

# Diabetes and insulin: 1921 and beyond

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Perhaps, the existence of diabetes was known to us since dawn of civilization. The first documented description of diabetes and its treatment was discovered on papyrus papers, which was dated back to 1552 BC, in the Valley of the Kings in Luxor, Egypt. The writings were discovered by German Egyptologist Georg Ebers "Ebers papyrus in 1889".

Diabetes is one of the most studied diseases in the history of medicine. The term 'diabetes' was probably introduced by great physician Demetrius of Apamea or by Aretaeus of Cappadocia (129-199 AD), meaning "passing through" or "siphon". Modhumeha (honeyed urine) was described by Indian physicians as early as 400 BC, gaining notability in 500-600 AD. In "Monusamhita", it was found that the Indian physician Charak and Sushruta, not only described diabetes but also outlined treatment. Chinese textbook also described diabetes in those days. Physicians of early Greek, Roman and Byzantine civilization described diabetes differently between 500 BC to 500 AD, some thought diabetes came from kidney's inability to retain urine. Various descriptions were given by different authors "melting down the flesh in urine", "The Pissing evil" etc. and some thought it came from gastro-intestinal complications, as there were success in treatments by restricting food intake. During the Islamic Golden Age and European medieval period, physicians used to diagnose and treat diabetes. They also noticed the relationship with hunger, weight loss and carbuncle. The term "diabetes mellitus" was introduced by Thomas Willis (British Physicians) in 1674 referring the particular sweetness of urine of diabetic patients. Treatments with various plant medicines, diet and exercise were performed, which lasted for about 1000 years until 1500 AD.

## Pre-insulin era

Before insulin arrived, the only means of treatment were diet restriction (John Rollo, 1706), sugar free diet

(Bouchardart's treatment, 1870) and so-called starvation diet (Frederic Allen) along with some exercises.

Experimental science started after 1500 century AD and finally, pancreas and its secretion was found to be responsible for the disease. Undoubtedly, the discovery of insulin was a major breakthrough but frequently characterized by controversies and dispute among scientists, as well as disappointments, failure and hope. In late 1800's and early 1900's, many scientists like George Zuelzer (Germany), Fugene Glay (France), Nicolae Pouloscu (Romania) Szobolev (Russia) were close to the discovery of insulin and its link to diabetes, until the final discovery of insulin in 1921.

In the pre-insulin era, diabetes mellitus was almost like a death sentence. People used to die within weeks to months or within few years. No successful pregnancy outcome was then among ladies with diabetes. Thus, 1921 is the year of one of the greatest discoveries in medical science.

Insulin was discovered by a team at the University of Toronto, Canada. Frederick Banting, a young physician, surgeon and lab scientist with the help of Charles Best, a lab assistant at that time, pioneered the discovery. Banting conceived the idea of isolating internal secretion of the pancreas from the works of previous scientists. In October 31, 1920 Banting wrote in diary:

"Diabetes: Ligate Pancreatic duct of dog. Keep dog alive till acini degenerate leaving islets, try to isolate internal secretion of these islets to relieve glycosurea". In August 1921, Banting with the help of Best started the experiment to extract secretion from a duct of ligated pancreas which causing atrophy of exocrine portion of a dog and inject the secretion in previously pancreatectomized diabetic dog. First dog that received the extract named "Marjorie", which showed effectivity of reducing hyperglycemia. Subsequently, they successfully repeated the experiment with many animal models.

### The human experiment

One of the significant red-letter-day in the history of Mankind was 11<sup>th</sup> January, 1922. A young boy of 13, Leonard Thomson, was dying of diabetes in Toronto General Hospital. He was the first recipient of Fetal-Calf Pancreatic Extract named "Iletin". After the first dose there was severe reaction, abscess formation and he was almost in a dying condition due to huge impurities. Subsequently, after repeated purification with alcohol, the extract became tolerable. Subsequent injection was much tolerable and the blood sugar came down from 520 mg to 120 mg in 24 hours. So, world saw the miracle of insulin.

Simultaneously, six other persons with diabetes were given the extract with encouraging results. One of them was Joe Gilchrist, a young doctor. Lessons learned from each insulin formulation were: a. Insulin rapidly corrects acute metabolic disturbances, b. Reaction due to impurities, c. Purity improve tolerance, d. Solution of unmodified insulin are too short acting, needing multiple injections, e. Inconvenience.

The discovery of insulin has truly revolutionized both therapy and progress of diabetes. After discovery of insulin, Connaught Laboratories of Canada teamed up with University of Toronto (UOT) to prepare purified insulin and mass production. In 1922 after obtaining permission from UOT, Georg Walden, an Eli Lilly scientist was able to purify and yield commercial level insulin.

At the same time Danish noble prize winner in 1920, August Krogh met Banting and John Macleod Team and get approval to produce insulin. And he teamed up with Hagedorn to produce Insulin at the Nordisk insulin labororium in 1923 in Denmark.

By the end of 1923, insulin was made available to majority of patients. In 1922 two prominent doctors were recipient of insulin, Sir Norman Walker, treasurer of Royal College of Physicians of Edinburg and Dr. Georg Minot, a young physician of USA who got Nobel prize in 1934, for discovering the treatment of "Pernicious Anemia".

What were the issues of early formulations?

a. Injection of thick solution of few cc 2-3 hourly, b. Painful and abscess formation, c. Had reactions, d. Route of administration IM/IV, e. Very short duration of action, needing multiple daily injection.

After few days it was observed that impurities caused immune response. Early source of insulin was from pig and cattle, structurally which are not same as human insulin structure. In 1928 presence of insulin degrading features in plasma were observed.

### Evolution of insulin: 30's and 40's

The first burning question "Can I have fewer injection, but still in good control?" In 1936, Hagedorn observed that addition of protamine prolongs the duration of action of insulin. Further addition of Zinc (PZI) even more prolonged the action, beyond 72 hours, but addition of zinc causes significant glycemic variability. NPH was marketed in 1946 and Lente in 1953. Ultra-Lente having much longer action than NPH abandoned after few years due to glycemic variability. Impact of insulin on life expectancy was observed in late 1940's which showed life expectancy shoot up by 25 to 35 years in young patients. So, discovery of insulin was a "Worthy solution" for diabetes subjects. As stated by Colwell, the introduction of insulin has heralded the end of so-called "Pre-insulin era" or "Frustration era" paving the way for new era and clinical advancement.

### Pure: purer: purest insulin

Since the start of insulin therapy, scientist observe brief increase of glucose due to glucagon impurities which was made free after citrate crystallization and also observed different action profile between porcine and bovine insulin.

World observed few more discoveries in the field of diabetes:

In 1955 Frederick **Sanger**,(England) determined sequence of insulin.

In 1956, WW Bromer (USA), determined sequence of glucagon.

In 1956, Rosalyn Yalow (USA), formation of insulin-binding antibodies in insulin treated patients.

In 1959 Yalow and Berson discovered technique of insulin measurement by radio-immune assay.

1969, Dorothy Hodgkin discovered three-dimension at structure of Insulin.

### Mono component insulin

So, after discovery and use of insulin since 1922, scientists observed allergic reactions, dermal reaction

at injection site. Even after repeated purification in 60's there was presence of impurities.

Insulin secreted as proinsulin, though immediate splitting of C-peptide is usual, but some may remain as proinsulin causing antibody formation. These observations led to further purification and preparation to mono component insulin (MC Insulin). MC insulin led to decrease in need of insulin dose. In 1970's number of studies confirmed relationship of MC Insulin and reduction of dermal allergy.

Thus, until then it can be said that since discovery of insulin few stages have passed till 70's. Discovery phase > to mass production phase > to prolongation of action phase > to purification advances. Even then as the porcine or bovine insulin have different structures there is still possibilities of antibody formation. These observations further led to develop "Human Insulin"

#### **Genetically engineered insulin production:**

After discovery of insulin structure and RIA technique, insulin science started. It was observed porcine insulin differ by one amino acid and bovine insulin differ by three amino acids from human insulin. So, most patients still developed antibodies to foreign bovine or porcine insulin. With the advent of recombinant DNA technology and determination of nucleic acid sequence by Sanger in 1982, era of genetically engineered insulin production started, and it was made possible to make new production method for completely structurally pure human insulin.

The success by recombinant RNA technology are restructuring insulin molecule, to overcome some therapeutic limitation of conventional animal molecule and safeguarding future insulin supply. Eli Lilly produced human insulin by encoding colony of *E. coli* and Novo used baking yeast "**Saccharomyces cerevisiae**". Since 1987 Human insulin made available throughout the world.

#### **Diabetes control controversy**

Initially physicians were quite happy with treatment, but question arose in 60's and 70's: "Are the complications preventable?" In a study UGDP (University group Diabetes Program) in 1970 observed that "improved control failed to control or delay the microvascular complication. Using RIA technique, Yalow and Berson found that people of T2DM were unable to process insulin not only because they lack insulin but

also their body produce an antibody that reject the insulin action. Still beyond 60's & 70's, there were constant efforts to reduce insulin related

reactions and complications. Subsequently many studies e.g. UKPDS (1977-1994), DCCT (1993) etc. confirmed that good glycemic control significantly reduce microvascular complications.

Ultimately target blood glucose fasting and post prandial and HbA1c was described for prevention or delay of complication. But the limitation of reaching to the target were frequent hypoglycemia and weight gain. The reasons of these side effects were difference of physiological action profile in terms of Pk/Pd variability of normal insulin and exogenous insulin used. Though conventional human insulin is safer than previously used animal insulin, but still genetically engineered human yet insulin is not the safest.

There was variability in action profile even day to day, causing frequent hypoglycemia or hyperglycemia, undue eating, mostly out of fear, so gain weight and also that lead to fear of appropriate dose titration. These observations led to further innovation of not only the purest insulin but also the safest (?) insulin.

#### **Era of designer insulin ensued**

Evolution of insulin analogue started keeping in mind more physiological action profile using recombinant DNA technology by simply changing the amino acid sequence of genetically engineered human insulin. New generation of both short (aspart, lispro, glulisine) and long-acting insulin (Glargine, Detemir) production started in 1996 and in 2001 onward respectively.

Previously discovered NPH or Lente are intermediate acting insulin not matching normal basal insulin profile. New generation long acting insulin analogue Glargine, Detemir overcome that limitation. Degludec (2013) even longer acting with much more physiological action profile These new generation insulins analogues both short and long acting, all were more physiological in term of PK/PD and thus variability and thus cause much less hypoglycemia and it is easy to initiate the dose and titrate to reach to the target and there is less fear. User friendly co-formulation of Aspart and Degludec and Glargin U-300 was marketed after 2014

Though Lispro, Aspart have almost same physiological action profile scientist discovered even faster acting

(Fiasp) insulin (2018) to mimic more physiological action profile, thus causing even less glycemic fluctuation and less hypoglycemia.

### **Insulin delivery system**

Simultaneously, scientists were still working to further improve not only insulin but also on insulin delivery system. Previously used glass syringe was painful as used I/M (Intramuscularly) later S/C became less painful. Later come hypodermic needle with disposable syringe in 60's, then came pen device in 80's with more comfortable smaller gauge needle, flexible and convenient. Some insulin devices designed for blind with audible device, digital display, memory function.

Insulin pump designed by Dean Kamen in 1970. Which was a size of backpack, subsequently user-friendly Insulin pump (CSII) was made available in 1978. Needle free injectables are being developed.

### **What's next?**

Non-invasive insulin delivery, weekly or monthly insulin, inhaled insulin, buccal insulin spray, oral insulin are in the horizon. Inhaled insulin: Afrezza/Exubera are developed but yet not popularized due to certain limitations.

### **Further innovation in pipeline: 2020 and beyond**

In the last decade world saw the development of long-acting weekly basal insulin, U-300 regular insulin for severe insulin resistant patient. Scientists identified hot spot for digestive enzyme causing degradation of oral insulin, thus creating scope for oral insulin. Data of both oral insulin and weekly insulin (Icodec) were presented for the first time in EASD conference in 2020.

Second generation basal insulin such as degludec and U-300 glargine appear to give benefit in reducing hypoglycemia in CKD patients with low eGFR. Scientists are working on glucose sensitive insulin analogue with the idea, insulin to be released only when needed, keeping flat glucose profile and thus no hypoglycemic event.

### **Post insulin era: beyond insulin**

Cure of diabetic was a dream from the very beginning. The dream if Banting was pancreatic transplantation. On 20th December 1893, P Watson Williams (Bristol) grafted three fragments of pancreas obtained from a sheep into subcutaneous tissue of a 15 years old boy, but was not successful. Frederick Pybus also tried in the year of 1916-1924.

First success of pancreas transplant was carried out in 1966 by Kelly and his group. Islet cell transplantation, stem cell technology are showing promising outcome specially for type 1 diabetes.

Artificial Pancreas, "A close loop control of diabetes, in a system combining a glucose sensor, a control algorithm, and an insulin infusion device" is another promising approach in diabetes treatment.

In 2015, Edward Damiano, introduces the "Islets", a bionic pancreas that delivers both insulin and glucagon every five minutes "Bridge to a Cure".

### **Insulin: a life-saving discovery turns 100 years**

Teddy Ryder, born in 1916 diagnosed with Type 1 DM at the age of 4, who received first insulin shot on 10 July 1922 is the longest survivor since the year of discovery, he is the only recipient of all types of insulin so far developed, died in the year 1993 at the age of 76, with no serious diabetes related complication.

Undoubtedly, one of the best compliments written in a panel on the wall of Joslin diabetes centre Boston, USA, "The evolution of medicine is in reality history of man and his religion, those who have contributed to its advancement are 'Legion'.

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