1 The History of Diabetes Mellitus Robert B. Tattersall University of Nottingham, Nottingham, UK Textbook of Diabetes, 4th edition. Edited by R. Holt, C. Cockram, A. Flyvbjerg and B. Goldstein. © 2010 Blackwell Publishing. Keypoints • Polyuric diseases have been described for over 3500 years. The name " diabetes " comes from the Greek word for a syphon; the sweet taste of diabetic urine was recognized at the beginning of the fi rst millennium, but the adjective " mellitus " (honeyed) was only added by Rollo in the late 18th century. • The sugar in diabetic urine was identifi ed as glucose by Chevreul in 1815. In the 1840s, Bernard showed that glucose was normally present in blood, and showed that it was stored in the liver (as glycogen) for secretion into the bloodstream during fasting. • In 1889, Minkowski and von Mering reported that pancreatectomy caused severe diabetes in the dog. In 1893, Laguesse suggested that the pancreatic " islets " described by Langerhans in 1869 produced an internal secretion that regulated glucose metabolism. • Insulin was discovered in 1921 by Banting, Best, Macleod and Collip in acid - ethanol extracts of pancreas. It was fi rst used for treatment in January 1922. • Diabetes was subdivided on clinical grounds into diab è te maigre (lean subjects) and diab è te gras (obese) by Lancereaux in 1880, and during the 1930s by Falta and Himsworth into insulin - sensitive and insulin - insensitive types. These classifi cations were the forerunners of the etiological classifi cation into type 1 (insulin - dependent) and type 2 (non - insulin - dependent) diabetes. • Insulin resistance and β - cell failure, the fundamental defects of type 2 diabetes, have been investigated by many researchers. The " insulin clamp " method devised by Andres and DeFronzo was the fi rst accurate technique for measuring insulin action. Maturity - onset diabetes of the young was described as a distinct variant of type 2 diabetes by Tattersall in 1974. • Lymphocytic infi ltration of the islets (insulitis) was described as early as 1901 and highlighted in 1965 by Gepts who suggested that it might be a marker of autoimmunity. Islet cell antibodies were discovered by Doniach and Bottazzo in 1979. • The primary sequence of insulin was reported in 1955 by Sanger and the three - dimensional structure by Hodgkin in 1969. Proinsulin was discovered by Steiner in 1967, and the sequence of the human insulin gene by Bell in 1980. Yalow and Berson invented the radioimmunoassay for insulin in 1956. The presence of insulin receptors was deduced in 1971 by Freychet, and the receptor protein was isolated in 1972 by Cuatrecasas. • The various types of diabetic retinopathy were described in the second half of the 19th century as were the symptoms of neuropathy. Albuminuria was noted as a common abnormality in patients with diabetes in the 19th century and a unique type of kidney disease was described in 1936 by Kimmelstiel and Wilson. The concept of a specifi c diabetic angiopathy was developed by Lundbaek in the early 1950s. • Milestones in insulin pharmacology have included the invention of delayed - action preparations in the 1930s and 1940s; synthetic human insulin in 1979; and in the 1990s novel insulin analogs by recombinant DNA technology. • The fi rst sulfonylurea carbutamide was introduced in 1955, followed by tolbutamide in 1957 and chlorpropamide in 1960. The biguanide phenformin became available in 1959 and metformin in 1960. • That improved glucose control in both type 1 and type 2 diabetes was benefi cial was proved by the Diabetes Control and Complications Trial (1993) and the UK Prospective Diabetes Study (1998). • Landmarks in the treatment of complications include photocoagulation for retinopathy fi rst described by Meyer - Schwickerath; the importance of blood pressure to slow the progression of nephropathy (demonstrated by Mogensen and Parving); the introduction of low - dose insulin in the treatment of diabetic ketoacidosis in the 1970s; and improvements in the care of pregnant women with diabetes pioneered by White and Pedersen. Ancient t imes Diseases with the cardinal features of diabetes mellitus were recognized in antiquity (Table 1.1). A polyuric state was described in an Egyptian

papyrus dating from c. 1550 bc , discovered by Georg Ebers (Figure 1.1), and a clearly recognizable description of what would now be called type 1 diabetes was given by Aretaeus of Cappadocia in the 2nd century ad (Figure 1.2 a). Aretaeus was the fi rst to use the term “ diabetes, ” from the Greek word for a syphon, “ because the fl uid does not remain in the body, but uses the man ’ s body as a channel whereby to leave it. ” His graphic account of the disease highlighted the incessant fl ow of urine, unquenchable thirst, the “ melting down of the fl esh and limbs into urine ” and short survival. The Hindu physicians, Charak and Sushrut, who wrote between 400 and 500 bc , were probably the fi rst to recognize the sweetness of diabetic urine (Figure 1.2 b). Indeed, the diagnosis was made by tasting the urine or noting that ants congregated round it. Charak and Sushrut noted that the disease was most prevalent in those who were indolent, overweight and gluttonous, and who indulged in sweet and fatty foods. Physical exercise and liberal quantities of vegetables were the mainstays of treatment in the obese, while lean people, in whom the disease was regarded as more serious, were given a nourishing diet. The crucial fact that diabetic urine tasted sweet was also emphasized by Arabic medical texts from the 9 – 11th centuries ad , notably in the medical encyclopedia written by Avicenna (980 – 1037). The 17th and 18th c enturies In Europe, diabetes was neglected until Thomas Willis (1621 – 1675) wrote Diabetes, or the Pissing Evil [1] . According to him, “ diabetes was a disease so rare among the ancients that many famous physicians made no mention of it … but in our age, given to good fellowship and guzzling down of unallayed wine, we meet with examples and instances enough, I may say daily, of this disease. ” He described the urine as being “ wonderfully sweet like sugar or honey ” but did not consider that this might be because it contained sugar. The fi rst description of hyperglycemia was in a paper published in 1776 by Matthew Dobson (1735 – 1784) of Liverpool (Figure 1.3) [2] . He found that the serum as well as the urine of his patient Peter Dickonson (who passed 28 pints of urine a day) tasted sweet. Moreover, he evaporated the urine to “ a white cake [which] smelled sweet like brown sugar, neither could it by the taste be distinguished from sugar. ” Dobson concluded that the kidneys excreted sugar and that it was not “ formed in the secretory organ but previously existed in the serum of the blood. ” The Edinburgh - trained surgeon, John Rollo (d. 1809) was the fi rst to apply the adjective “ mellitus ” (from the Latin word meaning “ honey ”). He also achieved fame with his “ animal diet, ” which became the standard treatment for most of the 19th century. Rollo thought that sugar was formed in the stomach.s