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Editorial

LANDMARKS IN THE HISTORY OF ROMANIAN DIABETOLOGY

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Introduction – Diabetes as a mysterious disease

Diabetes is a disease with a large spectrum of clinical phenotypes, most of them (over 75%) having only a discrete or atypical symptomatology. Severely symptomatic diabetes, with polyuria, polydipsia, polyphagia and weight loss is usually encountered in type 1 diabetes in children, adolescents and young people, more rarely in adults, especially in type 2 diabetes. Let us imagine the context in which a physician from antiquity, even famous, could have the chance to meet and follow-up a case of diabetes mellitus. In order to be studied, the cases of overt, symptomatic, diabetes had to evolve for at least a few months. Obviously, the patient had to possess enough financial resources to come to the doctor. Moreover, taking into account the vulnerability of patients with symptomatic diabetes, the majority of patients with clinically overt diabetes (with classic symptoms) died before reaching a physician. We should not forget that even today, there are still some cases of lethal inaugural diabetic ketoacidosis, without an already known diagnosis of diabetes. Before insulin therapy, this was almost the rule. This explains the paucity of diabetes reports from antiquity. Araethaeus, who described nicely the disease, state that he encountered two cases while Galenus also two cases. Indeed, apparently diabetes was a rare disease.

During the antique and medieval periods, when availability of information was very limited, the description of diabetes made in different parts of the world, (China, Egypt, Middle East, Greece, Rome or elsewhere in Europe) could not be known by other medical schools but accidentally. During those times, it happened more often that a physician traveled a long distance just to hear the lecture of a magister from a renowned medical school than to be able to access a medical manuscript. Even after the inventing of the print, for several hundreds of years only the Greek-Roman classical work was published and not the medical findings of contemporary physicians. This is why the observations made in different parts of the world and in different periods could not be put together. Maybe totally different would have been the evolution of knowledge regarding diabetes if *internet* was discovered before the *print*.

It is also true that diabetes mellitus is indeed "***a mysterious disease***" with many unknowns in the complex inter-relation between carbohydrate, protein and lipid metabolisms. In depth

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knowledge regarding diabetes became possible only after the development of biochemical techniques: incipient in the XVIIIth century, vigorous in the XIXth, more and more refined in the XXth. In the current millennium, there is high hope that genomic and proteomic studies will be able to unravel more cellular, biochemical and molecular details of the disease, not only of the full blown phenotypes, but also of asymptomatic forms that dissipate in the large continuum of the "dis"-metabolic syndrome.

Important dates and events in Romanian diabetology

Coming back to the issue of Romanian diabetology history, the same pattern of evolution as described but with a delay of ~100 years was noticed. Progresses were slow in the XIXth century but exploded in the XXth with the magnificent work of Nicolae Paulescu and foundations of diabetes specialty by Ion Pavel. In the following pages we shall attempt a brief description of the most important landmarks between the 1800's and 1975 when the first modern congress of the Romanian Society of Diabetes was organized.

1870 – **M. Kalinderu** obtains his PhD degree in Paris where he studied medicine between 1858 and1863. He worked as a physician in "Colentina" Hospital (1874-1878) and "Brâncovenesc" Hospital (1878-1902). In 1893 he published „*Tulburările nervoase în diabet*" (*Nervous disorders in diabetes*) (România Medicală 1: 185-192) [1,2].

1883 – **Christea Buicliu** (1857-1918) defends in Paris his PhD thesis entitled *"Notes sur quelques points de la symptomatologie du diabete"* (*Notes on some points regarding the symptoms of diabetes*). After his return from Paris, he will be Professor in the "Brâncovenesc" Hospital", being one of the first physicians with an interest for diabetes.

1892 – **Alexandru N. Vitzu** (1853-1902), with the financial support of the paleontologist Grigore Cobălcescu (1831-1892), studies physiology in Sorbone, Paris (1877-1882), in the laboratory of physiologist and state's man Paul Bert (1833-1886). In 1892, he established in Bucharest the „Institute for Experimental Physiology" as an extension of the Animal Zoology and Physiology department of the Science Faculty. He performed studies in the field of the endocrine function of the pancreas and kidney and neurophysiology studies. In 1894 he published „*O nouă funcţie a pancreasului. Diabetul pancreatic. Rolul secreţiilor interne în actele de nutriţie*" (*A new function of the pancreas. Pancreatic diabetes. The role of internal secretions in nutrition processes*). In 1895 he published „*Doctrina secreţiilor interne din punct de vedere al rolului ce-l au în organism*" (*The doctrine of internal secretions from the point of view of their role for the organism*), being in fact the first Romanian "Small textbook of diabetes". In 1901 he published „*Recherches expérimentales sur la sécretion interne des reins*" (*Researches on the internal secretion of kidneys*) [3].

1893 – **E. Sterian** publishes „*Reflexiuni făcute asupra afecţiunilor medulare în diabet*" (*Considerations regarding the medullary diseases in diabetes*) (România Medicală 1: 459-462).

1897 – **Nicolae Paulescu** sustains in Paris his PhD thesis in medicine entitled "*La structure de la rate*" (*The structure of the spleen*) – a clear description regarding the arterio-venous and lymphatic connections in this organ. This thesis is so interesting that we decided to translate it in Romanian and English and to publish it [1,2,4,5].

1901 – **Nicolae Paulescu**, coming back from Paris where finally he sustained another 2 PhD theses in Sorbonne, establishes the Department

of Physiology of the Faculty of Medicine in Bucharest. He will lead this department without pause until his death in 1931 [1,2,4,5].

1907 –**Nicolae Paulescu** publishes in „*L'Hypophyse du cerveau*" (*Hypophysis of the brain*), Ed. Vigot. [6] This is one of the most important medical writings from the beginning of the XXth century. The technique of trans-temporal hipophysectomy (original method invented by Paulescu) was considered by the famous American Physician Harvey Cushing as the most important contribution in the field [1,2,4,5]. The contribution of Paulescu in this field of endocrinology will be however shadowed by his prodigious researches in the field of diabetes between 1911 and 1928.

1907 – **Constantin Parhon** (1874-1969) and **M. Goldstein** (1872-1955) publish in Paris „*Les secretions internes. Pathologie et Physiologie*" (*The internal secretions. Pathology and Physiology*), Ed. Masson. In 1930, Parhon publishes „*Cercetări asupra acţiunii vasculare a insulinei*" (*Researches on the vascular action of insulin*), 32 pages [1,2].

1911 – **Nicolae Paulescu** publishes in „Annales de Biologie" in Paris (vol. I, p. 228) the first of his paper regarding the origins of liver glycogen, continued until 1920. These studies aimed in fact to the unraveling of the cause of diabetes [7]. In addition, by comparing the effects of the administration of glucose by oral or intra-portal routes, Paulescu observes that the liver glycogen increases only after the oral administration. In fact, he described the "incretin" effect, a term that was introduced after 60 years.

1913 – In the „Betleem" Hospital in Bucharest (later known as *St. Vincent de Paul* and currently *National Institute of Endocrinology "CI Parhon"*), **Nicolae Paulescu** opens an outpatient department, especially for diabetes subjects. In the opening session, on 12 May 1913, Paulescu said: „*Medicine studies the human being and, unique among sciences, has the human being as its sole subject of study*" [1,2].

1915 – **Theodor Mironescu** publishes „*A severe case of pancreatic diabetes*" (Bul. Soc. Med. and Nat., Iaşi, 10-12, 109-114).

1920 – It is published the second volume of „*Traité de Physiologie Médicale*" (*Textbook of Medical Physiology*) by **Nicolae Paulescu**. The book is published in French and distributed by Vigot Publishing House in Paris, France. In this textbook are published *in extenso* the first experimental data regarding the isolation and characterization of the endocrine pancreatic secretion [1,2,4,5,8]. We tend to believe that this book could be found in the library of Toronto University, where head of the physiology department was Prof. J. J. R. MacLeod, personality recognized as an authority in the carbohydrate metabolism. In fact Prof. MacLeod published in 1926 an important paper entitled, „*Carbohydrate Metabolism and Insulin*", paper where the work of Paulescu was cited correctly.

1921 – On **23 July**, in „*Comptes Rendus de la Societe de Biologie*" in Paris are published the 4 short communications of **Nicolae Paulescu** including the results of his systematic research of the physiologic and pharmacodynamic features of the pancreatic endocrine secretion [9]: (1) Action of the pancreatic extract injected in the blood of a diabetic animal; (2) Action of the pancreatic extract injected in the blood of a normal animal; (3) Influence of the amount of pancreas used for the preparation of the extract injected in the blood of a diabetic animal; (4) Influence of the time elapsed after the intravenous injection of a pancreatic extract in a diabetic animal. All these 4 communications were published in the same issue of the Journal and were known by the Canadian "discoverers"

of insulin that cite Paulescu's work in their first article, published in February 1922 [1,2,4,5].

1921 – On **31 August Nicolae Paulescu** publishes in „*Archives Internationales de Physiologie*" (vol. 17, p. 85-109) his main paper that sums all his systematic work regarding the pancreatic endocrine secretion. The paper is entitled „*Recherches sur le rôle du pancrèas dans l'assimilation nutritive*" (*Researches on the role of the pancreas in the nutritive assimilation*). This is the birth certificate of insulin [10].

1930 – **Nicolae Paulescu** mentions glycation of plasma albumin in volume IV of „*Tratatul de Medicină Lancereaux-Paulescu*" (*Lancereaux-Paulescu Textbook of Medicine*), in the following paragraph on page 5: „*Otherwise, when injecting glucose into blood, it passes quickly in urine. Moreover, physiologic chemistry shows that glucose is present in the blood in combinations more or less stable with albumins - from which only a part can be removed – either with alcohol (the so called apparent sugar) or with a mixture of acids (the so called protein sugar) – and can be subsequently evidenced with the copper-potassium reactive"* [1,2].

1930 – **Gheorghe Litarczek** (1888-1954) publishes „*Contribution aux rélations qui existent entre l'obesité et le diabète, à l'aide des epreuves fonctionalles de l'appareil insulaire*" (*Contributions to the relationship between obesity and diabetes using functional tests of the islet apparatus*) (Bull. Mem. Soc. Med. des Hopitaux). In 1943, he will publish „*Problema diabetului*" (*The problem of diabetes*) (Spitalul 63: 3-4, 57-69). In 1948 he publishes another important paper: „*Elemente de fiziopatologie generală a nutriţiei*" (*Elements of nutrition general physiopathology*), in which the biochemical issues of diabetes are analyzed in depth. In this paper he mentions the period of Rockefeller scholarship (1925) and collaboration with Prof. Folin and Prof. Benedict. From 1949 to 1954 he led the Medical Clinic from "*Cantacuzino*" Hospital, with a close collaboration with the Nutrition Clinic (located one floor up in the same building) led by Prof. Ion Pavel [1,2].

1934 – In the department of internal medicine from "*Colţea*" Hospital, led by Prof. Ion Nanu Muscel (1862-1938), the young physician **Ion Pavel** (1897-1991) organizes a small compartment for diabetes. This is attested by the French diabetologist Jean Vague who visited during that period the clinic of Prof. Ion Nanu Muscel. Jean Vague made for the first time a clear distinction between the abdominal and peripheral adipose tissue [1,2].

1953 – The first "anti-diabetic centers" are established in Timişoara and Craiova by the students of Ion Pavel: **Gheorghe Băcanu** in Timişoara and **V. Sfârleză** in Craiova. The next ones will be established by **Viorel Gligore** in Cluj-Napoca (6) and **Gheorghe Creţeanu** in Iaşi [1,2].

1957 – **Nicolae Chişiu** establishes in the clinic of Prof. Ion Pavel laboratory of „**Experimental Medicine**" (also known as „animaleria"). In this laboratory were developed several immunologic techniques with a large practical applicability. This laboratory was closed in 1977 [1,2].

1963 – After receiving the Prize of the French Academy of Medicine for his monography „*Le diabète*", **Ion Pavel** is elected correspondent member of the Romanian Academy (he was elected as a titular member in 1990 before his death) [1,2].

1963 – The **Section of Nutrition Diseases** is established as a section of the Society of Internal Medicine (part of the Union of Medical Science Societies). It is led by **Ion Pavel** until 1974.

1968 – At the International Diabetes Federation Congress in Buenos Aires, **Ion Pavel** re-opens the issue of insulin discovery. This finally led to the creation of an IDF Expert Committee in order to clarify the events that led to the discovery of insulin and the contribution not only of Banting and MacLeod but also of other researchers, with an accent on **Paulescu's** major contribution. The conclusions of this committee were published in an IDF bulletin from 1971 [8].

1975 – With the occasion of the first National Congres of Diabetes, Nutrition and Metabolic Diseases (organized annually since) the presidency of the society is transferred to **Prof. Ion Mincu** [1,2].

There is not the aim of this editorial to describe the difficult time of the "power transfer" between these personalities and the dramatic events of those times. Despite these, Romanian diabetology continued its pathway of development. Its "modern" evolution will be described in another editorial.

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