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From Leningrad to London: The Saga of Kulchitsky and the Legacy of the Enterochromaffin Cell

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Key Words

Carcinoid · Diffuse neuroendocrine system · Enterochromaffin cell · Kulchitsky · Neuroendocrine

Abstract

By the end of the 19th century, the subject of internal secretion and the consequences of its perturbations had been explored in considerable depth but with little clear understanding. Despite the anatomic delineation of the majority of the glands and tissues that comprised the gross endocrine system, the cellular basis and the interactions between the 'internal glands' and the nervous system had not been clearly delineated. Prominent early investigators in the field included Rudolf Peter Heidenhain (1834–1897), who described a novel class of clear cells (1868), Paul Langerhans (1847–1888), who identified pancreatic islets in 1869, and M.C. Ciacco (1877–1956), who coined the term 'enterochromaffin' (1906). Their contributions facilitated the description of the diffuse neuroendocrine system (DNES) by F. Feyrter (1938) which allowed for the understanding of a syncytial regulatory system that consisted of both endocrine and neural components. This rich developmental history often reveals the name of Kulchitsky, but little recognition has been given to his seminal contributions. Indeed the Russian, Nikolai Konstantinovich Kulchitsky (1856–1925), both due to his modest and unassuming nature and the tragic events of his life, was little recognized and has been relegated to a mere eponymous attribution. In reality, his life bears legacy to rich scientific contributions spanning a great teaching and scientific career at Kharkov University, to responsibilities as the Imperial Minister of Education for all of Russia. He identified the Kulchitsky cell, trained and mentored numerous professors of histopathology, was incarcerated by the Bolsheviks and worked in a soap factory to save his life. He and his family finally fled on a British battleship with the remnants of the Russian Royal family to England where he secured a position with Bayliss and Starling at University College, London (UCL). His mysterious demise in a lift-shaft accident on his 69th birthday tragically terminated a life of great service to science and teaching. He excelled as a histopathologist and was responsible for the early description of tonsillar and gut epithelial leucocytes as well as defining components of the *Ascaris* life cycle. At UCL, his contributions to the anatomic delineation of muscle nerve endings were highly regarded and widely admired. It is, however, his identification of the enterochromaffin cell in 1897 for which he is most remembered since this observation formed the basis for the subsequent delineation of the DNES and provided the cellular framework on which the discipline of gut neuroendocrinology would be established.

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Introduction

Although the contributions of William Bayliss (1860–1924), Earnest Starling (1866–1927) and Ivan Pavlov (1849–1936) to the discipline of neuroendocrine regulation are well known, time and the long shadow of the Bolshevik revolution have obscured the role of Nikolai Kulchitsky (1856–1925), who played a pivotal role in describing the enterochromaffin cell of the gut. Although the concept of internal secretion and the role of the neural system had been studied extensively in the final years of the 19th century, there was much debate regarding the cells that comprised the endocrine system and their relationship to the neural elements of the body [1]. Rudolf Peter Heidenhain (1834–1897) of Breslau, Prussia – a prodigy who received his doctorate at the age of twenty – first identified enterochromaffin cells in the gastric mucosa of a rabbit and a dog by describing the yellow (chromic acid) stained cells in 1868, and in 1870 also identified small, granulated, yellow staining cells on the surface of the gastric glands (almost certainly now recognized as the histamine-secreting enterochromaffin-like cells; ECL cells) [2]. Further contributions to the delineation of neuroendocrine cells were provided by Paul Langerhans (1847–1888) under the guidance of R. Virchow (1821–1902) who, while a medical student, first described the pancreatic islets. Langerhans, however, freely admitted that he had no knowledge of the cells he described [3]. His 1869 medical thesis, *Beiträge zur Mikroskopischen Anatomie der Bauchspeicheldrüse* (Contributions to the Microscopic Anatomy of the Pancreas), utilized microscopic studies and novel staining techniques to delineate the cellular anatomy of the pancreas. Although he recognized the islets as novel structures, he did not identify their endocrine function [3] and 8 years would elapse (1877) before Gustave Edouard Laguesse (1861–1927) of Dijon, proposed their relationship to diabetes. His magnanimous recommendation that the cell aggregations be accorded the name 'Islets of Langerhans' reflected his appreciation of the contributions of Langerhans who had in 1888, died prematurely of tuberculosis on the island of Madeira [4]. Adolphe Nicolas (1861–1939) in 1891 reported the distribution of the enterochromaffin cells of the gastrointestinal tract in lizards and thus laid the framework for the subsequent development of the concept of diffuse neuroendocrine system (DNES) [5].

In 1897, the Russian scientist Nikolai Kulchitsky noted similar granular cells in the crypts of Lieberkuhn in the intestinal mucosa of cats and dogs: 'In the epithelial coverage of the intestinal tract, I had the opportunity to study elements which, as far as I know, have not been described by other scientists up to now and which are with no doubt of great interest in relation to the present knowledge of histology of the intestinal tract' [6]. Kulchitsky's cells were fixed and stained with the Ehrlich-Biondi mixture and after 24 h, the intracellular granules turned bright yellow. When the staining process was extended for several days, the granules took up fuchsin acid and became red thus exhibiting acidophil characteristics as previously described by Heidenhain. It is of interest to note that Kulchitsky was aware of Heidenhain's work since he had 29 years previously also described leukocytes with acidophil granules within the intestinal mucosa. Despite this, Kulchitsky did not comment upon the parallel findings in both cell types and failed to draw further conclusions that might have facilitated classification of his and Heidenhain's work as describing the same cellular entity.

Unfortunately, the limited scope of histochemistry at the turn of the 19th century as well as the paucity of information regarding chemical messengers prohibited identification of the function of the enterochromaffin cells. Speculation was therefore the order of the day and Kulchitsky [6] postulated that 'acidophil granules within the epithelial cells are a result of the digestive activity of the intestinal tract', noting that granules in the epithelial cells only exist during the digestive act and are absent in starving periods. Indeed, such were the controversies among the scientific community with regards to the diverse functions proposed for the 'clear cells' that they were often eponymously labeled to identify their investigators rather than to reflect their real physiological function! As a consequence, a variety of cells were respectively described as, 'cells of Nicolas-Kulchitsky', 'yellow cells of Schmidt', 'enterochromaffin cells of Ciaccio', 'argentaffin or silver reducing cells of Masson', and 'chromoargentaffin cells of Cordier' [7]. Such annotations remained in the physiology and histopathology texts for the next 50 years, causing much confusion and misinterpretation. A curious example of such uncertainty was provided by the 'Nicolas-Kulchitsky cell', where the phonetic ambiguity provided by Kulchitsky's first name, Nikolai (in Russian), when anglicized as Nicholas, displaced the contributions of the French scientist, A. Nicolas only by a consonant! In 1906, C. Ciacco (1877–1956) suggested that the term enterochromaffin (EC) cell be adopted to reflect the special staining properties and anatomical location of the cell and thus replace the confusing heterogeneity of the diverse archaic eponymous appellations [8].

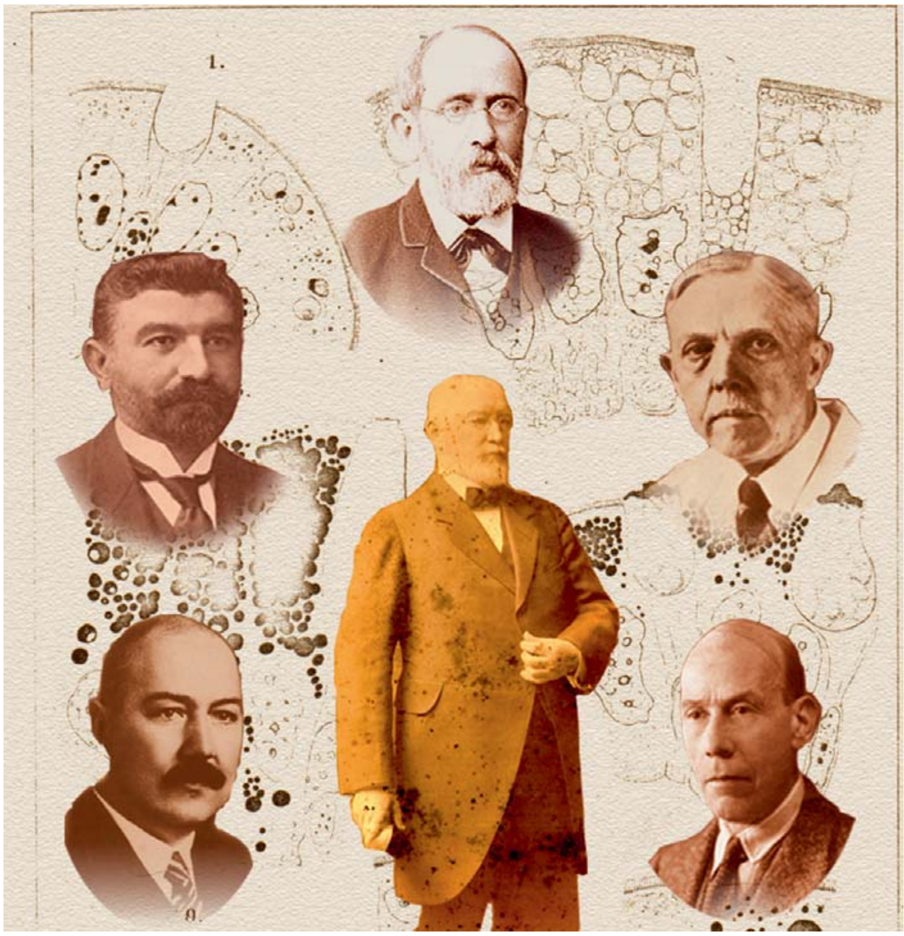

Fig. 1. The legacy of the enterochromaffin (EC) cell. Rudolf Peter Heidenhain (1834–1897) (top) was the first to identify EC cells in the gastric mucosa of rabbits and dogs in 1868. Nikolai Kulchitsky (1856–1925) (center) noted similar cells in the crypts of Lieberkühn in the intestinal mucosa of cats and dogs in 1897. The EC cell origin of appendiceal 'carcinoid' tumor was proposed in 1914 by A. Gosset (1872–1944) and P. Masson (1880–1859) (center left and right) utilizing silver impregnation techniques. In 1906, C. Ciacco (1877–1956) (bottom right) suggested that the term 'Enterochromaffin Cell' be adopted to reflect the special staining properties and anatomical location of the cell. Finally, in 1938, Friederich Feyrter (1895–1973) (bottom left) introduced the concept of a diffuse endocrine system and proposed that this novel entity was the source of 'carcinoid' tumors.

At issue at the turn of the 19th century was the nature of the interaction between the lumen surface of the gut and the motor and secretory effector system. Since there was controversy as to whether the signals were neural or chemical and which cells were responsible for such interactions, the relationship between the neural and endocrine regulatory system remained unclear. Some clues were apparent based upon early studies of tumors that were proposed to originate from enterochromaffin cells. Thus, in 1914, A. Gosset (1872–1944) and P. Masson (1880–1859) utilizing silver impregnation techniques, demonstrated the argentaffin-staining properties of appendiceal 'carcinoid' tumors and proposed an EC cell origin [9]. The term 'carcinoid' had been coined by Siegfried Oberndorfer (1876–1944) in 1907 in reference to his description of an unusual group of lesions that he considered to be benign neoplasms distinct from adenocarcinoma of the small bowel [10]. Although Langhans (1867) [11], O. Lubarsch (1860–1933) (1888) [12], and W. Ransom (1860–1909) (1890) [13] had previously referred to similar entities, they had not extrapolated their observations to include the idea that these lesions represented a different form of neoplasia. Subsequent studies by H. Kull (1925) confirmed that 'carcinoid' tumor cells exhibited argentaffinity and argyrophilia in their response to silver salts [14]. Using Altmann's technique (a staining procedure utilizing a mixture of picric acid, anilin, and acid fuchsin which stains mitochondria crimson against a yellow background) Kull demonstrated the fuchsinophilic properties of the argentaffin granulations and described the existence of similar granular cells in the gut submucosa. Based upon these observations, Kull hypothesized that argentaffin cells were of mesodermal origin and would 'secondarily' migrate into the epithelium (fig. 1).

In 1938, Friederich Feyrter (1895–1973), Professor of Pathology at the Medical Academy of Danzig (currently Gdańsk, Poland), noted that argentaffin-positive and argyrophilic 'clear cells' ('helle Zellen') that failed to take up conventional stains, were present throughout the gut and pancreas [15]. He proposed that this 'collection' of cells represented a diffuse endocrine system [16] and that this novel entity was the source of 'carcinoid' tumors. In 1948, Alden B. Dawson (1892–1968), professor of Anatomy and Zoology at Harvard University, developed a more elaborate technique by which enterochromaffin cells of the gastrointestinal tract could be stained using silver nitrate; this demonstrating the argentaffin-staining properties of carcinoid tumors [17]. This technique did not utilize a reducing solution and identified other granulated cells of the gut mucosa which were not demonstrated by the Masson-Hamperl and Bodian methods then employed to recognize argentaffin cells. In 1953, F. Lembeck (1922–) of Graz biochemically confirmed the presence of serotonin (5-hydroxytryptamine; 5-HT), in an ileal neuroendocrine tumor [18]. In 1969, E. Solcia refined the methodology to differentiate EC cells by utilizing a variety of chemical staining techniques (including chromaffin, argentaffin, and diazonium) which reacted specifically with 5-HT in ileal carcinoid tumors [19].

Although much has been written about the respective roles of Heidenhain, Lubarsch and the early investigators of the neuroendocrine system, Kulchitsky's role has been obscured by the aftermath of the Bolshevik revolution. The succeeding intrigue further obfuscated his contributions as survivors of the purges sought either anonymity or safety in distant countries and the new leaders sought to obliterate the memory of their aristocratic predecessors. Kulchitsky, in particular, suffered grievously, becoming a refugee and losing his title, administrative position, laboratory, personal property and finally his life in London where he had fled to survive. His contributions, however, are noteworthy and represent a fundamental component of the work that led to the elucidation of gastrointestinal endocrinology and the delineation of the DNES.

Scientific Career

Nikolai Konstantinovich Kulchitsky was born on January 29th 1856, in Kronstadt, thirty kilometers west of St. Petersburg, on the small island of Kotlin near the head of the Gulf of Finland. This vital stronghold harbored the Russian Baltic fleet and was the custodian of the passage to St. Petersburg, founded in 1703 when Peter I (the Great) (1672–1725) acquired the islet from Sweden and fortified it. Kulchitsky's father was a junior officer in the Czar's Army and Nicolai received his elementary education at the Tambov Gymnasium, well recognized as a nurturing ground for exceptional students. Even at an early age, his intelligence was evident and he graduated with exceptional honors and a silver medal in 1874. Such was the legacy of Tambov that one of Russia's great romantic poets, Mikhail Lermontov (1814–1841), memorialized it in *The Tambov Treasurer's Wife* (1838) [20]. Shortly thereafter, Lermontov perished in a duel that many considered to be little more than a tsarist conspiracy to eliminate the agitator.

After graduating in 1875, Kulchitsky attended medical school at the prestigious University of Kharkov in Southern Russia, then regarded as the premier medical and intellectual research center of Imperial Russia. Kharkov University had been founded in 1804 by Vasyl Nazarovych Karazin (1773–1842) and had produced luminaries including Ilya Ilyich Mechnikov (1845–1916) who received the 1908 Nobel Prize in Medicine for his description of phagocytosis and contributions to the elucidation of the mechanisms of immunity [21]. In 1880, Kulchitsky was awarded an undergraduate degree with distinction and published his first manuscript describing the terminations of motor nerves in muscle *О строении окончаний двигательного нерва в мышцах произвольного движения* (On the structure of nerve endings in motor muscles) [22]. This was followed by a work on the origin of the red blood corpuscles *О происхождении окрашенных телец крови млекопитающих* (On the origin of red blood corpuscles in mammals) [23]. In 1882, he was awarded a Doctor of Medicine (MD) degree having successfully written a thesis that evaluated the structure and function of the tactile corpuscles that occur in the papillae of the beak and tongue of birds, *О строении телец Grandry* (On the structure of corpuscles of Grandry) [24]. He thereafter joined the staff of Kharkov University where he would remain for 27 years earning a formidable reputation as a teacher and scientist. In November 1883, Kulchitsky was promoted to the rank of Privat-Docent, and within the decade (June 16th, 1890) was appointed Professor-extraordinarius. Three years later, on August 17th 1893, he was elevated to the full Professorship of Histology, a position he retained for 17 years until 1910.

Although there is little information regarding the details of Kulchitsky's work at Kharkov, his rapid elevation in status suggests that his skills were much admired and his contributions held in esteem. The productivity and quality of his work in years between 1887 and 1897 as well as his intense involvement in the careers of his students, renders it unlikely that his rapid advance was purely a product of his connections. In a magnanimous gesture,

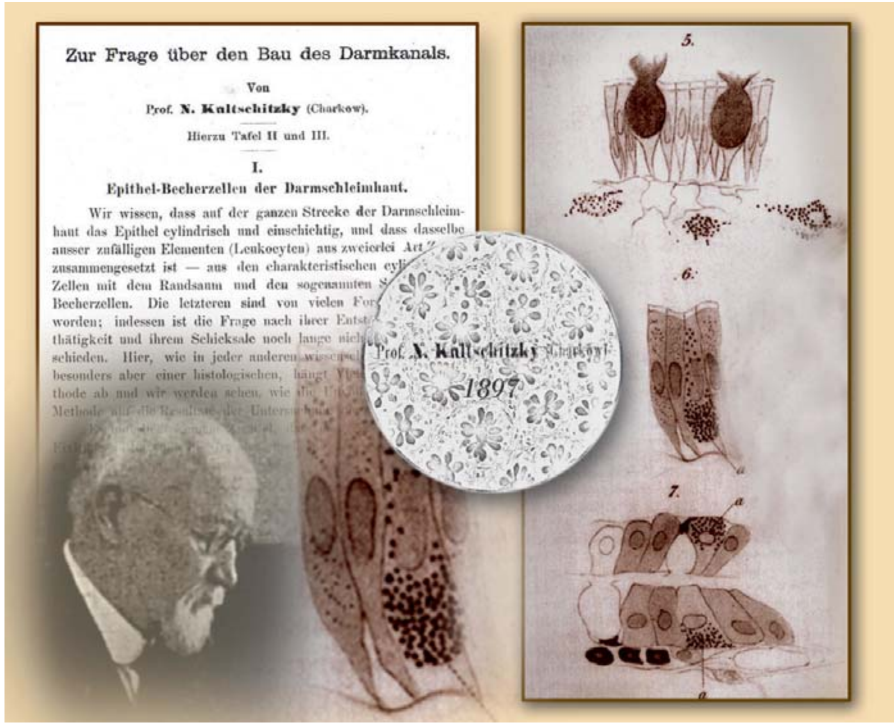

Fig. 2. In 1897, while at Kharkov University, Nikolai Kulchitsky (bottom left) described the 'unique' cells of the intestinal epithelium, eponymously referred to as Kulchitsky cells (right), but currently referred to as enterochromaffin (EC) cells. His work, *Zur Frage über den Bau des Darmkanals* (Questions on the structure of the intestinal channel) (top left) was published in Arch Mikr Anat 1897.

Kulchitsky in 1910 voluntarily retired to ensure that younger members of his staff might have better prospects of promotion. Indeed, such was the success of his mentorship that 14 of his pupils subsequently occupied the Chair of departments in a variety of Russian Universities. It seems obvious that Kulchitsky was not only an individual of scientific substance but a significant role model and academic leader.

Scientific Contributions at Kharkov

The scope of Kulchitsky's histological investigations was broad although in most instances not especially novel or creative. He described the presence of leukocytes in the tonsillar and gut epithelia [25] and contributed to the assessment of the fertilization process in *Ascaris* nematodes [26]. Indeed, his work might broadly be characterized as a careful elaboration of observations initially documented by others. Of particular importance, however, was his description of the presence of three varieties of cells in the cardiac glands of the mammalian stomach (mucous neck cells, parietal cells, and chief cells) and his proposal that different physiological (digestive) functions were possible within one gland [27]. In 1897, his most important report documented the delineation of the 'peculiar' cells of the intestinal epithelium [6], that were subsequently referred to as 'Kulchitsky' cells (fig. 2). Kulchitsky first identified these structures at the surface of the intestinal villi and in the glands of Lieberkühn and drew a parallel to studies that had been undertaken earlier by Heidenhain, albeit failing to comment upon key similarities. Both scientists were somewhat unclear as to whether the cells they had noted were components of the gut mucosa or had migrated from elsewhere. 'Equal to Heidenhain, I tried to elucidate under which conditions the epithelial cells with the acidophil granules emerge. The results of my observations are slightly different from those that Heidenhain obtained from his work on leucocytes' [6].

By 1902, Kulchitsky's scientific contributions had earned him a national and international reputation further amplified by publications of books on the subject of histology and microscopy *(Teachings of Microscopy and Techniques of Microscopic Investigations)* and methods of research. His texts, especially the *Foundations of Histology in Animals and Humans* (fig. 3) completed in 1902, were regarded as the standard Russian texts on the subject and by 1912, had encompassed five editions. This contribution was recognized by the award to Kulchitsky of the Zagorsky Prize of the Army-Medical Academy in St. Petersburg (1912). Apart from descriptive histology,

Fig. 3. While at Kharkov University (background), Kulchitsky (left) published a number of books including *Foundations of Histology in Animals and Humans* (top left) and *Teachings of Microscopy and Techniques of Microscopic Investigations* (right). These books were highly regarded and became the standard Russian texts on the subjects.

Kulchitsky was an accomplished histochemist and was responsible for a number of modifications of the Weigert-Pal method of hematoxylin staining for medullated nerve fibers. The subsequent widespread adoption of this methodology and its relevance to the characterization of diverse lesions of the central nervous system led to his global recognition by neurologists.

Administrator and Educator

After retiring from Kharkov University in 1912, Kulchitsky was not idle and at the request of the Government accepted the position of Director of Education in Kazan [28], the capital city of the present day Republic of Tatarstan. Such was his success that in 1914 he was promoted to the far more prestigious responsibility of Director of Education for the St. Petersburg district and in 1915 the Czar himself recognized his distinguished services as Professor and Administrator, conferring upon him the high honor of an appointment as a Senator. By 1916, his contributions were of such note and so highly regarded that Kulchitsky was advanced to the position of Imperial Minister of Education for all Russia, thereby assuming the educational leadership for the entire nation of 182 million people. Unfortunately, the impact he might have made will never be known since the turbulent times that thereupon enveloped him and his family sundered the political and social infrastructure of the vast Russian Empire and a lifetime spent in science and education became as a mote in God's eye.

The Revolution and Kulchitsky's Flight

By October 1916, Russia had lost ~1.8 million soldiers, with an additional 2 million prisoners of war and 1 million missing. Such staggering losses, coupled with widespread opposition to the autocratic system, escalated into the February Revolution of 1917 and a year later, on 17th of July, Czar Nicholas II and his family were murdered in the basement of the Ipatiev House in Yekaterinburg (a contemporary Bolshevik stronghold). Many of Kulchitsky's colleagues also perished, but fortune smiled, al-

Fig. 4. Kulchitsky (center) aboard HMS Marlborough (top right), commanded by Captain C.D. Johnson, destined for Malta. The card is signed by the aristocratic refugees on board and the inset pictures (except Kulchitsky) were taken by Francis Pridham, First Lieutenant of the HMS Marlborough. The vessel had been provided by the British government to rescue members of the Russian Imperial Family, most notably Her Imperial Majesty, Empress Marie Feodorovna (1847–1928) (top left), the Grand Duchess Xenia Alexandrovna (1875–1960) (bottom left), as well as Princess Irina (1895–1970) and the Oxford-educated Prince Felix Felixovich Yussupov (1887–1967) (bottom right), who had arranged the murder of Rasputin.

beit weakly upon the Minster of Education and vouchsafed him a chance of survival. In 1917, the Temporary Government (pre-Bolshevik) incarcerated Kulchitsky in the 61st cell of the Trubetsky prison, but released him after only 9 days. The reason for this miraculous reprieve remained a mystery to Kulchitsky but provided the opportunity nevertheless for him and his family to survive. Although his life was saved, the respite was bitter sweet in that it stripped him of all property, position and personal assets. Nevertheless, the family remained physically unscathed and his wife Evgeniya Vasil'evna (1862–1932) and children [daughters: Ksenia (1893–1946) and Mariya (1896–1972), and sons: Aleksandr (1894–1970) and Dmitriy (1898–1985)] – were banished to Kharkov. There Kulchitsky, who had previously acquired experience making soap for embedding histological tissues, labored at the Technical Institute of Kharkov supervising the production of commercial soap, at that time a scarce and expensive commodity. Doubtless, the irony of cleansing the aristocracy was not lost upon the Revolutionary supervisors of the Kharkov soap factory!

During the summer of 1918, the appalling conditions at Kharkov created by the pillaging Bolshevik armies forced Kulchitsky and his family to flee their city apartment and embark on an arduous 394-mile journey to Sevastopol where his eldest daughter Ksenia resided. Such was the elderly Kulchitsky's determination that the family endured an average of 18 miles a day for 22 days in their flight to Sevastopol. Upon arrival in Sevastopol, Kulchitsky with his wife and daughter Mariya stayed until 1920 at the house of their eldest daughter Ksenia who had married Evgenij Petrovich Goloubinov (1880–1937). Ksenia and Evgenij had two children, Natalja and Vladimir (the father of Victor Goloubinov – a co-author on this manuscript). Despite the brief reprieve afforded by the escape from Kharkov, political stability in Russia continued to deteriorate as the Bolsheviks, in an attempt to maintain control of Moscow, defeated General Anton Denikin's (1872–1947) army in October 1919 at Orel. Faced with the prospect of the rapidly advancing Bolshevik front pushing south, Kulchitsky and his family reluctantly fled to Malta. As members of the elite, they were afforded passage on an English Iron Duke class battleship, the HMS Marlborough, commanded by Captain C.D. Johnson, which had been provided by the British government to rescue members of the Russian Imperial Family (fig. 4). Other fugitives included most notably Her Imperial Majesty Empress Marie Feodorovna (1847–1928), the aunt of King George V (1865–1936) of England as well as Prince Felix Felixovich Yussupov (1887–1967) who had plotted the death of Rasputin (1869–1916) (known in the West as the 'Mad Monk'). In 1920, Denikin's successor, General Peter Wrangel (1878–1928), assumed the command of anti-Bolshevik forces in Crimea, and Kulchitsky ever the monarchist optimist returned to Sevastopol and once more resumed soap-making, albeit now for the Russian Fleet. Kulchitsky's persistence in returning to his homeland was characteristic of many Russian academics and patriots of the time, reflecting both the failure to recognize the end of the old order as much as their intrinsic national pride. The hopes that stability would be restored were fleeting and elusive because in December 1920, Wrangel's front had collapsed and chaos supervened. Despairing of a solution and fearing for the safety of his family, Kulchitsky once more joined about 5,000 Russian refugees who comprised the remnants of the defeated White Army, civilians, aristocrats, and academics and escaped aboard a squadron of 33 Russian War ships, once part of the Black Sea Fleet, to the port of Bizerte, a French stronghold in Tunisia. After 3 months at the refugee camp it became apparent that the divide between the Bolsheviks and the Russian Aristocracy was irreparable and Nikolai and family were accorded a safe passage to England in April of 1921 together with 74 other scientists, 31 of whom were of Professorial status [29].

From Soap to Secretin and Starling

While the tragic events of the Russian Revolution unfolded, Starling, the famed English physiologist and his equally illustrious brother-in-law, Bayliss, jointly responsible for the concept of chemical messengers (hormone – notably secretin [30]), proposed a plan to the college council for an Institute of Medical Sciences at University College London (UCL). By mid-1909, the physiology building was completed and the pharmacology extension followed 3 years thereafter (1912). Possessed with the capacity to perceive the future of science and eager to change what he considered the current stagnant mode, Starling persuaded a brilliant neuroanatomist Elliot Smith (1871–1937), who had himself earned a reputation for shaking up archaic anatomy teaching, to resign his Manchester chair and join the faculty of UCL to establish a new Anatomy Department. It was Smith who, having learned of the presence of the eminent and penniless Russian scientist Kulchitsky in London, secured his services for the newly created Department of Anatomy (fig. 5) [31, 32]. The recruitment of a histologist with the expertise of Kulchitsky proved pivotal in securing the future of the Department, especially with a Rockefeller Foundation gift of GBP 370,000 for new buildings devoted to anatomy, histology and embryology and a further GBP 835,000 to the University College Hospital (UCH) Medical School, for the maintenance and endowment of medical, surgical, and obstetric hospitals.

Kulchitsky and UCL

In keeping with his life-long work ethic, Kulchitsky resumed his scientific investigations with vigor at UCL and was soon fondly referred to as the 'Old Professor'. Since there were no vacancies fit for Kulchitsky's level of expertise and he lacked knowledge of English, he was initially assigned as an assistant to the Australian anatomist Raymond Dart (1893–1988), who had also joined the group. Kulchitsky proved to be a source of inspiration and invigorated the anatomic histology group as Dart and Craig [33] would later recount: 'I ran to the laboratory where I found the bold intellectual. Only recently, during the Czarist regime, he was the Minister of Education in Russia and additionally one of the most renowned explorers of the microstructure of the nervous system. Soon, we learned to communicate in broken French and German. Although, and unjustly so, he was a meager assistant in my laboratory, it was from him that I learned so

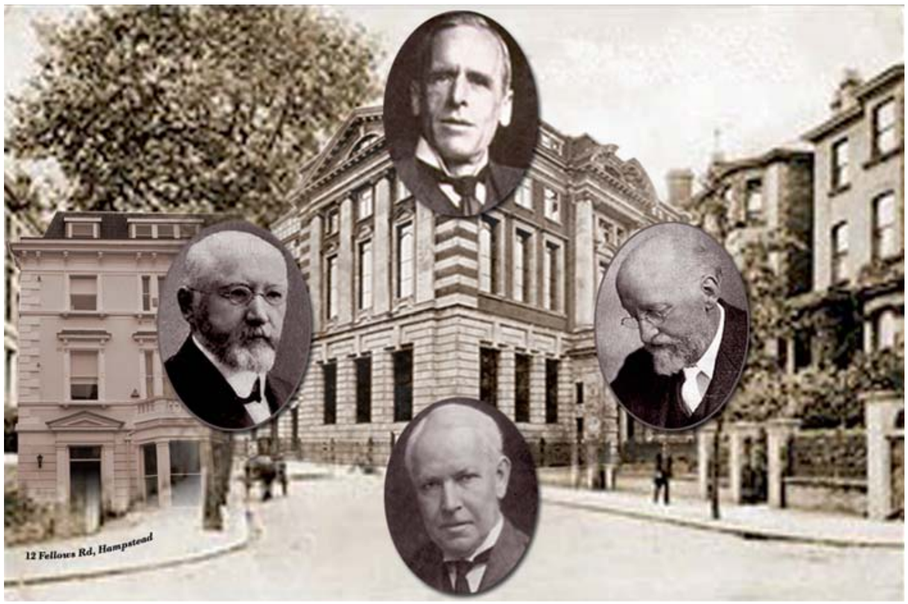

Fig. 5. The neuroendocrine quadrumvirate (approx. 1921) of University College London (UCL). E.H. Starling (1866–1927) (top) and his brother-in-law and close friend W.M. Bayliss (1860–1924) (right) had proposed a plan to the College council for an Institute of Medical Sciences at UCL (center). Starling persuaded Elliot Smith (1871–1937) (bottom) to resign the Manchester chair of Anatomy and join the UCL faculty to supervise the establishment of the new Anatomy Department. Elliot Smith secured the appointment of Nikolai Kulchitsky (left) who, following his exile from Russia now dwelt in penury at Fellows Road, Hampstead in London (far left, background) to the group.

much, which in 1923, upon my arrival to Johannesburg, allowed me to present lectures in micro- and macrobiology.'

In 1921, Professor Jan Boeke (1874–1956) of Utrecht, a well-known neurohistologist, anatomist, and historian, visited London and shared his expertise on the double innervations of striated muscle. Following the lectures, Kulchitsky's intellect was aroused and within six months, he had prepared a superb series of gold chloride demonstration slides of python muscle, that culminated in the publication of *Nerve Endings in Muscle* [34]. The paper demonstrates the presence of two distinct types of nerve endings in snake muscle, typical motor end-plates connected with medullated nerve fibers and more diffuse grape-like endings connected with non-medullated fibers, which Kulchitsky regarded as possibly sympathetic.

Despite the major translocation from an Imperial administrator and Senator of the Czar to the role of a modest university fellow, Kulchitsky adapted without demur and was well received by the scientific community and University faculty. On July 11, 1924 he was informed of his reappointment to the Anatomy Department at UCL, which he accepted with gratitude despite the fact that only a few years previously, he had been responsible for overseeing hundreds of academic institutions and the entire education system of country a thousand fold larger than England. In October 1924, Kulchitsky produced his second UCL paper on the nerve endings in frog's muscle *(Nerve Endings in the Muscles of the Frog)* [35], which utilized the methylene blue technique of which he was a well-known authority. Kulchitsky was cautious in his work and rarely speculated upon his findings noting that: 'Young men can afford to make mistakes, they have time to correct them but that is not possible for me.' In this respect, Kulchitsky appears to have been consistent throughout his career in preferring to describe and define rather than opine. Possibly, in later years, this reflected the maturity of a dedicated scientist coupled with the insecurity of his current position and the concern that scientific errors might culminate in dismissal. It is of interest and surprising that Kulchitsky, Bayliss or Starling given the proximity of their interests, failed to investigate the role of the Kulchitsky cell in the theory of chemical messengers. Indeed, almost half a century would elapse before the pivotal role of the Kulchitsky cell in the gut endocrine system was appreciated.

A Tragic Ending to a Long Journey

On Thursday morning of January 29th 1925, employees of the Waygood-Otis Lift Company were carrying out their monthly inspection of the elevator in the Anatomy Department at UCL. Ineptitude of the laborers led to the lift gate on the ground floor being left open with no elevator present and thus ensued the tragedy that would terminate the life of Kulchitsky (fig. 6). J.P. Hill

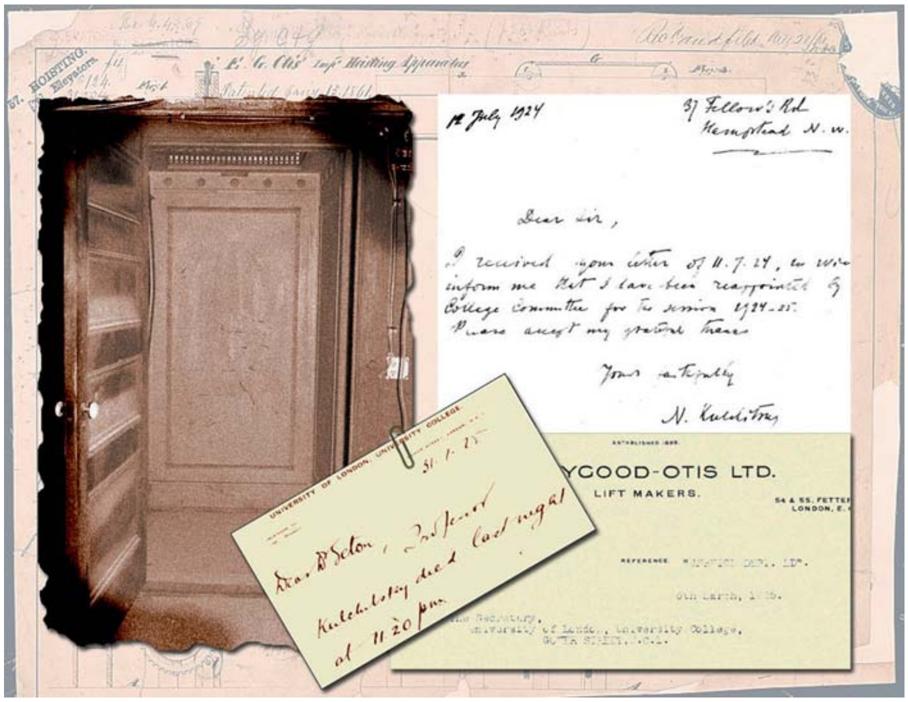

Fig. 6. Kulchitsky's acceptance of reappointment to the Anatomy Department (top right) occurred only 6 months prior to the tragic elevator shaft accident. His death was attributed to the negligence of the Waygood-Otis Elevator Company, manufacturers of the patented 'safe break' elevator (left and background) that ironically was equipped with a door that would not open unless the elevator cabin was safely at ground level.

(1873–1954), Professor at the Embryology Department, noted in his letter to the Provost of UCL, Lord Chelmsford: 'The Professor, apparently assuming that the lift was there, walked into the well and fell two floors to the sub-basement' [36]. The fact that it was on his birthday and that he had survived the Russian Revolution, while progressing from a Baltic island to an Imperial minister to die falling down a lift shaft in London, may have briefly crossed his mind as he plummeted to his fate. Kulchitsky died at UCL Hospital on the evening of the following day at 12:20 a.m. and the funeral service took place on Thursday, February 5th at 9:45 a.m. at the Russian Church on 188 Buckingham Palace Road, the present-day site of the Victoria Coach Station. How Kulchitsky came to walk into that empty lift shaft will forever remain a mystery. We shall never know how so extraordinary a man and his journey came to finality in so ignominious a fashion. Perhaps he was reminiscing about his birthday and the events of his life, possibly he was absent mindedly thinking of his just completed third paper on the nerve endings in the muscles of the lizard *Trachysaurus*, finished only the night before. This manuscript had been dedicated to the memory of John Irvin Hunter (1898–1924), a brilliant anatomy professor from Sydney, who inspired by Kulchitsky's work *Nerve Endings in Muscle* had come to London to join the group. Hunter died tragically on December 10th 1924, a few months earlier having contracted typhoid fever.

In the aftermath of the tragedy, a series of correspondences between UCL, legal representatives and the Waygood-Otis Lift Company plumbed the depths of morbid reflection and mundane bureaucratic preoccupation with minutiae and mendacity. An agreeable resolution was finally reached, 'The accident was clearly caused by the negligence of Waygood-Otis Co. Ltd. who was repairing the lift at the time' [37]. Of concern was the question of liability and damages, particularly since the Kulchitsky family was impoverished. Waygood-Otis proffered a meager sum of GBP 50 and a further munificent GBP 41 was provided by UCL to cover the expenses of the funeral. No evidence exists that Lift Company's money was accepted, but family's legal representative J.J. Withers noted in correspondence that the sum was 'absurd'. No legal action followed given the circumstances of the Kulchitsky family and the fact that his wife had not mastered English. A further issue that obfuscated the resolution was that the UCL's legal counsel concluded that since Waygood-Otis had been invited onto the property of UCL, technically it was UCL who were primarily responsible for the accident! Thus, to prevail in a court of law Mrs. Kulchitsky would have to successfully sue UCL who would then in turn be forced to sue the elevator company!

It is of interest to note that although all correspondence was addressed to Madame Kulchitsky, all responses (gracious and elegant in composition) emanated from Nikolai's youngest daughter Mariya who was 29 and whose role included caring for her mother. The emotionally devastated Madame Kulchitksy, in great distress and unwilling to negotiate monetary compensation after suffering such a painful loss, must surely have reflected bitterly on the tribulations of fate with the fall of her husband and the family fortunes from being confidantes of the Russian Royal family to needing to borrow funds for a funeral. While rumors of the involvement of a Russian secret society 'CHEKA' dedicated to the eradication of aristocrats and politicians who had escaped revolutionary justice abounded, these were never established. Kulchitsky's cremated remains lie interred with his wife Evgeniya and daughter Mariya at Beckenham cemetery, London, marking the final destination of a great journey and a life abounding in service, and dedication to science and education.

Conclusion

Nikolai Kulchitsky was a modest and unassuming man dedicated to science and education. Indeed, even in the days when he held high office as an Imperial Minister, his youngest son, Dmitriy, when questioned by school fellows as to the occupation of his father, was only able to reply that he polished violins! In reality, Kulchitsky's contributions and range of interests were focused mainly on anatomic histology and he is well remembered for his identification of the three varieties of cells in the cardiac glands of the mammalian stomach, his description of leukocytes in the tonsillar and gut epithelia, and his contributions to the elucidation of fertilization in *Ascaris*. As an educationalist and administrator he displayed considerable talent, but his impact in this area of endeavor will never be assessable given the dissolution of the Russian scientific system at the time of the revolution. At UCL, his work on the nerve endings of muscle provided important information but was prematurely terminated by his tragic demise. Kulchitsky must, however, be honored for the identification of the enterochromaffin cell in 1897, which led to the subsequent delineation of the diffuse neuroendocrine system and provided the cellular basis on which the discipline of gut neuroendocrinology would be founded.

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References

1 Sharpey-Schafer E: Endocrine physiology. Irish J Med Sci 1931;69:483–505.
2 Heidenhain R: Untersuchungen über den Bau der Labdrüsen. Arch Mikr Anat 1870;6:368.
3 Langerhans P: Beiträge zur Mikroskopischen Anatomie der Bauchspeicheldrüse. Berlin, 1869.
4 Laguesse G: Sur la formation des Ilots de Langerhans dans le pancreas. C R Soc Biol 1893;5:819–820.
5 Nicolas A: Recherches sur l'épithélium de l'intestin grêle. Intern Monatssch Anat Physiol 1891;8:1.
6 Kulchitsky N: Zur Frage über den Bau des Darmkanals. Arch Mikr Anat 1897, p 49.
7 Simard LC, Campenhout E: The embryonic development of argentaffin cells in the chick intestine. Anat Rec 1932;53:141–159.
8 Ciaccio M: Sur une nouvelle espece cellulaire dans les glandes de Lieberkuhn. C R Seances Soc Biol Fil (Paris) 1906;60:76–77.
9 Gosset A, Masson P: Tumeurs endocrines se lappendice. Presse Méd 1914;25:237–240.
10 Oberndorfer S: Karzinoide Tumoren des Dünndarms. Frankf Z Pathol 1907;1:426–432.
11 Langhans T: Ueber einen Drüsenpolyp im Ileum. Virchows Arch Pathol Anat 1867;38:550–560.
12 Lubarsch O: Ueber dem primären Krebs des Ileum nebst Bemerkungen über das gleichzeitige Vorkommen von Krebs und Tuberculose. Virchows Arch Pathol Anat 1888;111:550–560.
13 Ransom WB: A case of primary carcinoma of the ileum. Lancet 1890;ii:1020–1023.
14 Kull H: Die chromaffinen Zellen des Verdauungstraktus. Z Mikr Anat Forsch 1925;2:163.
15 Rindi G, Leiter AB, Kopin AS, Bordi C, Solcia E: The 'normal' endocrine cell of the gut: changing concepts and new evidences. Ann NY Acad Sci 2004;1014:1–12.
16 Feyrter F: Ueber diffuse endokrine epitheliale Organe. Zentralbl Innere Med 1938;545:31–41.
17 Dawson A: Argentophile and argentaffin cells in gastric mucosa of rat. Anat Rec 1948;100:319–329.
18 Lembeck F: 5-Hydroxytryptamine in a carcinoid tumor. Nature 1953;172:910–911.
19 Solcia E, Sampietro R, Capella C: Differential staining of catecholamines, 5-hydroxytryptamine and related compounds in aldehyde-fixed tissues. Histochemie 1969;17:273–283.
20 Moser C: The Cambridge History of Russian Literature. Cambridge, Cambridge University Press, 1992.

21 Mechnikov I: L'immunité Dans Les Maladies Infectieuses. Paris, 1901.
22 Kulchitsky N: О строении окончаний двигательного нерва в мышцах произвольного движения. Труды общества испытателей природы при Императорском Харьковском университете 1881, p 15.
23 Kulchitsky N: О происхождении окрашенных телец крови млекопитающих. Труды общества испытателей природы при Императорском Харьковском университете 1881, p 15.
24 Kulchitksy N: О строении телец Grandry. Труды Общества испытателей природы 1881, p 17.
25 Kulchitsky N: Выделение лейкоцитов в связи с деятельностью некоторых органов. Труды II-го Пироговского съезда врачей 1886.
26 Kulchitsky N: Die Befruchtungsvorgänge bei *Ascaris megalocephala*. Arch Mikr Anatomie 1887, p 31.
27 Kulchitsky N: Zur Lehre vom feineren Bau der Speicheldrüsen. Z Wiss Zool 1884, p 41.
28 Krapotkina I: Учебное дело должно развиваться-Казанский учебный округ в попечительство Н.К. Кульчицкого. Эхо Веков 2003;1:248–250.
29 0черк деятельности Русской академической группы в Великобритании (с ноября 1920 по 18 мая 1921 гг.) in Berlin, А.И. Каминка, Editor. 1923, Slovo.
30 Bayliss W, Starling E: The mechanism of pancreatic secretion. J Physiol 1902;28:325–353.
31 Hill J: Obituary notice: the late Emeritus-Professor Nicholas Kulchitsky. J Anat 1925; 9:336–339.
32 Nicholas Kulchitsky (1856–1925): Nature 1956;17:164.
33 Dart RA, Craig D: Adventuring with the Missing Link. New York, Harper & Brothers, 1959.
34 Kulchitsky N: Nerve endings in muscles. J Anat 1924;58:152–169.
35 Kulchitsky N: Nerve endings in the muscles of the frog. J Anat 1924;59:1–17.
36 Chelmsford, Kulchitsky Personal Correspondence. London, University College, 1925.
37 Kulchitsky Personal Correspondence. London, University College, 1925.