Hospital Medical Staff in 1936 and 1955 respectively. My brother, Arthur C. Jay M.D., trained in pathology at Methodist. My Aunt Iona Jay Foreman (Mrs. Harry L. (Peggy)) was President of the White Cross Guild of Methodist Hospital, 1942-1944. (33)

In the 1980s, I was involved with Methodist administrative and medical staff leadership in developing the Joslin Diabetes Clinic Affiliation. Dr. Paul Boyce (Methodist Endocrinologist and Diabetologist) and I shared some of the early Methodist history regarding the insulin clinical trials with Joslin leaders.

Dr. Boyce in 2013 shared some of his memories of Dr. Warvel (Sr. and Jr.) including the personal relationship Dr. Warvel Sr. had with George Henry Alexander Clowes. (32)

Diabetes:

As a second year medical student at Indiana University School of Medicine, I was in a small group of students in Pharmacology class where we produced Alloxan Diabetes in rats. Dr. Ashmore PhD, Chairman of the Department, guided us through this great "hands on" learning experience. We summarized our project at the end of this class at his home, over pizza.

As a first year medical student Indiana University School Medicine, 1964, I spent a summer working in the Laboratory of Morris Aprison, PhD with my supervisor, Robert Jackson PhD. We were purifying acetyl cholinesterase from Caudate Nuclei of calf brains. We used large Lilly glass columns for chromatography, columns used in Lilly's insulin and other chemical purification work.

Sjj Jan 20, 2015

Indianapolis Literary Club

