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Dr. Zaharina Dimitrova (1873-1940): A Pioneer in Research of the Pineal Gland's (Corpus Pineale) Microstructure

D. Paskalev[1], D. Radoinova[2], B. Galunska[3]

[1]Clinic of Nephrology and Dialysis,
[2]Department of Forensic Medicine,
[3]Department of Biochemistry
Medical University "Prof. Dr. Paraskev Stoyanov" – Varna, Bulgaria

Dr. Zaharina Dimitrova is a still forgotten Bulgarian scientist who did ground breaking research in the field of histology of the pineal gland. Born in Ressen, Macedonia on 26-th November 1873, Dimitrova left to study Medicine in France. Under the supervision of Prof. M. Nicolas, she researched the fine structure of epiphysis cerebri and for the first time made an accurate description of the pinealocytes. Dr. Zaharina Dimitrova pointed out the characteristic vacuoles in the nuclei of the cells and related the finding with a possible endocrine function. At present, it is known that the pinealocytes produce the hormone melatonin. She graduated with honors from the Medical School in Nancy, France, and published her PhD thesis "*Recherches sur la structure de la glande pineale chez quelques mammiferes*". Her highly acclaimed work was awarded the Gold Medal from the Medical School and published in La Nevraxe Journal (vol. 2, 1901, 257-361). Dr. Zaharina Dimitrova died on April 14, 1940.

Key words: Dr. Zaharina Dimitrova, pineal gland, morphology, history of medicine.

The name of Dr. Zaharina Dimitrova cannot be found in Encyclopaedia Bulgaria, Concise Bulgarian Encyclopaedia or any of the specialized biographical reference books for famous and not so famous Bulgarian physicians. A little over a century ago, she completed a fundamental research on the pineal gland producing the hormone melatonin. Today modern science uses melatonin to fight aging, insomnia, some hormonal dysfunctions, oxidative stress, etc. [2, 9]. Famous scientists have cited Dimitrova's dissertation. She was also awarded a gold medal for her accomplishments [6, 7].

Short History of the Pineal Gland and its Function

It is accepted that the first more accurate description of the pineal gland was made by the famous Roman physician Claudius (Clarissimus) Galenus of Pergamon (129-200 A.D.). He stated that the anatomists from the renowned Alexandrian School were also familiar with the organ. Galenus named the gland "conarium" because of its resemblance to a

pine or the cone-like tip of the pine twig. The organ's Latin name, Corpus Pineale (from the Latin word for pine – pinus) derived from this resemblance as well. Galenus was one of the first to notice and document the accumulation of small increments in the pineal gland known as acervuli (from Latin acervus – accumulation) or sabula (from Latin sabulum – one-grain sand). For a long time scientists have believed the brain sand to be closely linked to some mental diseases. This belief spread even wider after the famous French philosopher Rene Descartes (1596-1650) declared that corpus pineale was the throne of the soul in the human body [3, 5].

Today it is accepted that the pineal gland develops as a pine-like caudal excrescence of the epithalamus. The phylogenetic predecessor of this small organ is the parietal eye found in some reptiles (Reptilia), which is partly responsible for the pigmentation [10]. In 1958 A. Lerner confirmed that an extract from bull's pineal gland caused paling of a frog's skin due to the melatonin [4, 5]. The melatonin was officially recognized as a hormone in 1963 [5, 10]. Pinealocytes, the main cells of the pineal gland [3, 5] produce melatonin. In 1901 Z. Dimitrova was the first to describe these cells in detail [1].

Dr. Zaharina Dimitrova: Life and Work

Dr. Z. Dimitrova was born on the 26th of November 1873 in Ressen, Macedonia, which at that time was under Turkish rule. As a result of the decisions made at the Berlin congress in 1878 the region remained under Turkish governance even after the neighboring regions gained their independence. This fact would have a serious impact on the life of the talented Bulgarian woman. Simeon Radev (1879-1967), a famous Bulgarian historian and diplomat, was also born in Ressen. He was Bulgarian ambassador extraordinary and envoy plenipotentiary in many countries such as Romania (Bucharest, 1913-1916), Switzerland (Bern, 1916-1917), Netherlands (Hague, 1920-1921), USA (Washington, 1925-1933), UK (London, 1935-1938), and Belgium (Brussels, 1938-1940). S. Radev, remotely related to Dr. Z. Dimitrova, described their birthplace Ressen as a beautiful valley "960 meters above the sea level – surrounded from all three sides by tall mountains and expanded southward by the Lake of Prespa… It is (Ressen) particularly beautiful in the spring when the numerous gardens and cherry trees blossom and give the lawns multiple colors above which rise the narcissi spraying their hypnotic scent. Here the land is fruitful…" [8].

Dr. Z. Dimitrova comes from an old ancestry with deeply rooted Bulgarian traditions. Her grandfather on her father's side, Velyo, fought against the Ottoman Empire for religious and national freedom. In 1848 he became a member of the first Bulgarian province in Istanbul. Later, in 1871, he was elected representative of the Ohrid-Prespan eparchy in order to participate in the National Convocation [8]. Simeon Radev elaborated further on Dr. Z. Dimitrova's ancestry in his book *Early Memories*:

"I have to mention some other leaders whose patriotism was on par with everyone's but who also avoided being constantly present in the public eye. One of them was Mitse Velyov, the son of Z. Dimitrova's grandfather Velyo, whose role in the Instanbul's church matters I already discussed. Tall and a little hunched over, dry and with a fairly dismal character, he kept to himself. Everyone who knew him praised his wisdom… One of Mitse's daughters, Zaharia (Zaharina), graduated with Medicine in Nancy and for her excellent results received a gold medal. Ressen can be proud that it gave the Bulgarian nation one of the first female physicians." [8].

Dr. Z. Dimitrova (Fig.1) graduated from the Bulgarian Ladies' High School in Thessaloniki, Greece and left for Russia to study Obstetrics. Her thirst for knowledge brought her in 1895 to Nancy, France, where she enrolled in medical school. One of her mentors was Prof. M. Nicolas. He was internationally renowned for his research work on the histology and embryology of the intestinal epithelium and absorption mechanisms

Fig.1. Dr. Z. Dimitrova's photo at the time of her graduation

[7]. On February 27, 1901 Dr. Z. Dimitrova graduated with honors. Her dissertation "Recherches sur la structure de la glande pineale chez quelques mammiferez" was distinguished and received the honorary award of the Faculty of Medicine along with a gold medal bearing her name. Later, her interest-stirring work was published in the popular Belgian Journal – La Nevraxe, 1901, 2, 257-361. With her impressive research work started during her years at the medical school in Nancy, Dr. Z. Dimitrova could be recognized as the first Bulgarian histology scientist [7].

Dr. Z. Dimitrova's scientific work was partly studied during one of the congresses of the French Anatomical Association by both Prof. P. Petkov and Prof. E. Leger – General Secretary of the Association and Director of the Faculty of Anatomy in the University in Nancy [7]. Later, the work of Dr. Z. Dimitrova found a place in the already classic textbooks of the famous Bulgarian Professor Assen I. Hadjiyolov (1903-1998) – Head of the Department of Histology and Embryology at the Medical faculty in Sofia (1930 – 1968) [3].

During her study in Nancy, Prof. M. Nicolas drew Dr. Z. Dimitrova in his research team. He provided her with a rich collection of pineal glands of mammals, including human, and opportunities for all kinds research work in his lab. She used the modern for the time impregnation methods for cell staining in the nerve tissue, originally developed by the Nobel Prize winners Camillo Golgi (1843-1926) and Santiago Ramón y Cajal (1852-1934) [7]. For the first time in her dissertation Dr. Z. Dimitrova described accurately the main cells in the pineal gland – pinealocytes. She depicted them as extended or cone-like cells with heavily granulated cytoplasm and large bright eccentrically located nucleus. In addition, the young researcher documented for the first time the typical for the pinealocytes nuclear vacuoles [1]. Later, Prof. A. Hadjiyolov called them the "Dimitrova's Nuclear Spheres" [3]. They most commonly appear during puberty and their size reaches 4-5 μm and stain in blue by the method of Mann (eosine – methylene

blue) [3]. Today it is known that these spheres or vacuoles are cytoplasmatic intrusions in the nucleus that encompass membranes of the granular endoplasmatic reticulum. They are also characteristic of other cells with internal secretion when activated. Dr. Z. Dimitrova considered them quite interesting: "If the presence of granules is enough to classify a certain cell as glandular, then the pineal cells are at least glandular if nothing else." [1]

Dr. Z. Dimitrova's dissertation was cited more than 30 times in the publication of Dr. Bargmann, one of the founding fathers of the research of neurosecretion [7].

Unfortunately, after her return to Macedonia, Dr. Z. Dimitrova could neither continue her promising research nor practice medicine (Fig. 2). At that time Macedonia was still under Turkish rule and women were not allowed to work as physicians. Therefore Dr. Z. Dimitrova left for Sofia. After passing a rigorous state exam she received the right to practice medicine in Bulgaria [7].

Fig. 2. Dr. Z. Dimitrova's photo as a medical doctor in Bulgaria

From 1901 to 1910 Dr. Z. Dimitrova worked in the town of Sliven where she started a family with the military pharmacologist Major Panaiot Dimitrov. Her family moved to the South-Bulgarian town of Tatar-Pazardjik where she became a school and regional physician and later a freelance doctor. In 1930 she discontinued her practice due to illness. Dr. Z. Dimitrova died on April 14, 1940 [6]. During the last ten years of her life she was engaged in a lot of charity work serving as head of the charity organization "Budna Makedonka" and the ladies' organization "Prosveta". Through her charity activities Dr. Z. Dimitrova and her family provided support to many homes

for old people and birth centers. They also assisted refugees and their children in need of financial support for their education. One of the most beautiful public fountains in Pazardjik is "Gergana", built with the financial support of Dr. Z. Dimitrova and her husband.

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