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Mini Review

The Centenary Celebrations-Insulin and Diabetes.

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Most people will know the word diabetes. Few people will not know it has something to do with sugar. Diabetes mellitus is the complete name for the condition, mellitus meaning sweet or honey taste found in the urine. Not to be confused with Diabetes insipidus, a condition of the pituitary gland, the kidney or the Psyche where water cannot be retained by the body and very severe thirst and huge polyuria (passing a huge amount of urine occurs). The condition Diabetes mellitus was known in Egyptian times and in recent times has become so much more prevalent. Alas most people will have a relation with the condition and will be aware that complications can occur such as blindness. Even today with all our new medications and all our new knowledge, still diabetes shortens life span by 10 or so years but this figure is rapidly getting less due to earlier diagnosis and better treatment for high blood sugar, cholesterol and high blood pressure.

To go back more than 100 years obese patients who developed diabetes could cure the symptoms which include thirst, passing a lot of urine, tiredness and genital itch by weight reduction and exercise. The reason for this improvement is now known in much more detail than it was then. The hormone insulin which is secreted by the islet cells in the pancreas lowers blood sugar. A deficiency of insulin leads to a rising blood sugar and the high blood sugars are the cause of the thirst. The high blood sugar is no longer able to be contained by the kidney and is secreted in the urine. The high concentration of sugar in the urine pulls out sugar by osmosis, drags with it, water, so the higher the glucose in the blood and urine the more water is pulled through the kidneys which are filters. The increased amount of water thus lost, results in frequency of passing water which is now full of glucose. The loss of water is recognised by the thirst mechanism which gets switched on and being very thirsty the patient with diabetes starts to drink and drink to make up for the loss of water in the urine. Sometimes the patient who might have been keen on lemonade or other sweet drinks just drinks more and more not realising that the drinks are heavily laden with sugar. This results in increasing the blood sugar even higher and even more thirst until the whole system collapses. The patient becomes unconscious very dehydrated and will die unless given intravenous fluids and then insulin. One such lady was a patient of mine. The African lady was so complicated that after she recovered we wrote up her case in one of the medical journals to inform others of the problems we faced and the treatments we gave which resulted in her recovery. Hyperosmolar coma is the name of the condition and thankfully rare. I can of course remember other patients who we were not successful in saving but they are too painful to relate.

The failure of the Islets to secrete enough insulin leads to high blood sugars and that is the definition of diabetes. But how high before the condition of diabetes is the diagnosis? Just like height and weight how high before normal becomes abnormal. So we needed a committee to decide and then many countries decided that they needed committees of their own.!The major criteria for the diagnosis is harm. If a blood sugar of say 6.5 is not associated with any of the complications of diabetes then why label that patient Diabetic? But a problem In pregnancy, which is a 9 month experiment, as the foetus is very sensitive to glucose levels which are not considered a risk in the rest of the population. Really strict control of blood sugars in pregnancy leads to a normal outcome. Risk of vascular complications arising from raised blood sugar is linear and starts at high normal. The real problem is that raised blood sugar and diabetes are due to so many different causes. There are so many different causes of B cell failure. The beta cells cells lie in the islets in the pancreas and secrete insulin. In 1921 it already had been discovered that if you removed the pancreas from dogs they developed diabetes. This was the famous discovery by Oskar Minkowski who worked with Von Meering in Strasburg. Minkowski was born in Aleksotas, near Kaunas, which is now in Lithuania. My Grandparents came from Akmene in Lithuania and perhaps they knew one and other. Minkowski died in 1931 but his wife survived and escaped Germany in 1941 with the help of Charles Best and ended up in Buenos Aoires. One of his brothers was a world famous mathematician and a mentor to Einstein in Zurich. A son became Professor of astronomy at Berkley in California. Oscar Minkowski made many very important discoveries. He was described as 'The greatest experimental pathologist of his time. The discovery of the pancreas as the organ which held the secret of diabetes occurred by serendipity. He and Von Meering were investigating the absorption of fat. Minkowski carried out a total pancreatectomy on a dog to examine fat absorption and found to his surprise that the dog developed Diabetes. He carefully measured all parameters he could while the dog survived and realised that the pancreas contained an internal secretion which was necessary for survival.

Minkowski went on to do a pancreatectomy and then attach a small part of the pancreas to the abdominal wall. No diabetes resulted until this remnant was removed. Solid proof of the endocrine function of the pancreas. And that, 10 years before the term Hormone had been introduced (Luft R Diabetologia 1989 32 399-401.)

Minkowski converted to Christianity later as many Jews did, to try to become accepted into universities and other government jobs. Alas Hitler demonstrated that even this sacrifice was not enough. Minkowski died in 1931 so was spared the devastation of losing his place in the University and then the gas chambers. My Grandparents took the other route and emigrated to Ireland where they prospered. Minkowski's amazing discovery that removal of the pancreas caused diabetes and therefore that there must be some sort of regulator in the pancreas that regulated blood glucose, was game changing. This momentous discovery that diabetes was caused by a disease of the pancreas led, the way to the discovery of Insulin. His discovery is and was so important that the European Association for the Study of Diabetes, has a special Prize in his honour at their annual conference, which 16000 delegates attend. The Minkofsky prize is given each year to the most outstanding young diabetes researcher and these prize winners have almost all gone on to have illustrious research careers. Still the enigma of why the pancreas fails in the diabetic patient remains. A famous Itialian researcher working in London, Bottazzo, entitled a lecture "The death of the beta cell, Suicide or Homocide" and still we debate this. Is the attack on the B Cell an outside job in the environment or inside from autoimmunity the body attacking the B Cell with auto antibodies, ie being attacked from within the body.

One hundred years ago in the University of Toronto there was a young Surgeon called Fredrick Banting. He had an idea that if he ligated the bile duct, the duct that secretes bile into the gut to help digestion he might be able to extract an internal secretion, a secretion which would metabolise carbohydrate. He got the reluctant support from the professor of physiology Prof Macleod, who was an expert on carbohydrate metabolism. Prof Macleod arranged for a lab to be made available in the summer of 1921 and assigned a student, Charles Best to help Banting with the experiments. Then Macleod went off on his holidays to Scotland. There was a dog called Marjorie. Banting removed her pancreas and she also developed diabetes. They then gave her pancreatic extract. Marjorie lived for 70 days demonstrating how well the extract worked and how with the extract the dogs lived after pancreatectomy and without it they died within a few days. This was an incredible discovery. It must have been like the biggest dream one could imagine. If the extract could be given to humans, then people with diabetes could be saved from inevitable death. The famous British diabetologist, RD Laurence was a young man in 1921 when he developed Diabetes. He had been sent to Switzerland to spend his last days when he got a telegram that Insulin had been discovered. He returned to London and with insulin he lived a long and distinguished life, dedicated to looking after diabetic patients in Kings Hospital. He wrote the famous "Living with Diabetes" handbook which was reprinted many times. He, in 1935 founded the British Diabetic Association with HG Wells who also had diabetes. What must his parents have felt when the discovery was made and inevitable death changed to a long and illustrious life. There are many stories about Laurence, one such story, relates to his behaviour when he became hypoglycaemic (low blood sugar). This apparently was not an unusual occurrence in his clinic. As with hypoglycaemia, irritability and loss of control resulted in him yelling at his houseman in front of all the nurses and doctors "you are fired and don't come back". The nursing sister would go away, get sugar, tea, biscuits, and insist that Laurence would take his medicine. After a few minutes calm would return to the clinic the house man reinstated and the work continue! This story rang a bell with me. I was a houseman in Sir Patrick Duns hospital in Dublin And worked for the very famous Prof RH Micks. A Physician with an interest in Diabetes. Through his articles about Diabetic coma and its treatment in the British Medical Journal he saved so many diabetic lives. I was looking after a large English gentleman under his care. I remember he had a large handlebar moustache. He had been Lord Left Tennant of one of the English Shires in the South of England. He had diabetes and the first day I met him he proudly told me that one time he became hypoglycaemic and knocked the Houseman across the room with just one punch. After that I stayed at the door when I visited him!

The problem was that having made the discovery of an extract in the pancreas, that would be called insulin, how to test in Humans. It had become clear that the pancreatic extract lowered blood sugar and stopped ketosis, the burning up of fat that was usually the cause of death in diabetic patient before insulin. The problem was how to effectively and consistently purify the extract. Collip was a chemist working on a sabbatical in Toronto and he was employed to use his special skills to purify the extracts. He became a legend in his ability to extract hormones in his later years and then there was Leonard Thompson. He was a 14 year old boy with a 2 year history of Diabetes. He had been kept alive by starvation. As recorded in the wonderful and so exciting book by Prof Michael Bliss, (McCloud and Stewart inc Toronto Canada) Leonard was just skin and bones. He weighed 65lbs dull and listless and smelling of acetone (Ketosis) 'All of us knew he was doomed' Banting and Best took their extract over to the Ward H in Toronto general Hospital. It was injected by an intern. Leonards blood sugar fell 440 to 320, but he developed a sterile abscess. He received no further injections. That is until Collip managed to purify the abstract in reproducible way. Leonard Thompson received his powder by injection later in the month.

At 11 am on 23 January Leonard was given his Collip extract and in the evening another and next day 2 injections. His blood sugars became normal and the ketones disappeared. 'The boy became brighter looked better and said he felt stronger' (as quoted by Bliss). It is hard to describe what this miraculous cure of diabetes must have been. The astonishment of Doctors Nurses and parents when they saw that moribund patients came back to full life and vigour. When I read Bliss's book it still brings tears to my eyes. Elizabeth Hughe's case is written by Bliss under the heading 'Resurection'. 'Doctors from all over the world who come to Toronto to see for themselves the workings of this wonderful discovery and I wish you could see the expression on their faces when they read my chart'.

The fairy story of the discovery of insulin alas, was tempered by the human condition. The happy pair Banting and Best made the discovery but were both very inexperienced and young. Banting was very shy and had little experience of speaking in public. Best was only a student and when they gave their first results at a meeting their presentation was something of a disaster. Professor McCloud was chairman of the meeting and he intervened on their behalf trying to help. Alas Banting saw this as being the professor seeking the limelight and he became consumed with jealousy so much so that he hid himself in his room and started drinking very heavily. Collip was working away on purification and when he became successful, one evening came to Banting and Best in their laboratory and said he was not going to tell them how he did it and he was going to take his secret with him but eventually peace was brokered by Professor McCloud and other senior figures in the hospital and University. They were of course very worried that the discovery would go elsewhere and Toronto would lose out Banting was very bitter as he was excluded from the hospital , having no appointment and was therefore not allowed to administer the extract and did not have access to the diabetic data generated by the treatment in the beginning. The hospital eventually gave in and appointed him on the staff with a stipend. The story goes That a doctor friend went to visit Banting in his room shortly after some wealthy Doctors made a visit. His friend looked him up and down and asked "surely you did not meet them in that suit" Banting replied, that was the only suit he had so the friend marched him to his tailor and ordered a suit and overcoat.

A problem arose when they went to manufacturing the extracts in large quantities. They had little experience and lousy equipment. At one stage they needed urgently some equipment costing $10,000. Banting went to the chairman of the bord who was a banker but the old man refused him. Banting got up in a temper and said to the old man, well if I go and get it for you will you handle it for me? The banker thought for a minute and sad "I suppose so". Banting went home and phoned a physician friend whose child had diabetes and within a few hours had his $10000. There were other hiccups. Macleod realised that they did not have the know how to manufacture in large scale. He sought the expertise of Eli Lilly who had realised from the start how important this discovery was. George Clowes was a serious researcher working for Lilly and it was to Clowes that McCloud made his request. For a couple of months Ely Lilly also could produce no insulin and that must have been heart breaking with so many patients with diabetes being denied insulin.

On October 25th the 19 assembled professors voted by secret ballet to award the 1923 Nobel prize to Banting and Macleod. When Banting received the news he was furious and said he would not accept the prize. He was later persuaded that he should accept the prize in the interest of Science and Canada. Banting cabled Best who was giving a lecture in Harvard. The telegram read "I ascribe to Best equal share in the discovery, hurt that he is not so acknowledged by Nobel trustees. I will share it with him. Macleod shared his prise with Collop.

One hundred years on and a lifetime of looking after patients with diabetes, I still find it hard to comprehend what this discovery meant to people with diabetes. The joy of seeing a very dehydrated vomiting very ill patient, whether they be a child or adult, come back to full life is still to me a miracle. Diabetes is still a very difficult condition to manage. Every meal has to be matched to the insulin. Every exercise matched to the insulin requirements. No days off. Anxiety may increase insulin needs. Short burst of exercise may increase blood sugar but long exercise lowers blood sugars. Too much insulin leads to coma and sometimes this coma can come on without warning, making living alone hazardous yet many take this risk willingly. As a child your parent's attention and anxiety to the detriment of your siblings makes for disharmonious relationships. I well remember a drawing a child did of his family's seaside holiday. The siblings are running but the child with diabetes is holding her Mothers hand. The child with diabetes was 16 and the child who drew the picture was 7.

One hundred years ago insulin was a 'cure' The patient survived. Alas in later years it became clear that some patients who initially did so well developed what we call complications of diabetes. Meticulous control of blood sugars are, in real life, mostly not feasible. High blood sugars after many years may damage the blood vessels leading to blindness, loss of sensation (neuropathy) and kidney failure. Damage to the large blood vessels lead to heart attacks, strokes and amputations. The wonderful improvements in management with, for example, continuous glucose sensors, insulin pumps and semiautomated insulin delivery systems have made an enormous difference. Experimentally, artificial pancreases can almost mimic normal pancreatic function. Pancreatic transplants are sometimes an option as are transplantation of pancreatic islets. Most importantly it is now very rare to become blind because of revolutionary treatment by Ophthalmologists. High Blood pressure and high cholesterol frequently accompany diabetes in middle age. Wonderful treatment for both have increased life expectancy to normal or near normal. But diabetes is still a huge burden, particularly in late adolescence and young adulthood, making acceptance of the imposition of diabetes management too difficult for some to manage.

Looking after someone with diabetes over many years is fascinating, instructive and humiliating. You get to know so many things about your patient and their families. The honour of being trusted by a patient is hard to describe. You make so many friends and when you retire all this joy is taken away from you. You give your expertise and guidance and for each patient it will be different, but sometimes you fail, and that failure really hurts. I remember one girl of about 24 who burst into tears when I suggested that her blood sugars were too high and that she needed to take more insulin. 'You tell me that every time I come to see you and I try my best'. I felt awful as I suddenly thought that she was right. She was unable to follow my instructions and that was my failure as her Physician not hers.

On another occasion in the clinic the parents of a 20 year-old came to see me. They asked whether their son was a good patient and whether he followed all the rules and I said yes indeed he was a model patient. 'Well he is dead' The father said. He was unsteady one morning because of low blood sugars. The next morning more unsteady and the third morning he fell down the stairs and broke his neck. I did not know how to

comfort them or myself. Had I not taught him that if blood sugars drop, then if no reason like unusual exercise or reduced food, then you must reduce your insulin. My fault that he did not understand.

On a happier note the patient who could not stand the pregnancy diabetic clinic and I agreed to look after her during pregnancy. We had a healthy baby between us and she had a happy pregnancy.

One hundred years on from the discovery of insulin we still do not know what kills the B cells, but we know so much more about treating patients with diabetes. Prevention of diabetes is a hurdle still to be jumped and progress is slowly being made.

Read the discovery of Insulin by Michael Bliss. You will enjoy.

Having discovered insulin and having translated the discovery into therapy for many tens of thousands of patients with diabetes there remained a problem in how to measure insulin and how to measure the concentration in each batch made. The best way at the time was to see how effective the sample was in lowering the blood sugar of an animal, such as the rabbit. Other methods were tried none very specific or sensitive. There was a girl called Rosalyn Yalow whose Mother was an immigrant from Germany and whose Father was the son of a Russian immigrant also from the Bronx. They had little high school education but their daughter overcame all obstacles to being Jewish and a woman. In particular, she became only the second woman ever to win the Nobel Prize. She records that after getting A's in physics both laboratory and theoretical, the chairman of the physics department looking at her results said' That proves that women do not do well at laboratory work'!

Solomen Berson grew up also in New York. His father came from Russia and was a chemical engineer. Berson had remarkable school record but still was rejected by many medical schools before being accepted by New York City University. Yalow was excited by nuclear Physics and took a position in the Veterans Administration Hospital in the Bronx to develop medical use of radioactive isotopes. Berson had already accepted a job in Long Island when he dropped in to talk to Yalow. They apparently were fired by each other's intellect and so the two of them set up shop in an old Janitors closet in the Hospital. Together they developed the radio immunoassay for insulin which was very sensitive and specific. They showed that the technique could be used to measure many other hormones. They discovered that Type 2 diabetes, then known as non-insulin-dependent diabetes, was not a problem of no or little insulin but rather of insulin resistance. They discovered so much more. Their seminal paper was rejected by Science, the prestigious Science Journal, and at first rejected by the Journal of Clinical investigation and only accepted when they changed the title. There was so much scepticism about their work. Now their paper holds the record for being one of the most cited papers of that journal. Their discovery revolutionised diabetes and endocrinology research. The award of the Nobel prize in 1977 did not also go to Berson as alas he had died prematurely some years before

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