

Editorial
**REGARDING THE CLASSIFICATION, PREDICTION
AND PREVENTION OF DIABETES**

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Preliminaries

I don't know who did use for the first time the terms of diabetologist and diabetology. *Diabetologia*, the most famous European journal in this field has already 53 years and those who created it were, of course diabetologists. “*The antidiabetic center*” from Bucharest was established 72 years ago, thus the author of this success becoming the first Romanian diabetologist. The “CI Parhon” National Institute of Endocrinology in Bucharest was established in 1946. Fortunately, the relationships between Constantin I. Parhon (President of the Great National Assembly in 1947) and Ion Pavel (a close of the Romanian Royal House) were of mutual respect. This is why in Romania endocrinology never included diabetes and the Romanian diabetology could develop progressively and independent, without barriers but also without the backup it would have deserved. C.I. Parhon (1874-1967) lived for 93 years while I. Pavel (1897-1991) lived for 94 years. Each of them left behind a medical specialty in its own.

During the period of its creation, the National Institute of Endocrinology benefited of an excellent location and similar hardware and resources. Thus, at the beginning, the scientific research was initially equal in importance with

the current medical activity. In 1967 I failed to join this institution on a research position that was “dedicated” to someone else. I was young and I still believed in the value of the individual as the only argument for obtaining such a position. Life proved to me that things are different. However, 1967 was the year during which my interest for diabetes was raised by a stimulating article published by Henri Lestradet (1921-1997) in *Presse Medicale*. Subsequently I met Prof. Lestradet who later became one of the supporters of Paulescu's priority in the discovery of insulin. By chance, he was born in the same year with the great discovery.

The necessity of a medical specialty different from endocrinology is proved by the fact that endocrinologists that deal with diabetes consider themselves to be *diabetologists*, even if on their medical diploma is mentioned the specialty of endocrinology. I never encountered yet the opposite situation, that of a diabetologist that deals only with classic endocrine diseases.

The epidemics of obesity and diabetes

The figures reported by the International Diabetes Federation (IDF) regarding the prevalence of diabetes and obesity are always surpassed by the de facto reality which indicates higher percentages. If overweight and obesity currently affects around 2 billion persons

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worldwide and taking into account the fact that ~25% of them are already or will become diabetics, we can conclude that diabetes will affect soon some half of billion persons. The preliminary results of the national study PREDATORR [1] seem to indicate that the real situation is even worse than that predicted by the IDF figures, based on data collected several years ago and using official data, sometimes collected by more or less devoted public clerks. An “anti-PREDATORR” action needs to be urgently initiated in order to prevent what can be still prevented.

Prevention requires efficient prediction

An efficient prevention of diabetes requires a correct prediction and prediction requires supplementary costs, costs that Romania cannot provide yet, the amount of money allocated for the health care of diabetic patients being always lower than what it is necessary. Moreover, prevention needs also research, but the “budget fight” for money between the pensions fund and research fund is always won by the pension fund.

For the prevention of type 2 diabetes (T2DM), the solution seems to be relatively easy: since the epidemic of diabetes was preceded by the epidemic of obesity, we should focus on the prevention of obesity. There is a strong scientific basis proving that applying preventive measures on large groups of persons is followed by good results [2,3]. However, to obtain these results on datasets of a couple of thousands of subjects, millions of US dollars were spent in the USA and of Euros in Europe.

Since the predisposition for T2DM covers almost half of the world adult population and since this population is extremely heterogeneous, preventive measures should be individualized. They are based on lifestyle optimization, with its two main components: *physical exercise* that dramatically decreased during the last 50 years

and it should be brought back were it was before, and *diet*. The last encountered even more dramatic changes during the last decades, both quantitative („portion size” increased progressively in order to stimulate consumer spending) and qualitative (vegetables in diet are usually represented only by a few leafs used as an ornament around a bigger and bigger steak and chips). The number of calories increased (use of foods with high caloric density), based predominantly on animal products (meat, cheese, eggs). All these are easily wrapped in a pastry cover. Shaorma, burgers and gyros have conquered the street fast food in Europe.

Obesity, diabetes and their direct consequence, cardiovascular diseases and other degenerative diseases were boosted by the modern socio-economic system that tempts consumers with the commercials covering the streets of the cities and with the TV shows that transmit these pathogenic messages, using all the persuasion methods to which people are very sensitive.

In theory, the best prevention method would be the education of children, youth and young adults in order to protect themselves from these dangerous chemicals present in what they eat, drink and breathe. The best education vehicle would be again the media. However media at its turn should be paid, but for education enough funds were never found. Collective prevention remains a solution but we cannot say by which method it will become successful. Individual prevention should be based on the prediction of the individual risk for disease, based on the assessing of some clinical, biochemical or genetic risk scores. All these, evidently require increased costs. Moreover, the calculation of the genetic risk score does not provide significant information beyond that already offered by the biochemical risk scores or even simple clinical examination as shown decades ago [4]. The genetic revolution developed before our eyes at

the beginning of this millennium and is a great investment for the future. Researchers have now numerous data regarding the genetic architecture of metabolic diseases that is more complex than we would have expected. The number of genes associated with type 1 diabetes – T1DM (~ 50 loci) [5] or T2DM (~ 60 gene loci) [6] will provide research topics for laboratories for at least two decades from now on. Maybe some of the un-fulfillments of diabetology will be recovered in the near future. We shall describe some of these in the next few pages.

Issues related to the classification of diabetes

The previous classifications of this complex syndrome that is diabetes mellitus should be treated with indulgency. It was a construction made without a well-defined plan, suffering modifications when new pathogenic elements were identified or when old and obsolete concepts had to be removed. Between 1877-1883, Etienne Lancereaux (1829-1910), based only on clinical observation corroborated with forensic studies, was impressed by the heterogeneity of the cases he followed and reached the conclusion that diabetes is not a simple disease but a complex syndrome. He identified two clinical forms, based on 3 clinical elements: age at onset, presence or absence of obesity and the speed of disease evolution. Thus, he described the “*thin*” diabetes (which appears at a young age, is characterized by a speedy decrease of weight and rapid evolution towards death) and “*fat*” diabetes (which appears at adult age in the presence of obesity, has a hereditary nature and usually slow and torpid evolution). This was the seed of the “black and white” diabetologic thinking which soon an obsession became. Thus, the 4 WHO classifications of diabetes (from 1965, 1980, 1985 and 1998) presented in contrast “juvenile diabetes” vs. “maturity onset diabetes” (1965);

„type 1 diabetes” vs. „type 2 diabetes” (1980); “insulin dependent diabetes” (IDDM) vs. “non-insulin dependent diabetes” (NIDDM) (1985). The 1985 classification of diabetes, not very inspiring based on the treatment modality (insulin or non-insulin dependent) was adjusted in 1998 and diabetes came back to the classes of „type 1 diabetes” (autoimmune and non-auto-immune) and type 2 diabetes (predominantly with insulin resistance or predominantly with beta cell dysfunction) [7]. The impersonal nature of the two numbers (1 and 2) avoided the confusion created by the terms of insulin-dependent and non-insulin dependent when a patient treated previously with oral drugs was transferred to insulin treatment, thus changing its category of classification.

In 1985, I presented at a EASD meeting [8] a paper in which we demonstrated that in addition to the 7% of patients represented by the T1DM subjects (patients that were insulin treated from diabetes onset and were known also as *primary insulin-dependent*), around 1% of the non-insulin-dependent diabetic subjects were each year transferred to insulin treatment. Thus, after 15 years of evolution, this group represented ~15% of the total diabetic subjects while after 20 years they represented 20% of the total number of patients. In contrast to the T1DM patients (primary insulin dependent subjects), the last were named „*secondary insulin dependent patients*”. This “intermediary” category of diabetes, which sometimes resembles clinically and pathogenically T1DM while other times it resembles T2DM was given various names, from which the most used is that of Latent Autoimmune Diabetes in Adults (LADA) [9-13]. Under this designation were included patients with various age limits, both for the inferior (18 years) and the superior (45 years) limits. The genetic analysis of this phenotype pointed out some important features, including its association with genes

characteristic for both T1DM and T2DM [14,15]. In an analysis of the promoters of genes associated with the two major diabetes phenotypes (T1DM and T2DM) we signaled that among the “atypical” genes (non-specific for both the two phenotypes) are included *TCF7L2*, *SLC30A8*, *INS*, *RBB3* and *HHEX1* [16]. This is a subject that requires a more detailed analysis in the future.

Coming back to the WHO classifications of diabetes proposed over time, I reviewed a paper we published in 1975 in Romanian Journal of Internal Medicine [17] in which we analyzed the age distribution of 5000 cases consecutively registered, belonging to every age groups: 0-20; 20-40; 40-60 and >60 years (Figures 1 and 2). These groups were classified as belonging to the groups of “juvenile diabetes”, “diabetes of the young adult” (partially overlapping with the modern LADA group), “maturity onset diabetes” and “senile diabetes”. For the last group of patients I noticed the higher frequency of insulin treatment compared to the patients with “maturity onset diabetes”.

The classification of diabetes remained for us a constant preoccupation [18], and in the “Paulescu” Textbook of Diabetes published in 2004 [19] we made several proposals for the next classification of diabetes, starting with a new definition of the disease. Currently numerous evidence exists that in both the T1DM phenotype, LADA and T2DM phenotype, the autoimmune pathogenic process (in T1DM) and the non-autoimmune identified in the beta cell dysfunction (in T2DM), begin months or years (for T1DM), years or decades (for T2DM) before the appearance of glucose metabolism decompensation. This is the most important stage, stage during which up to 90% (in T1DM) or 50% (in T2DM) of the beta cell mass/function is irreversibly lost [20-23]. Hyperglycemia should remain the last and final stage of diabetes (*Hyperglycemic diabetes*). The costs for the

identification of the *pre-hyperglycemic diabetes* are not very high if, at least initially, we use only static (and not dynamic) tests for assessing the beta cell function/mass. Calculation of the proinsulin-to-insulin ratio or of the proinsulin-to-adiponectin ratio could identify in subjects with a high clinical risk score for diabetes more than 90% of the cases that will finally develop diabetes. Dynamic tests (first of all assessment of the first phase insulin response) can increase this percentage up to 95% or even more.

All the above data relate to T2DM. For type 1 diabetes, apart the identification of beta cell autoimmunity by assessment of the 4 specific beta cell auto-antibodies (IAA, GADA, IA2A and ICA, eventually ZnT8) in significant titers, the concomitant evaluation of the proinsulin-to-insulin ratio could be an indicator of the beta cell dysfunction present even in descendants of diabetic parents [24,25]. In our vision, this marker could predate the autoimmune reaction and even represent its trigger [26]. If this will be confirmed by the studies performed on descendants from diabetic subjects, we could proceed to real interventions for the prevention of T1DM. The repeated failure of all attempts for prevention performed until now [27-29] was predictable since the inclusion criteria for the study imposed the presence of “advanced” anti-beta cell autoimmunity (presence of at least 3 of the 4 anti-beta cell antibodies in significant titers). In fact, such advanced autoimmune process cannot be stopped any-longer. Currently, there are numerous attempts to identify in the cells involved in the autoimmune process (T and B lymphocytes, NK cells, etc.) of markers for increased reactivity that could indicate the stage anterior to the appearance of anti-beta cell antibodies [30-33]. This could represent the only chance to prevent this important phenotype that affect the human being in its most sensible period of life, childhood.

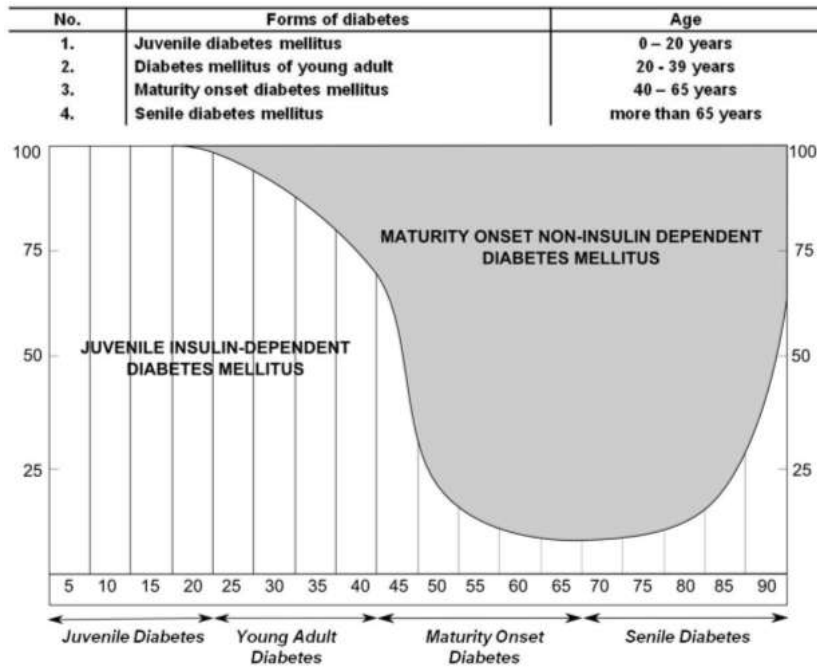


Figure 1. Incidence of „insulin-dependent” and „non-insulin-dependent” diabetes according to age at onset in 1975. Adapted after [17].

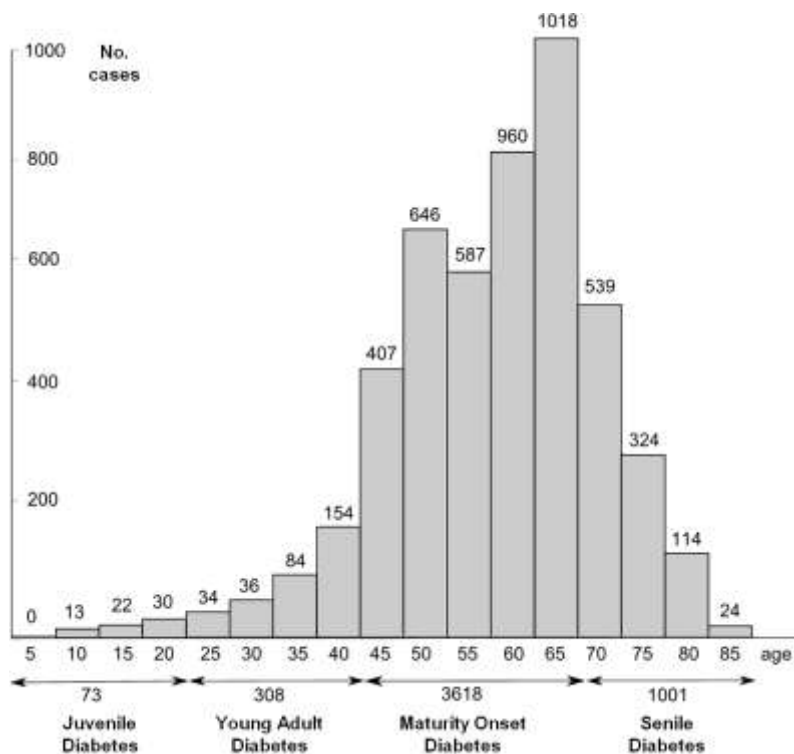


Figure 2. Frequency of diabetes according to the age group at onset in 1975. Adapted after [17].

The third recommendation made by us in 2004 [19], was related to the intensely mediatized “genetic revolution” from which we all expected the identification of patients at high risk for diabetes, but also the deciphering of the

pathogenesis of the various diabetes phenotypes. This revolution occurred, and the number of genes associated with T1DM and T2DM increased to more than 50 for each phenotype as we stated above [5,6]. However, this proved not

to contribute significantly to the diabetes risk score efficacy [34,35]. On the other hand, the discovery of some new genes, and a couple of new molecules involved in diabetogenesis represents a field with a high potential for research.

Finally, we have to mention here maybe the most important gene discovered by the first wave of Genome Wide Scans (GWAS) for T2DM [34,36] and confirmed by all the subsequent GWASs [6,37], namely the Zinc Transporter (ZnT8) gene (*SLC30A8*), that could represent the link between the two main diabetes phenotypes. It was formally associated with T2DM, quite naturally if we take into account that the pancreatic beta cell represents a “factory of secretory vesicles” and that maturation of these vesicles involves the compulsory intervention of Zinc atoms [38,39]. The highest surprise was represented by the fact that ZnT8 represents a specific beta cell antigen and that anti ZnT8 antibodies are at least as important in predicting T1DM as the classical beta cell auto-

antibodies (IAA, IA2A, GADA and ICA), pointing out to a potential beta cell defect present before the onset of autoimmunity and possibly related to the initiation of this process [40].

The last recommendation made by us in 2004 was represented by the need to include among the early markers of the diabetogenic process of some small molecules (branched chain amino-acids or lipids) associated with the complex diabetic metabolic dysfunction. This request found its answer in the *metabolomics* that exploded during the last few years [41]. This comes as a confirmation to the statement of Paulescu from 90 years ago, that diabetes is a disorder of the whole energy metabolism, not only of carbohydrates but also of lipids and proteins. Decreased HDL cholesterol and the increase of the Triglyceride-to-HDL ratio is a finding we made and that must be rapidly transferred in the biochemical evaluation of all subjects at risk for diabetes, irrespective of its phenotype.

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