

Works of Napoleon Cybulski (1859-1919) and Władysław Szymonowicz (1869-1939) on Adrenal Function



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ABSTRACT

It is well recognized by the historian of medicine, that the discovery of the effect of adrenal medullary hormones on the peripheral and central control of circulation occurred independently by Szymonowicz and Cybulski at the Jagiellonian University in Cracow, and by Georg Oliver and Edward A. Schäffer, University College London, England.

Napoleon Cybulski was born to a Polish gentry family in 1855 at Krzywonosy, close to Vilnius. He studied (1875-1880) medicine at Military Surgical-Medical Academy in St. Petersburg, Russia. In 1885 Cybulski was appointed the Chair of Physiology at Jagiellonian University, Cracow. In 1893 he encouraged his younger colleague Dr. W. Szymonowicz to verify the already published studies on adrenal gland and to conduct new experiments on the effects of the extracts from adrenal tissue on physiological parameters in normal animals, and in animals post adrenalectomy. Extracts from the adrenal medulla had stronger effects, than those from the adrenal cortex, on blood pressure, heart rate and respiration of the dogs.

Cybulski and Szymonowicz call the extract “nadnerczyna”, which can be translated as supranephrine/epinephrine. They noted: “Blood of the suprarenal vein contained the active principle of the gland in sufficient amount to mimic effect of adrenal extract.” These studies were published in March 1895 in *Centralblatt für Physiologie* volume 9, page 173-175 and *Gazeta Lekarska* 1895: 15, page 300-308.

The studies of Oliver and Schäffer, published in *Journal of Physiology* 1895: 17; 230-276 came to similar conclusions. There were some discrepancies between the observed effects of adrenal medullary extracts between Polish and British physiologist, especially regarding direct action of the substance on the vascular tone and the effects modulated through the central nervous system.

In subsequent years, Napoleon Cybulski pioneered world research on the electrical activity of the brain cortex and heart, and on electrical currents in the muscle. He published the first Polish handbook of physiology with interesting observations on kidney function. He was great advocate of woman’s education and admission to medical schools. Napoleon Cybulski died of stroke on April 24, 1919 in Cracow.

KEYWORDS: History, adrenal glands, nadnerczyna, epinephrine

Introduction

The end of the 19th century was a time of rapid acceleration in scientific discoveries overall, but particularly in the field of chemistry, biology and medicine. Still, the understanding of the physiological role of many organs was lacking (1). The following is a good example of that.

Napoleon Cybulski, 40 years old professor of physiology at the Jagiellonian University in Cracow was working in 1893 on his Human Physiology part III (2) and “concluded after careful readings, that handful of studies on thyroid and adrenals suggested that these puzzling glandule can be part of the system through which the body is controlling various organs” but “he did not come across even single work which was devoted solely to explain the function of adrenals” (3).

He was aware of the studies of Charles-Édouard Brown-Sequard (1817-1894). The year after Thomas Addison’s description in 1855 of damaged adrenal glands associated with hyperpigmentation and death, Brown-Sequard showed that experimental animals died within few hours after bilateral adrenalectomy.

Finally Cybulski complained that over previous three years he could not find a single collaborator to pick up a research project to explain the function of adrenals /suprarenals.

Finally near the end of 1893, Dr. Szymonowicz decided to study systematically the development of adrenal, its histology, and physiological response to adrenal ablation and to the injections of the extracts from adrenal glands.

Napoleon Cybulski – Biography and Scientific Works

Napoleon Nikodem Cybulski was born on September 14, 1854, in Krzywonosy, which was then in Polish/Lithuania territory under Russian rule (4) (Table 1 and Figure 1).

Table 1 - Life of Napoleon Nikodem Cybulski

He was born at Krzywonosy, Vilnius region, Poland/Lithuania in moderately wealthy family, descended from the gentry.	September 13 th , 1854
Gymnasium at Minsk Litewski	Graduated in 1875 with Silver medal
Military Surgico-Medical Academy in St. Petersburg	1875-1880 Summa cum laude

Assistant to the Chair of Physiology Professor Tarchanow. First paper: "The effect of body posture on blood pressure, heart rate and respiration in animals"	1877-1885
PhD dissertation: <i>Studies on blood flow velocity based on photohemotachometer</i> (in Russian)	St. Petersburg April 13 th , 1885
Chair of Department of Physiology, Jagiellonian University in Cracow	May 1885- April 1919
Elected by the Faculty twice as a Dean of the School of Medicine and Rector of the Jagiellonian University	1887-1888 1895-1896 1904-1905
Nominated for the Noble Prize	1911, 1914, 1918
He died in Cracow due to stroke	April 26 th , 1919

He finished high school at Minsk (currently capital of the Belarus), and in 1875 he was admitted for medical studies at



Figure 1 - Portrait of Napoleon N Cybulski 1854-1919.

the prominent Imperial Medical and Surgical Academy in St. Petersburg. As a second year student he started working at the Institute of Physiology under mentorship of Professor Trachanov.

Despite their age difference they became friends. Later (1901) when Trachanov was demoted by a group of reactionaries in administration of

Academy, he was helped by Cybulski and continued to work and live in Cracow, Poland. Cybulski's student work on "The effect of body posture on blood pressure, pulse and respiration in animals" was awarded a first-class gold medal. He collaborated with another future star of physiology, Ivan Pavlov. In 1880 he finished the Academy *cum eximia laude* (with the highest distinction) and obtained a doctorate in 1885 (5), with a thesis on the velocity of blood flow as detected by an apparatus called photohemotachometer, of his own construction.

In 1885 he was offered the position of chairman at the Department of Physiology at the Jagiellonian University, Cracow (then part of the Austro-Hungarian Empire). He was dean of the Medical Faculty, and subsequently rector of the University.

Napoleon Cybulski published more than 100 articles and dissertations. His research interest was broad and deep at the same time. His main contribution was in the field of cardiovascular system. He was the first who presented graphically the variation of blood flow velocity with various phases of heart cycles with the use of photohemotachometer and explained "dirotic acceleration" in carotid artery, in contrast to the lack of it in femoral artery. Together with his pupils he demonstrated that blood velocity was attenuated in pregnant women with jaundice, and accelerated in working

muscles. The fifth edition of Starling's Principles of Human Physiology, 1930 provides description of the use of Cybulski's photohemotachometer for measuring the velocity of the blood. The last studies on blood flow with the use of his apparatus were conducted in the 1970s.

Cybulski had impressive neurophysiological research such as recordings of sensory potentials in cerebral cortex (1890), studies of cortical activity (1914), and muscular and nervous excitability (1890-1916). He defined the "resting current (potential) as a property of the membrane, and "action current" as consisted with the movement of positive ion along the muscle fiber.

His "Fizjologia Czlowieka", the first Polish physiology textbook, was published (1891-1896) in 4 volumes. Volume 3 contains a chapter on body fluid excretion, and a comprehensive discussion on kidney function. He presented in detail the use of onkometer methodology for measuring changes in blood volume going through the isolated kidney and its impact on urinary flow.

Władysław Szymonowicz: Biography and Scientific Works

He was born on March 21, 1869 at Tarnopol/Ternopil, Western Ukraine/Galicia, to a Polish/ Armenian family. He finished high school in Lemberg/Lwow, Galicia, and then studied at Medical School at Jagiellonian University in Cracow (1887-1893). He became assistant to Napoleon Cybulski in the 1893. Szymonowicz had chosen laboratories of Rudolf Virchow (pathology) and O. Hertwig (embryology/histology) in Berlin as a place for postgraduate studies (1893-1895). At the same time he was working on morphology and on the physiological role of adrenals in Cracow. These studies led to the new discoveries and allowed him to finish habilitation thesis, important step in academic development. He was invited to establish and to chair the Department of Histology and Embryology Medical School at Lwow (1897-1937). Other than his adrenal work, major scientific achievements were studies the development of nerve endings in skin of human and other animals.

Szymonowicz was also recognized for his *Textbook of Histology and Microscopic Anatomy*. This work reached 12 editions between 1901 and 1931 and was published in many languages including German, English, Italian, Spanish and Polish.

He died in March 10, 1939 and was buried at Lyczakowski Cemetery in Lwow.

Work on adrenal gland by Cybulski and Szymonowicz

Szymonowicz conducted the first experiments on seven dogs with adrenal extirpation between May 1894 and December 21, 1894. On December 17, 1894 he started experiments with eleven control dogs and 1 cat to evaluate the physiological effect of adrenal gland extracts. In two more dogs, he injected extracts after adrenalectomy. His last experiment was on September 20, 1895. Starting January 1895 Szymonowicz was intermittently absent in the laboratory, and Professor Cybulski carried himself experiments on dogs, rabbits and cats with water, glycerin and alcohol adrenal extracts (3, 6).

Experiments with bilateral ablation of adrenals confirmed previous reports of animal death within day with shock. Injection of one cc of 10% water solution of adrenal extract to those dogs caused within seconds improvement in BP, heart rate, and respiration. Cybulski observed that adrenal extract did not affect BP and heart rate in animals after section of the

spinal cord and emphasize the effect of the extract on cardio-inhibitory center in medulla oblongata rather than direct effect of it on peripheral vessels.

Extract from the adrenal medulla had much stronger effect than that from the cortex. The findings that blood from the suprarenal vein contains the active substance were also unique at that time. Cybulski noted, "Blood of the suprarenal vein contained the active principle of the gland in sufficient amount to mimic effect of adrenal extract." They call the active, stimulating substance (Greek: hormao) from adrenal medulla "NADNERCZYNA". Nadnerczyna can be translated into English as epinephrine/ supranephrine.

Some of the experiments were consistent with hypothesis that extreme stress conditions in dogs are inducing the generation of nadnerczyna in blood of those animals enough to cause similar effects on the circulation in normal dogs (although milder) to the injection of the isolated extracts. In his lecture to the members of the Cracow Society of Physician on March 6, 1895, Cybulski stated that "this substance (nadmierzyna), without which the function of nervous system is impossible change the way we understand interaction between different organs".

Oliver and Schäfer Work on Adrenal Function (1893/1894)

George Oliver (spa practicing physician in N. Yorkshire, England) and Edward A Schäfer (Professor of Physiology at University College, London presented in March 1894 to the Physiological Society studies on adrenal extracts. Their final paper was published in *The Journal of Physiology*, in 1894. This was a very well conducted study with extensive documentation of physiological effect of suprarenal extracts of various strength prepared with water, alcohol and glycerin. Experiments were done on rabbits, cats and dogs, and on isolated frog's heart (7).

Authors concluded "It appears to be established... the suprarenal capsules are to be regarded although ductless, as strictly secreting glands. The material which they form and which is found, at least in its fully active condition, only in the medulla of the gland, produces striking physiological effects upon the muscular tissue generally, and especially upon that of the heart and the arteries. Its action is to increase the tone of all muscular tissue, and this result is produced mainly if not

entirely by direct action. On the other hand the removal of the suprarenal capsules produces extreme weakness of the heart and muscular system generally, and great want of tone in the vascular system. A similar result is known to be characteristic of advanced disease of these organs (Addison's disease). It may fairly be concluded therefore that one of the main functions, if not the main function, of the suprarenal capsules is to produce a material which is added in some way or another to the blood, and the effect of which is to assist by its direct action upon the various kinds of muscular tissue in maintaining that amount of tonic contraction which appears to be essential to the physiological activity of the tissue" (7).

In the addendum to their paper they acknowledged independent work of Cybulski/Szymonowicz, which was in major part in agreement with their results. They complimented the observation that venous outflow from adrenals had similar effect as extract and that blood does not destroyed the active substance.

The main point of difference was that according to Cybulski/Szymonowicz the extract acts not directly upon blood vasculature but rather through a vasomotor center. Oliver and Schäfer conducted additional experiments with section of the cord and nerves going to the limb, but still observed a constrictive effect of their adrenal extracts on blood vessels.

Soon, in 1897, John Abel, professor of Pharmacology at J Hopkins University purified the adrenal extract and call it epinephrine. Japanese chemist Iokichi Yakamine working in New York obtained pure crystal form in 1901 and marked it "Adrenalin".

Legacy of Napoleon Cybulski

The legacy of Napoleon Cybulski was multidimensional (8). In the opinion of his contemporaries he was a very loving and humble person, full of scientific enthusiasm.

His pivotal work on the hormone of adrenal medulla is well recognized. He developed the Polish School of Physiology, conducted studies on the circulatory system and pioneered neurophysiological research. Cybulski was socially conscious, a propagator of medical science, and a strong proponent of women's admission to medical school.

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