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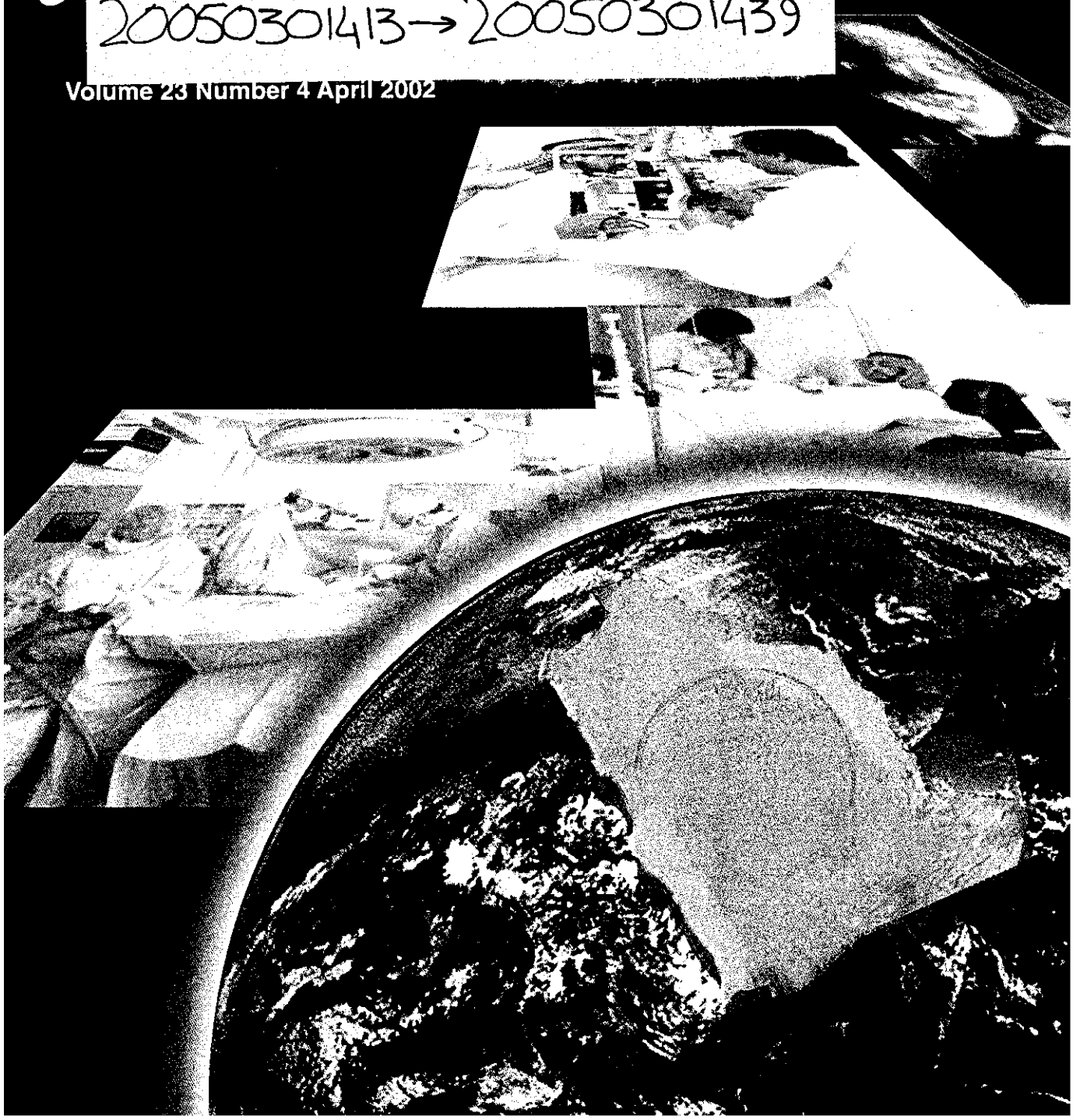

Short Review

History of Diabetes Mellitus

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ABSTRACT

Clinical features similar to diabetes mellitus were described 3000 years ago by the ancient Egyptians. The term "diabetes" was first coined by Araetus of Cappodocia (81-133AD). Later, the word mellitus (honey sweet) was added by Thomas Willis (Britain) in 1675 after rediscovering the sweetness of urine and blood of patients (first noticed by the ancient Indians). It was only in 1776 that Dobson (Britain) firstly confirmed the presence of excess sugar in urine and blood as a cause of their sweetness. In modern time, the history of diabetes coincided with the emergence of experimental medicine. An important milestone in the history of diabetes is the establishment of the role of the liver in glycogenesis, and the concept that diabetes is due to excess glucose production Claude Bernard (France) in 1857. The role of the pancreas in pathogenesis of diabetes was discovered by Mering and Minkowski (Austria) 1889. Later, this discovery constituted the basis of insulin isolation and clinical use by Banting and Best (Canada) in 1921. Trials to prepare an orally administrated hypoglycemic agent ended successfully by first marketing of tolbutamide and carbutamide in 1955. This report will also discuss the history of dietary management and acute and chronic complications of diabetes.

Keywords: Diabetes, history.

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Diabetes mellitus as a disease, for example a constellation of symptoms, but not its pathogenesis, has been known by physicians for nearly 3,500 years in ancient Egypt.[1] The Ebers papyrus dating from 1550 BC was found in a grave in Thebes region south of Egypt in 1862, and named after the Egyptologist Geary Ebers.[1] The papyrus contains descriptions of various diseases, among them is a polyuric syndrome, presumably diabetes. The Egyptians suggested various remedies to this syndrome including a decoction of bowes, wheat and earth.[1] The Verdic medical treatises from ancient India described, in detail, diabetes like conditions of 2 types: Congenital and late onset.[2] Also, the Indians noticed the relation of diabetes to heredity, obesity, sedentary life and diet. They suggested the freshly harvested cereals and bituminous preparations containing benzoates and silica as a remedy for diabetes. The first time association of polyuria with a sweet-tasting substance was reported in the Indian literature from the 5th-6th century AD by Sushrant (a notable Indian physician).[2] Araetus of Cappodocia (81-138 AD); who was best known for his differentiation between physical and mental disease, described diabetes as a polyuric wasting disease.[3] Araetus said "Diabetes is a wonderful affection being a melting down of the flesh and limbs into urine. The patient never stops drinking water but the flow is incessant as if from the opening of adequeducts. The patient is short lived".[3] Araetus used the Greek word diabetes, literally meaning to run through or siphon, to describe the disease. An Arab physician, Avicenna (960-1037) described accurately the clinical features and some complications of diabetes (peripheral neuropathy, gangrene and erectile dysfunction).[4] Avicenna emphasized the idea of sweet taste of urine and may have introduced it to the European observers as his book (Kanon) had influenced the medical practice for several centuries.

Diabetes in the modern times. The history of diabetes in modern time coincided with the establishment of the experimental foundations of

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modern medicine. Two prominent milestones in the history of medicine paved the way towards understanding the pathogenesis of diabetes. The first one was the application of chemistry as a diagnostic tool in the 2nd half of the 18th century.[5] The other milestone was the emergence of endocrinology as a formal discipline with the works of the Claude Bernard (1813-1878) and Brown-Sequard (1817-1894). Bernard established the concept of organs of internal secretions (glands), whereas Brown-Sequard demonstrated that death from adrenalectomy could be delayed by infusing blood from healthy animals.[5] The modern era in the history of diabetes started with the rediscovery of Thomas Willis in 1675 of sweetness of urine of diabetic patients.[5] Willis, who was a physician at Guy's Hospital in London, United Kingdom, stated unequivocally that the diabetic urine is "wonderfully sweet as if it was imbued with honey or sugar". He added the Latin word mellitus, literally meaning honey sweet to the Greek diabetes to describe the disease. But Willis could not attribute this urine sweetness to presence of sugar. Four years later, Frank classified the disease, on the basis of presence of sugar-like substance into diabetes insipdus (tasteless urine) and diabetes vera (sweet urine). Approximately a century later, Mathew Dobson (1735-1784), a Liverpool physician, confirmed the presence of sugar in both urine and blood of diabetic patients in 1776.[6] Later, in 1815, Michael Chevreal (a French chemist) demonstrated the sugar was in fact glucose. Dobson did not establish the origin of the excess sugar. He deduced that the excess urine sugar was not produced in the kidney as was thought but it previously existed in the blood and the body failed to assimilate it. Thus diabetes from Dobson's view was a systemic disease and not 'kidney malady'. This observation led the diabetes research in the right tract as a defect in carbohydrate metabolism.[6] John Rollo, a French physician, in 1798, erroneously concluded that diabetes was a disease of the stomach as a result of abnormal transformation of vegetable nutrients into sugar.[7] He suggested carbohydrate restriction as a treatment.[7]

Discovery of carbohydrate metabolism. Claude Bernard is considered to be the founder of experimental medicine by applying physical and chemical methods in artificial induction of diseases. Initially Bernard, from his famous piqure experiments thought that diabetes was due to disease of the central nervous system.[8] The great contribution of Bernard, in the diabetes history was his establishing of the concept of excessive glucose production in patients' livers with the aid of an enzyme.[5] Bernard explained the formation of liver glycogen and its fate in the liver and elsewhere in the body.[5] He found, in 1855, that the hepatic vein in an animal fed entirely on meat contained a large amount of sugar.[5] He concluded that the liver secreted the sugar, coining the term 'internal secretion' for this process. In the same year Bernard investigated 2 samples of liver extracts of an animal, immediately after its death. He examined one sample and left the other to the next day. He found that the 2nd sample contained much more sugar than the first one. Bernard concluded that the sugar was formed as a result of sugar-forming substance in the liver. In 1857 Bernard discovered this substance and termed it glycogen. Ninety years later Gerty and Cori discovered how the glycogen is catalytically converted into sugar by the phosphorylase enzyme and were awarded a Noble Prize, in 1947. Bernard is also credited as the first to ligate the pancreatic duct, a technique that was frequently employed in further attempts to insolate the endocrine secretion of the pancreas.[5]

Role of pancreas. In ancient times, the pancreas was thought of only as packing for the stomach and neighboring organs, or that it was the 'gallbladder' of the spleen. Excision of the pancreas of dogs was performed in 1673 by Johann Brunner (1653-1727) of Schaffhausen. He noted that some of his dogs showed excessive thirst and polyuria. Gross changes in pancreas of diabetic patients were reported by Richard Bright (1831) and von Recklinhausen (1864).[5] Paul Langerhans (1847-1888), in a dissertation published at Berlin in 1869 described the gross anatomy and histology of pancreatic islet cells of no direct connection to the glandular tissue proper.[9] Later these cells were named after Langerhans by Gustav Laguesse (1861-1927) of Lille, France in 1893. Solid proof that diabetes is due to a pancreatic lesion resulted from the crucial experiments of Joseph von Mering (1849-1908) and Oscer Minkowsk (1841-1904) then both at Strasbourg, France, who were considered the real discovers of the role of pancreas in pathogenesis of diabetes in 1889.[10] They showed that pancreateatomized dogs developed rapidly fatal diabetes unrelated to the loss of the flow of pancreatic juice to the intestine, as such the pancreas has some role in carbohydrate metabolism.[10] These experiments were, a few years later, confirmed by Laguesse who suggested in 1893 that the islets of Langerhans produced an internal secretion. In 1900, Eugene Opie (American pathologist) reported morbid changes in the pancreatic islets of diabetic patients but the well established connection between islets lesion and glycosuria was made by W. MacCallum in 1909.[11] The next task was the isolation of the active substance secreted by the islets of Langerhans that regulates carbohydrate metabolism. Edward Sharpy-Shafer, in 1916, proposed the name of insulin for this substances (a Latin word for island).[11] In 1909 Goerge Zuelzer (1870-1949) of Berlin obtained a pancreatic extract which was injected subcutaneously to 8 diabetic patients with good results but, unfortunately, this work was stopped at the start of

the first world war.[11] Although the role of the pancreatic islets in pathogenesis of diabetes was established by end of the 19th century, it took 30 years to discover, isolate and clinically use insulin.[11] The major difficulties included inability to estimate blood glucose (the Bernard's method applied then was technically difficult and require 50-100 ml for one test). Another difficulty was the destruction of insulin by trypsin. Ernest Scott (USA) was near to isolate insulin 10 years before Banting and Best, in 1910.[11] His published thesis on the effects of pancreatic extracts on depancreatectomized dogs ended with valuable conclusions. Scott concluded that there was a substance responsible for carbohydrate metabolism. Being easily destroyed by digestive enzymes and oxidation, this substance should be extracted by proper methods for clinical use. His antagonistic supervisor (Professor A. Carlson)[12] disappointed Scott. Also he was failed by his inability to accurately and easily estimate blood glucose.[12] At that period (1910-1922), several therapies for diabetes were tried such as pancreatic extract by mouth (Henry Sewal, 1911, Germany), pancreatic extract in acid-insoluble capsules (W Groftor, 1913, extracts of Pancreas, and duodenal mucosa, subcutaneously, Guralin and Kramar, 1914, England) and starvation (Joslin, 1915, USA).[13] Similar work to that of Banting and Best was carried out by Nicolas Paulesco (1869-1931), a Romanian physiologist and physician. He injected an aqueous extract of the pancreas into the jugular veins of diabetic dogs. But his work was interrupted in 1916 when the Germans took Bucharest. When he resumed his work after the war, Banting and Best were finished the task![11]

Banting and Best: dawn of insulin era. One of the greatest discoveries in the history of medicine was the isolation of insulin in the summer of 1921 by Fredrick Grant Banting (1891-1941) and Charles Herbert Best (1899-1965) of Toronto, Canada. They used the physiological laboratory of John Macleod (Professor of Physiology at the University of Toronto, Canada). The Macleod's laboratory was particularly well equipped for work in carbohydrate metabolism. Macleod himself published a book, Diabetes: its pathological physiology in 1913, in which he stated that it would be nearly impossible to isolate the internal secretion of the pancreas involved in carbohydrate metabolism. Banting met Macleod in 1920 and expressed his interest in investigating this internal secretion.[11] Although he was pessimistic of this work, Macleod offered the use of his laboratory to Banting.[11] Best was one of Macleod's undergraduate students and was asked to help in the laboratory in urine and blood tests. After an extensive review of the up-to-date literature, Banting noted the failure of the previous workers to isolate insulin. Apparently Banting and Best claimed that they had started from the point that Von Mering and Minkowskiy ended.[11,12] They may be aware of Scott's works, but they did not get use of the works of Zuelzer and Paulesco as they were published in German and French languages. The initial results of Banting and Best were similar to these works such as obtaining an impure pancreatic extract which reduced blood glucose in depancreatized dogs. Their works were different from the previous ones by involvement of James Collip, a biochemist, to purify the extract, so as to be safe for human use. This task ended with a great success in 1921. By the discovery of insulin and its introduction in clinical use a new era in diabetic treatment and in medicine had started. The life qualities of patients were much improved ending the miserable times of starvation and lethal ketosis and infections. In December 1921 Banting presented a talk regarding 'The beneficial influence of certain pancreatic extracts on pancreatic diabetes. By: Macheod, Banting and Best, to the American Physiological Society at Yale University. Macleod was involved as Banting was not a member of the society. In fact Macleod was away throughout the discovery period and played no part in the actual research work. Banting and Best published their research results in a historical paper in the Canadian Medical Association Journal in 1922 (surprisingly Macheod's name was absent!).[14] In 1923 the Noble's prize for medicine was awarded to Banting and Macleod. Banting considered that Macleod had stolen the limelight and shared his prize money with Best. Macheod shared his prize money with Collip, then took over their research in insulin standardization. Insulin was clinically used for humans in January 1922 in a 14-year-old diabetic boy named Leonard Thombson in Toronto, Canada.[12] He firstly received an extract made by Banting that failed, and caused an abscess. But the patient responded dramatically when he used another extract prepared by Collip (who refused to tell Banting and Best the method he used in extraction!). By then industrial mass production of purified insulin had started. Only soluble insulin was available until 1936 when protamine insulins were introduced (isophane and protamine zinc insulins). In the 1950s, insulin zinc suspension became available. The highly purified insulin, identical to human endogenous insulin, was introduced in the 1970s.[15] In 1955, Fredrick Sanger (Britain) elucidated the structural formula of insulin, and in 1960 Nicol and Smith described the amino-acid sequences of insulin and then the structural differences between porcine, bovine and human insulin's were revealed.[15]

Oral hypoglycemic agents. The hypoglycemic effect of sulphonamides was firstly detected in 1930.[16] This issue was reactivated in 1942 when Professor M. J. Janbon (Professor of Pharmacology at Monteplier, South of France) was working for a cure for typhoid fever.[17] He noticed that the substance testing on animals (P.amino sulphona-mide-

isopropyl-thioctiazole) could cause severe hypoglycemia.[17] By 1946, Loubatieres demonstrated experimentally that the sulphonamide group was responsible for the hypoglycemic action.[18] The sulphonamides lowered the blood glucose in dogs that had undergone partial pancreatectomy and that when injected into normal dogs whose pancreaticduodenal vein was anastomosed to the jugular vein of a dog whose pancreas had been removed, they lowered blood glucose level in the 2nd day.[18] The Loubatieres' work was little noticed until 10 years later when Frank and Fuchs in Berlin, Germany[19] rediscovered sulphanomides. Their work resulted in the development of the first 2 compounds to be evaluated (tolbutamide and carbutamide), then followed by tolazamide and chloropromide in the next decade. A stormy reaction against use of oral hypoglycemic agent followed the report in 1970 of the University Group Diabetes Program (UGDP) claiming lack of efficacy and cardiovascular risks of tolbutamide.[20] Then the use of sulphanemides largely declined until in late 1970s when the UGDP conclusions were disproved and then the use of sulphonamides was revived.[21] A herb called Galega officinals (goate's rue or French lilac) was used in medieval Europe as a treatment for diabetes.[22] The active ingredient of this herb was used to synthesize several antihyperglycemic agents in the 1920s but abandoned a few years later for fear of hepatotoxicity.[22] In the 1950s, Metfermin and Phenformin were developed from the active ingredient of Galega officinals. Phenformin was withdrawn from the market in the early 1970s as a the high frequency of lactic acidosis resulted from its use.

Dietary management of diabetes. The ancient physicians paid little attention to the role of diet in treatment of diabetes. The Egyptians suggested a decoction of wheat, bones, and other substances to treat this disease.[1] The Indians suggested freshly harvested cereals as a treatment for diabetes. In that era, certain types of foods were prescribed for all diseases.[2] John Rollo was the first to discuss the influence of food in management of diabetes in 1797.[23] Rollo's meat-based diet contained low carbohydrate.[23] Although compliance was poor, the diet lead to reduction of symptoms and weight loss. Over the following century various diets were tried. Starting from 1913 until the introduction of insulin, the Allen's starvation diet prevailed (intermittent fasting followed by a high-fat diet).[24] Although it was hardly accepted by patients, the Allen's diet increased the life expectancy of insulin-dependent patients from less than 18 months to more than 5 years.[25] The introduction of insulin in diabetes therapy necessitated the need for setting new dietary recommendations. Dr. Murray Lyon and Sister Pybus, in 1923, started to count calories and weigh diets for their diabetic patients, thus the dietary foundation for diabetic management was established.[25] The Lyon[15] work, also, was the first step towards establishing the role of the dietetic Department in the care of medical and surgical conditions. The dietary role in managing diabetes was greatly promoted by the studies of McCane and Laurence at King's College on the carbohydrate contents of foods in the late 1920s.[26] New and clinically applicable concepts such as 'available carbohydrates' and 'unavailable carbohydrates' or fibres dates from that work.[26] Unfortunately, in 1935, Himsworth discovered that low-carbohydrate diet reduced insulin sensitivity, and he tended to promote, unsuccessfully, high-carbohydrate diet. In 1938, Professor Dunlop reiterated the dietary fundamentals of Lyon.[27] From the start of insulin up to the present time the history of dietary management of diabetes showed successive changes toward increasing the recommended carbohydrates and decreasing the fat intake whereas the protein content was rather constant around 10%-15%. The increments in carbohydrate intake were 20% in 1921, 40% in 1950, 45% in 1971, 50% in 1985 and 50%-55% in 1996. The fat content decreased from 70% in 1921 and 40% in 1950 to 35% from 1971 until the present time. The search for sucrose substitutes for diabetic patients is an old dream. In 1874 Kulz observed that diabetic patients were able to utilize fructose better than other sugars.[28] Minkowskey (1893) found that fructose lead to formation of glycogen in pancreatectomized rats but did not happen with glucose.[29] Joslin (1923) after obtaining the same results recommended fructose in diabetic diets.[30] Since then several sucrose substitutes such as sorbital and xylitol have been used. Diabetic foods, based on these substitutes, were first introduced in the 1960s at a time of a low-carbohydrate and sugar-restricted diet. This trend continued up to the 1970s when strict restriction on sugar was thought unnecessary. In 1982, the British Diabetic Association recommended that a complex carbohydrate-rich diet and use of fructose and other bulk sweeteners would improve glycemic control. In 1984, it was suggested that the diabetic foods have to contain half of the amount of rapidly absorbable carbohydrates compared to equivalent

History of diabetic complications. Evidence of classification of diabetic comas dates back to 1886 reported by Professor Julius Dreschfeld when he delivered the Broadshaw lecture on diabetic coma.[31] He described the type of coma, today known as diabetic ketoacidosis as "affecting the largest number of cases, where dyspnoea was usually a most marked symptom, followed by coma, and where both the breath and urine of the patients showed characteristic color of acetone, and urine contained a peculiar body giving a deep claret color with perchloride of iron".[13] Dreschfeld also provided the first description of another diabetic coma, today's hyperosmolar non-

ketotic coma. To quote "chiefly characterized by drowsiness, soon passing into coma. Confined to older patients who are still stout and well nourished at the time of attack." [31] For unknown reasons the hyperosmolar coma disappeared from medical literature with the start of the insulin era and was rediscovered in 1957 in a patient in Baragwanath, a Hospital in Sweto, South Africa.[32] Lactic acidosis was first described by Daughday Lipicky and Rasinski in 1962 in 2 diabetic patients' presented with coma, hyperglycemia with no ketonuria or ketonemia, and low blood carbonate and high lactate levels.[33] Other causes of lactic acidosis, especially tissue anoxia, were excluded. The neurological complications of diabetes were so common that some early physicians concerned with diabetes were lead to suggest that diabetes was due to neuropathy.[8] Rollo[23] first recognized the association between diabetes and symptoms of peripheral neuropathy. In the period 1850-1870 both plantar ulcers and gangrenes were recognized as complications of diabetes. The association between neuropathy, vascular disease and foot ulceration was first recognized by Pryce (1887).[34] He wrote: "The patient was 56-years-old and had symptoms of diabetes for 18 months. For 3 months he had noticed ulceration on the region of the metatarophallengeal joints, there was impaired sensation on feet, absent knee jerk and livid and cold legs. At autopsy, degenerative changes were noticed in peripheral nerves. There was atheromatous disease of the posterior tibial artery and its smallest branches".[34] The hypothesis that microvascular disease underlies some major complications of diabetes (retinopathy, neuropathy and nephropathy) was put forward in 1941. However, in 1956 Oakley suggested that neuropathy, independent of vascular disease, might cause foot lesions.[35] The Oakley's classification of foot lesions is still widely used today. For a long time, automic disturbances like erectile dysfunction and sweating abnormalities were reported. The first scientific and exhaustive review of this subject was published by Jordan in 1936.[36] It was however only in 1945 that the autonomic symptoms were attributed by Rundle to damage in the autonomic nervous system.[37] Since then, and especially in the 1970s, a tremendous amount of knowledge has accumulated. Despite sophisticated investigations the precise cause and natural history of autonomic neuropathy are not clearly understood. Rundles[37] included the gastrointestinal complications of diabetes as part of the autonomic disturbances.[37] Dilatation of the stomach with retention and atony was first described by Boas in 1925, and by Chaiken and Klein (1961).[38] Kassender (1958) coined the term gastroparesis diabeticorum as a collective term for this syndrome.[39] He also described the symptomatic nature of this syndrome and its resemblance to gastric motor disturbances occuring after vagal vagotomy. Prior to the discovery o insulin, few diabetic women became pregnant, and if they did, many of them (more than 40%) died of ketoacidosis.[40] Likewise the offspring of these mothers died. After introduction of insulin the incidence of pregnancy in diabetic patients rose steadily, and maternal mortality fell dramatically (although fetal loss remained high).[40] By the 1950s the perinatal mortality had fallen to 25% and, a decade later, had fallen further to 10%-15%.[40] However, it was not until the early 1970s that the fundamental importance of diabetic control, and in particular the impact of prevailing glucose concentration on fetal growth and pregnancy outcome was recognized.

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