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Editorial

INSULITIS IN DIABETES – HISTORY AND SIGNIFICANCE

Constantin Ionescu-Târgoviște, Cristian Guja

National Institute of Diabetes, Nutrition and Metabolic Diseases "Prof. NC Paulescu", Bucharest

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"Insulitis" can be defined as the presence of lymphocityc infiltration inside or surrounding the islets of Langerhans. It seems that the first report of this kind of lesion in the medical literature has been published by Eugene L. Opie (1873-1971) in a paper from 1901 [1]. Soon, in 1902, the German pathologist Schmidt [2], using the optic microscope, observed a small peri-insular lymphocytic infiltrate in the pancreas of a small child that died soon after the diagnosis of diabetes at the age of 10 years. The next known report of this "strange" observation was published in 1927 when Warren [3] also described the presence of inflammatory infiltrate surrounding the pancreatic islets without significant comments.

The term "insulitis" will be used 13 years later by the Viennese pathologist Hans von Meyenburg, in 1940 [4]. Between 1958 and 1972, LeCompte [5,6] described the process of "insulitis" not only in juvenile diabetes, but also in older age patients, being the first to mention the immunological involvement in the diabetes phenotype that has been later called *latent autoimmune diabetes in adults* (LADA), a "stranger" term [7] than that of *intermediary diabetes mellitus* (IDM) proposed by us [8]. In 1963, Albert Renold described the insulitic immunologic response of calves (heifers) after the administration of homologue insulin (bovine) or heterologue insulin (porcine) [9].

In 1965, Willy Gepts (1922-2004) published several studies regarding the pathology of the pancreas in a high number of young diabetic patients, most of them deceased soon after the clinical onset of diabetes [10]. His data represent the most powerful argument in favor of the immunological involvement in the pathogenesis of "juvenile" diabetes, although at that time there were no other strong arguments in favor of what later has been clearly proven [11,12]. It is interesting to know that in the 1971 edition of *Joslins' Diabetes Mellitus*, in the big chapter "Pathophysiology of diabetes mellitus", Stauffacher and Renold [9] made an important inventory of the involvement of immunity in various animal models of diabetes, but also in immune reactions (insulin antibodies) after heterologous porcine and bovine insulin therapy and also in relation with some chronic complications of diabetes. The problem of "insulitis" was also discussed, but the final conclusion has been that there are not enough data regarding the immune related pathogenesis of "juvenile" diabetes in humans.

The landmark papers published in 1974 by John Nerup et al. [13] and Gianfranco Bottazzo

✉ 5-7 Ion Movila Street, Bucharest 2, Romania; Tel: 0040212108499
corresponding author e-mail: cit@paulescu.ro

et al. [14] founded the immunogenetic theory of "juvenile" diabetes, the diabetes phenotype that later was to be called type 1 diabetes (T1D). This theory renewed the interest for the "insulitis" process, considered to be the histological lesion proving that, indeed, the immune system is deeply involved in the pathogenesis of this diabetes phenotype, encountered not only in "pediatric patients" but also in older ages.

Unfortunately, the sinuous evolution of the most specific histological proof of the mechanism of β-cell destruction in T1D continued, so that in the last 5 years the autoimmune nature of the pancreatic changes has been challenged by several researchers [15-17]. Indeed, there was not any precise definition of "insulitis" according to the minimal number of lymphocytes surrounding (peri-insulitis) or present inside islets (intra-insulitis). In previous papers there was a large difference between various authors regarding this aspect, so that after a workshop devoted to this topic in the name of nPOD (network of Pancreatic Organ Donors), a consensus opinion was reached in this matter. The authors of this consensus proposed that "*the lesion should be established in a minimum of three islets, with a threshold level >15 CD45$^+$ cells/islet before the diagnosis can be made. The pathology report should include the total number of islets analyzed, the fraction of islets affected by insulitis, the fraction of (pseudo)atrophic islets, and a description of spatial relationship of the infiltrate to the insulin-positive islet cells*" [18].

This decision has been made because by analyzing the histological and histo-chemical data available in the publications from the last 70 years, less than 200 cases of insulitis were available for proper analysis. Few, very few. So, at the beginning of 2014, Donnath, Hess and Palmer [19] strongly suggested that the autoimmune mechanism of the β-cell destruction in T1D could be questionable for two reasons: (a) in contrast with other autoimmune diseases, for T1D all the immune therapy attempts for prevention have failed and (b) the autoimmune mechanism, which is obvious in NOD mice, including the efficiency of the immune approach in preventing autoimmune diabetes in these animal models, could not be similar with that in human diabetes [19]. Very soon, at the beginning of 2015, the NIH (National Institute of Health) and JDRF (Juvenile Diabetes Research Foundation) in USA have urged research to switch their interests for mice stuff to human islets studies, asking applications for the Human Islets Research Network (HIRN) initiative [20]. The aim of the HIRN initiative is that of doubling the availability of human islets from both type 1 and type 2 diabetic donors and also from controls. However obtaining human islets for research from living or cadaveric donors is difficult because of the low number of pancreas donors.

The contradictory data regarding the anatomo-histological markers of insulitis could be easily explained by the difficulty in obtaining pancreas sampling during patients' lifetime. This is because pancreatic needle punction [21] (or even obtaining a small fragment of pancreas in living patients) could be not representative for the whole of the pancreas, and sometimes the needle bioptic material is so small that no islets can be detected on the histological analysis. The attempt to obtain a larger piece of pancreatic tissue (minimal tail pancreatic resection) carried out in the framework of the nPOD research group [22] in six patients from whom informed consent has been obtained, has been associated with three important incidents. For the moment this approach has been interrupted in order to see if the histological information obtained in these cases is importantly enough, thus further justifying such a risky approach.

Another big problem is related to the fact that any information obtained after the clinical onset of diabetes, when more than 80% of β-cell mass is already lost [23-25], cannot inform us about the initial autoimmune process in the islet cells that could have happened 5, 10 or 20 years before.

Where are we now? We have many arguments in favor of the autoimmune mechanism operating in T1D, arguments provided mainly by the possibility to detect a higher number of islets antibodies [26,27] which reflect the beginning of the autoimmune process against β-cells. This process however does not evolve towards clinical manifest diabetes in all subjects and, when this happens, the delay between seroconversion and the onset of diabetes could be very short (onset at young age), long (onset after puberty) and very long (onset after 20-25 years of age). There is also uncertainty regarding the pathogenicity of antibodies, especially when their number and titer is not very high. The genetic argument is also important, but the complexity of the predisposing or protective HLA alleles [28,29] as well as that of the specific contribution of the other genes associated with this phenotype make difficult to obtain a very high risk genotype in order to include such a patient in specific prevention programes.

Due to the progress in the technology of pancreatic imaging, there is some optimism regarding the non-invasive determination of the β-cell mass [30] or even of the "insulitis" process [31].

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