Sultan Qaboos University Med J, August 2013, Vol. 13, Iss. 3, pp. 368-370, Epub. 25th Jun 13
Submitted 21st May 13
Peer Reviewed
Accepted 3rd Jun 13

MEDICAL HISTORY

The History of Diabetes Mellitus

Ritu Lakhtakia

نظرة تاريخية عن مرض السكري

ريتو لاكتكيا

"... no essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into urine." - Aretaeus of Cappadocia

Origins, Symptoms and Signs

A disease characterised by the 'too great emptying of urine' finds its place in antiquity through Egyptian manuscripts dating back to 1500 B.C.[1] Indian physicians called it *madhumeha* ('honey urine') because it attracted ants. The ancient Indian physician, Sushruta, and the surgeon Charaka (400–500 A.D.) were able to identify the two types, later to be named Type I and Type II diabetes.[2,3] Recognised for the last three millennia, recorded history attributes the first complete descriptions in the first century A.D. to Aretaeus the Cappadocian, who coined the word *diabetes* (Greek, 'siphon') and dramatically stated "... no essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into urine".[4–6] Avicenna (980–1037 A.D.), the great Persian physician, in *The Canon of Medicine* not only referred to abnormal appetite and observed diabetic gangrene but also concocted a mixture of seeds (lupin, fenugreek, zedoary) as a panacea.[7] The term *mellitus* (Latin, 'sweet like honey') was coined by the British Surgeon-General, John Rollo in 1798, to distinguish this diabetes from the other diabetes (*insipidus*) in which the urine was tasteless.[1]

Pathophysiology through Experimentation

In 1869, Paul Langerhans, then aged 22 and working on his medical doctorate, identified the cells that came to be known as the 'islets of Langerhans.'[8] However, the name *insulin* for the secretions of the islets (Latin, *insula* = island), which could bring down blood glucose levels, was coined only in 1909 and 1910, individually by de Mayer and Schaefer, respectively.[9,10] In 1889, von Mering and Minkowski, when experimenting on dogs, found that removal of the pancreas led to diabetes.[11] In 1921, Banting, Best and Collip, working in Macleod's laboratory, ligated the pancreatic duct, causing the destruction of the exocrine pancreas while leaving the islets intact. In their elegant animal experiments, by using canine insulin extracts to reverse induced diabetes, they conclusively established that the deficiency of insulin was the cause of diabetes.[12]

Diagnosis

Willis, a London physician, epitomised the true spirit of scientific enquiry by his bold action of tasting the urine of his patients—possibly because the passage of copious urine seemed to be the hallmark of the disease! This was a supreme and extreme example of bedside testing leading to labelling a patient as diabetic if his urine was 'honeyed'.[13]

Urine strips in the 1960s and the automated 'do-it-yourself' measurement of blood glucose through glucometers, produced by Ames Diagnostics in 1969, brought glucose control from the emergency room to the patient's living room. It imbued diabetic patients with a new sense of freedom, making the disease more comprehensible and manageable.

Department of Pathology, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman
E-mail: ritu@squ.edu.om

Routine blood sugar tests at prescribed intervals continued for a long time until the introduction of the glycosylated haemoglobin (HbA1c) estimation. That test, which measured blood glucose control over the previous three months (linked to the life of red blood cells), defined an extremely important aspect of diabetes management—tight control of blood glucose levels.[14] The latter directly determined the risk of the occurrence of devastating complications of target organs like the eyes, vessels, nerves and kidneys that ultimately influenced morbidity and mortality.

Treatment

With little understanding of pathophysiology, early remedies for diabetes included diverse and interesting prescriptions like "oil of roses, dates, raw quinces and gruel, jelly of viper's flesh, broken red coral, sweet almonds and fresh flowers of blind nettles" representing a variety of beliefs and practices of the times.[4] Later, in the pre-insulin era, calorie restriction reigned supreme, and graphic accounts of the terminal gasping and sighing and sweet smell (*ketosis*) surrounding the patient in a diabetic coma abound in the volumes written on the disease. Diet and exercise advocacy was the hallmark of treatment by 19th century physicians led by Joslin and Fitz from the Massachusetts General Hospital, among others.[15] This advice still remains an important component of diabetic management. It may sound bizarre today, but opium ('syrup of poppies') was prescribed liberally for the malady for over two hundred years from Willis (1675) to Joslin (1898).[15,16] The rationale could only have been an easing of the symptoms originating from complications like gangrene.

The 19th and 20th centuries heralded galloping advances in medicine in general and in diabetes treatment in particular. One of the miracles of the last century was the discovery of insulin by Canadian surgeon Banting and his assistant Best. Following experimentation on dogs, their life-saving infusion of a bovine extract of insulin (made by their biochemist colleague, Collip) to a 14-year-old boy, Leonard Thompson, in 1922 at the Toronto General Hospital, proved to be a sensation in the world of diabetic therapy.[12] It galvanised research into and the commercial production of several modifications of insulin with various durations of action, that changed the entire course of life of a significant proportion of the world populace.[17] It won Banting and Macleod the Nobel prize in Physiology and Medicine in 1923.[18] The hat trick of Nobel prizes for this important molecule was complete with subsequent winners in Chemistry and Medicine, respectively for its aminoacid sequence (Sanger, 1958) and radioimmunoassay (Yallow, 1977).[19,20] However, it was not until the 1950s that the first oral antidiabetic drugs (sulphonylureas) were added to the treatment armamentarium. Others, including metformin, glucosidase inhibitors and insulin sensitisers, followed in the succeeding decades with different sites of action to enable better handling and metabolic assimilation of ingested carbohydrates.[1,13] Traditional spices, herbs and indigenous plants used through centuries have provided supportive alternatives and potential for future research.[21]

In 1980, the first human insulin was manufactured by Graham Bell.[22] In 1982, the first biosynthetic insulin (humulin) was developed. Syringes appeared in 1961 but, being made of glass, brought with them the attendant hazards of infections until they were replaced with disposable plastic ones. It was only 15 years later that the introduction of the first needle-free insulin delivery system by Derata in 1979 provided relatively pain-free, metered doses. Insulin pumps, inhaled insulin and oral sprays in recent times have shown the way ahead for ease of administration.[13,23,24]

History in the Making

In the new millennium, pancreatic transplantation, first performed in 1966,[25,26] exists as a radical therapy for especially intractable Type I diabetes with advanced complications. Still in experiment mode, gene therapy with molecules like leptin and insulin may one day be a reality.[27,28]

Lessons from the History of Diabetes

1. The antiquity of early descriptions of diabetes underscores the importance of the observation and recording of medical conditions as humans evolve. Early physicians used whatever was in their capacity (smell or even taste!) in pursuit of knowledge, skills and diagnosis.

2. Age is no bar to contributing significantly to the profession; Langerhans, was a 22 year old student when he wrote a thesis identifying the cells that were

later known to be the source of insulin production.

3. Despite accounts of the acrimonious 'team' interactions building up to and following the groundbreaking discovery of insulin, the acknowledgement of fellow professionals is illustrated in Banting and Macleod's (Noble laureates) recognition of Best and Collip's immense contributions by sharing their Noble prize money with them.[29]

4. The refusal to patent insulin but to share this miraculous therapy freely with the world will remain an outstanding example of unreserved generosity towards mankind in the history of medical disease. Banting's colossal contribution has been globally recognised by the declaration, since 2007, of his birthday (14th November) as World Diabetes Day.

From unrecorded accounts to published knowledge, this human scourge is, simply put, a modern day epidemic. We, and future generations of medical professionals, share the task of taking this history forward.

References

1. MacCracken J, Hoel D. From ants to analogues: Puzzles and promises in diabetes management. Postgrad Med 1997;101:138–40, 143–5, 149–50.
2. Tipton MC. Susruta of India, an unrecognized contributor to the history of exercise physiology. J Appl Physiol 2008;108:1553–6.
3. Frank LL. Diabetes mellitus in the texts of old Hindu medicine (Charaka, Susruta, Vagbhata). Am J Gastroenterol 1957;27:76–95.
4. Sattley Melissa. The History of Diabetes. From: http://diabeteshealth.com/read/2008/12/17/715/the-history-of-diabetes/ Accessed: May 2013.
5. Ahmed AM. History of diabetes mellitus. Saudi Med J 2002; 23:373–8.
6. Sanders LJ. From Thebes to Toronto and the 21st century: an incredible journey. Diabetes Spectr 2002;15:56–60.
7. Dobson M. Experiments and observations on the urine in diabetes. Med Obs Inq 1776; 5:298–316.
8. Sakula A. Paul Langerhans (1847-1888): a centenary tribute. J R Soc Med 1988; 81:414–5
9. Schafer E. An introduction to the study of the endocrine glands and internal secretions. Palo Alto, California: Stanford University, 1914. Pp. 84, 86.
10. De Meyer J. Action de la sécrétion interne du pancéras sur différents organes et en particulier sur la sécrétion rénale. Arch Fisiol 1909; 7:96–9.
11. Von Mehring J, Minkowski O. Diabetes mellitus nach Pankreasexstirpation. Arch Exp Pathol Pharmakol 1890. 26:371–87. doi:10.1007/BF01831214.
12. Banting FG, Best CH, Collip JB, Campbell WR, Fletcher AA. Pancreatic extracts in the treatment of diabetes mellitus: preliminary report. CMAJ 1922; 12:141–6.
13. Barnett DM, Krall LP. The History of Diabetes. In: Joslin's Diabetes Mellitus. 14th ed. Boston, Massachusetts: Lippincott Williams & Wilkins, 2005.
14. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New Engl J Med 1993; 329:977–86.
15. Allan FN. The writings of Thomas Willis: Diabetes 300 years ago. Diabetes,1953; 2:74–8.
16. Holms OW, Hall M. Principles of the Theory and Practice of Medicine. Boston, Massachusetts: Little & Brown, 1839.
17. Allan FL. Diabetes before and after insulin. Med Hist 1972;16:266–73.
18. Nobel Prize Laureates, Medicine, 1923. From: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1923/ Accessed: May 2013.
19. Nobel Prize Laureates, Chemistry, 1958. From: http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1958/ Accessed: May 2013.
20. Nobel Prize Laureates, Medicine, 1977. From: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1977/ Accessed: May 2013.
21. Gilani AH. Medicinal value of food and dietary supplements. Diab Endoc J 2007; 35:4.
22. Bell GI. Pictet RL, Rutter WJ, Cordell B, Tischer E, Goodman HM. Sequence of the human insulin gene. Nature 1980; 284:26–32.
23. Dunn C, Curran MP. Inhaled human insulin (Exubera): a review of its use in adult patients with diabetes mellitus. Drugs 2006; 66:1013–32.
24. Generex Biotechnology. Oral-Lyn – Oral insulin for types 1 and 2 diabetes. Industry project. From: http://www.drugdevelopmenttechnology.com/projects/oral-lyn/2007 Accessed: May 2013.
25. Pancreas Transplant. From: http://www.mayoclinic.com/health/pancreas-transplant/MY00762 Accessed: May 2013.
26. Kelly WD, Lillehei RC, Merkel FK, Idezuki Y, Goetz FC. Allotransplantation of the pancreas and duodenum along with the kidney in diabetic nephropathy. Surgery 1967; 61:827–37.
27. Amitani M, Asakawa A, Amitani H, Inui A. The role of leptin in the control of insulin-glucose axis. Front Neurosci 2013; 7:51. Epub. 8 Apr 2013. doi:10.3389/fnins.2013.00051.
28. Gene Therapy in Dogs to Treat Diabetes. From: http://www.diabetes.org/for-media/2013/gene-therapy-used-in-dogs-to-treat-type1-diabetes.html Accessed: May 2013.
29. Louis Rosenfeld. Insulin: discovery and controversy. Clin Chem 2002; 48:2270–88.