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Max Schottelius: Pioneer in Pheochromocytoma

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First descriptions of diseases attract tremendous interest because they reveal scientific insight even in retrospect. Max Schottelius, the pathologist contributing the first histological description of pheochromocytoma, remains anonymous. We reviewed the description by Schottelius and weighed the report in modern context. Schottelius described the classical diagnostic elements of pheochromocytoma, including the brown appearance after exposure to chromate-containing Mueller's fixative. This color change, known as chromaffin reaction, results from oxidation of catecholamines and is reflected in the name pheochromocytoma, meaning dusky-colored chromate-positive tumor. Thus Schottelius performed the first known histochemical contribution to diagnosis, which is today standard with immunohistochemistry for chromogranin.

Freeform/Key Words: pheochromocytoma, chromaffine tumors, Max Schottelius, Müller's solution

Pheochromocytoma is a fascinating and challenging tumor that continues to intrigue physicians, scientists, and students. It is commonly referred to as "the great masquerader" because of its broad spectrum of signs and symptoms. Thus, the path to diagnosis frequently involves specialists from many fields, including endocrinology, cardiology, and genetics. Modern imaging by magnetic resonance imaging and nuclear medicine enable detection and localization with great sensitivity. Many cases are first discovered as incidentalomas or by genetic screening, performed to test for hereditary pheochromocytoma-associated syndromes, including multiple endocrine neoplasia type 2, von Hippel–Lindau disease, and paraganglioma syndromes.

Major advances are evident in the treatment of patients with these tumors, including new techniques of minimally invasive surgery with minimal morbidity and rapid return to normal life.

These clinical advances are paralleled by progress in pathology and new roles for pathologists, including detecting hereditary disease and risk stratification. A notable example of both is immunohistochemical staining of pheochromocytomas, paragangliomas, and syndromically associated tumors for succinate dehydrogenase B, which is lost in most tumors caused by germline mutations of *SDHB* [1, 2]. However, in relationship to the well-chronicled history of clinical progress, the historical record for pathology contains gaps. In this article, we pay tribute to a physician who, to our knowledge, contributed the first histopathological description of pheochromocytomas.

1. Historical Aspects

Textbooks and journal articles credit the first complete description of pheochromocytoma to Felix Fraenkel. His report, written in German, dates to 1886 [3]. An English translation has

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been published as "Classics in oncology. A case of bilateral completely latent adrenal tumor and concurrent nephritis with changes in the circulatory system and retinitis: Fraenkel, 1886" by the National Institutes of Health [4].

In 2007, we critically reviewed Fraenkel's report. Additionally, using a molecular genetic approach, we found that close relatives of the original patient have undergone resections of adrenal tumors fulfilling the current criteria for pheochromocytomas. We identified in this family germline mutation of the *RET* protooncogene. After reviewing the report by Fraenkel, we confirmed that it is correct to give him credit for the classic description containing both clinical and morphological findings [5]. A much earlier report, by Charles Segrue of Cork, provided a clinical narrative without histomorphology [6].

2. The Contributions of Felix Fraenkel and Max Schottelius

Felix Fraenkel was a clinician who provided a meticulous documentation of what would now be considered classical signs and symptoms of pheochromocytoma in a young woman named Minna Roll with bilateral adrenal tumors. The clinical account culminates in the patient's sudden death, consistent with a hypertensive crisis and myocardial infarction. Fraenkel correctly concluded that the signs and symptoms were caused by a process in which "either a chemical substance is secreted in the (tumor) cells and passes into the venous blood or in which the cells themselves are destroyed …." In reaching these conclusions, he also correctly inferred that the adrenal medulla is an endocrine organ, although the identity of the secretory product was not established until approximately 10 years later when adrenaline was purified by Takamine [7]. Professor Max Schottelius was Fraenkel's colleague who performed the histological investigation, working together with Professor Rudolf Maier who performed the autopsy. Maier (1824–1888) became the first director of the Institute of Pathology at the University of Freiburg, Germany, in 1864. Until 1867, the new building exclusively housing this institute was completed. Under this roof, not only classical pathology but also topographic anatomy, bacteriology and general hygiene, forensic pathology, and the history of medicine were unified. Rudolf Maier's name is still present and linked to polyarteritis nodosa or Kussmaul–Maier disease.

3. Description of the Adrenal Tumors by Max Schottelius

A partial translated excerpt of the pathology findings reads as follows: "The (right adrenal) tumor is surrounded by the normal preserved cortical substance of the adrenal gland. None of the reticularly arranged medullary substance is preserved, however. Rather, one sees large protoplasm-rich cells with one or more large nuclei, which appear very similar to proliferating medullary cells. Some of the nuclei have two or three times the size of the nuclei of normal medullary cells. Also, in some places the configuration of the cell clusters recalls the shape of the cell complexes in the (normal) medullary substance, but it loses any typical shape more and more as one moves closer to the core of the tumor. Here, spindle cells dominated." [4]

The complete detailed description of the autopsy documents a tumor larger than a fist in the left adrenal and a tumor of the size of a hazelnut in the right adrenal. From the gross description, the larger tumor was undoubtedly infarcted, and therefore most likely the immediate cause of death ("The entire mass looks as if it consisted entirely of clotted blood"). Sections fixed in alcohol were "grayish red or dark red," the typical appearance of pheochromocytoma, whereas sections fixed in Mueller's solution, which contained chromate, were "yellow to dark brown." Similarly, the small tumor was "reddish gray" when fresh and became brown in Mueller's solution (illustrated in Fig. 1). In the adrenal gland this color change in response to chromate salts, known as the chromaffin reaction, results from oxidation of catecholamines, and was used in diagnosing pheochromocytomas roughly from 1912 (Pick 1912) until the widespread use of immunohistochemistry in the 1980s. Although it had been discovered in the middle of the 19th century, the reaction was not named until later [8–10].

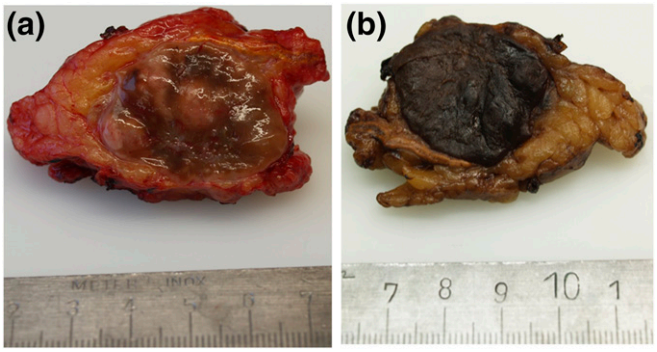

Figure 1. A selected pheochromocytoma fixed and stained by Mueller's solution. Shown is the macroscopic appearance of a cross-section through the middle of the tumor. (a) Unfixed and unstained. (b) Fixed and stained by Mueller's solution.

To illustrate the chromaffin reaction, we selected the next two pheochromocytomas operated after 15 January 2017 to be sent to the Institute of Pathology in Essen for staining with Mueller´s solution. The results were similar, and one specimen is shown in Fig. 1.

The microscopic descriptions of the tumors by Max Schottelius also contain elements familiar in descriptions of pheochromocytomas. These include an "apparently alveolar arrangement" of cells, a "network" of blood vessels, and mixed cell populations including spindle cells and "large protoplasmic cells … without doubt derived from the medullary substance" with a "shape very similar to the medullary cells." In regard to the small tumor, which was best preserved, it is also noted that the tumor "did not have a sharp boundary separating it from the surrounding normal tissue," consistent with possible lack of encapsulation of pheochromocytomas.

Notably, the term pheochromocytoma is absent from the Fraenkel paper and was not applied to this type of tumor until the second decade of the 20th century. Credit for naming the tumor is given to the German pathologist Ludwig Pick for his paper published in 1912 [10]. However the exact word "pheochromocytoma" does not appear there either, even in its German form [11].

4. The Life of Max Schottelius

Max (Maximilian) Bernhard Justus Georg Schottelius (Fig. 2) was born on 15 November 1849 in Braunschweig (Brunswick in English) in Lower Saxony, Germany. He studied medicine at the Universities of Tuebingen and Wuerzburg, Germany. In 1874, he wrote his thesis. In 1879, he passed his habilitation for the discipline of pathology (equivalent to the promotion to assistant professor) at the University of Marburg, Germany. There, in 1881 he received the *venia legendi* (Latin for permission to read, *i.e.*, lecture) for hygiene. In 1883, he became a member of the Institute of Pathology at the University of Freiburg, Germany. He had deep interest in hygiene and dedicated some years in bacteriological studies in Berlin, Munich, and Paris where he met Pasteur, which resulted in his commitment to teach hygiene from 1885. Interestingly, most of his known works related to hygiene and public health (list after references). In 1889, he became head of the Institute of Hygiene at the University of Freiburg, where he planned the first separate building of an institute of hygiene. The building was opened in 1897 and destroyed during World War II (Fig. 3). In 1889, Max Schottelius was honored as an ordinary member of the German Association of Medicine and Natural Sciences "Leopoldina" in Halle. In 1910, he was honored by being named an extraordinary member of the International Association for Cancer Research in Berlin.

Max Schottelius was married to Clara Gutheil on 9 March 1876. The couple had six children. His private passions were cars and sailing (Fig. 4). He was one of the first owners of a private car, a Mercedes, in Freiburg. For sailing, he frequently drove to Lake Constance, the largest lake in Europe, a distance of about 125 km from Freiburg. In an exceptional storm, he

Figure 2. Portrait of Max Schottelius.

died on the lake near the town of Ueberlingen. His body was never found. The day of his death is registered as 12 October 1919.

Max Schottelius shared a common ancestor, Justus Georg Schottelius (1612–1676), a Dr. jur. utr. (doctor of public and church law), who lived in Wolfenbuettel at the court of Duke August II of Braunschweig-Lueneburg (1579–1666), after whom the famous library in

Figure 3. The Institute of Hygiene at the University of Freiburg, Freiburg, Germany, when opened in 1897.

Figure 4. Max Schottelius and his passions. (a) Max Schottelius in his beloved car with his wife and his only daughter. (b) Max Schottelius (left, sitting) on his sail boat at Lake Constance.

Wolfenbuettel is named. Justus Georg Schottelius is arguably acknowledged as the father of German grammar and who invited poets and scientists to the court. His private house near the town hall is now integrated into the town hall complex and is still called the Schottelius house.

5. Discussion

The main findings at autopsy of the patient described by Felix Fraenkel are bilateral adrenal tumors. The histological investigation was performed by Max Schottelius. He used Mueller's solution for fixation of one half of the larger tumor and the entire contralateral tumor. This solution caused the tumors to change color to brown. This solution is composed of 2.5 potassium dichromate, 1.0 sodium sulfate, and 100.0 aqua destillata and is named after Johannes Mueller (1801–1854), pathologist and director of the Institute of Anatomy at the University of Berlin [12]. Mueller was succeeded by the legendary Rudolf Virchow who honored him in a memorable funeral oration. In Mueller's standard pathology book titled "*Upon the More Detailed Structure and the Forms of Pathologic Tumors* (Mueller 1838) he made the statement: "The essential features for distinguishing the tumors according to their inherent properties can only be expected from investigation of their chemical constitution, their histologic structure and their developmental history" [13]. In using Mueller's solution and reporting the color change, Max Schottelius gave the first report of a histochemical reaction to recognize the "chemical constitution" of pheochromocytoma. Today, histochemistry by the chromaffin reaction is replaced by immunohistochemical staining (Fig. 5).

Felix Fraenkel and Max Schottelius understood their tumors' possible endocrine function. Unfortunately, they apparently were misled diagnostically by the prominent spindle cells, which might have included both spindled tumor cells and fibroblasts in areas of ischemic damage. An additional, although less likely, possibility is that the tumors might have contained a component of ganglioneuroma with abundant Schwann cells [14]. Because of the spindle cells, Fraenkel and Schottelius interpreted the histologic findings as indicative of a sarcoma, possibly an angiosarcoma, rather than a new type of tumor. Paradoxically, however, they also noted "the complete latency of the tumor"—not a usual feature of sarcomas, which by definition are malignant. Had they recognized the true nature of the tumor they described, the significance of the spindle cells in predicting its biological behavior might still have been perplexing. To the present day, there are no generally accepted histological criteria for diagnosing a primary pheochromocytoma as benign or malignant, and malignancy is ascertained by development of metastases. To avoid ambiguity caused by conflicting

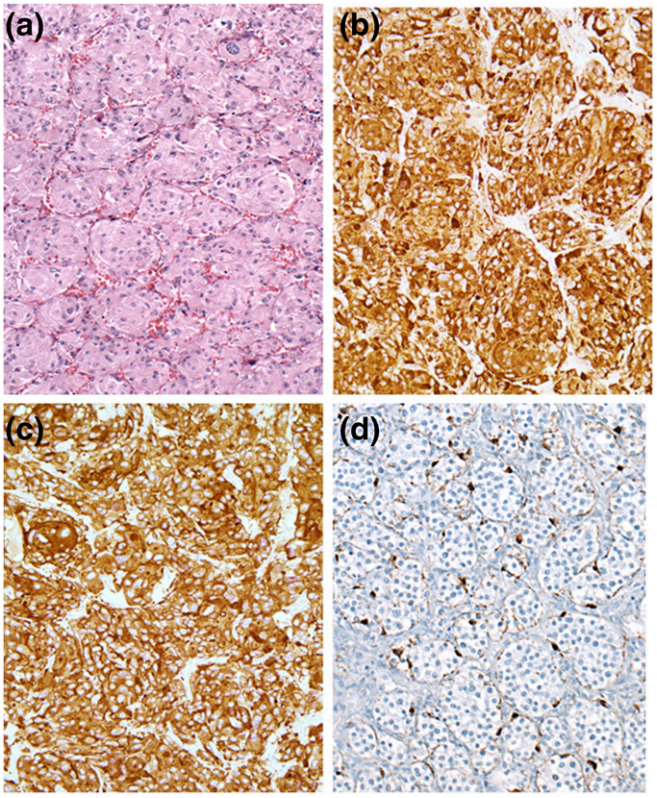

Figure 5. Modern histology of pheochromocytoma. (a) Hematoxylin and eosin stain. (b–d) Immunohistochemistry using chromogranin (b), synaptophysin (c), and S-100 (d).

definitions, the 2017 World Health Organization textbook on endocrine tumors replaces the word "malignant" with "metastatic" in chapters on pheochromocytoma [15]. At the same time, histological scoring systems have been proposed in attempts to stratify the risk that a primary pheochromocytoma will metastasize. Spindle cells are considered an adverse feature in the two major current systems, the Pheochromocytoma of the Adrenal Gland Scaled Score and the Grading System for Adrenal Pheochromocytoma and Paraganglioma, despite their frequent occurrence in pheochromocytomas that occur in patients with multiple endocrine neoplasia type 2A, which seldom metastasize [16, 17].

It is ironic that Schottelius' lasting contribution to modern biomedicine, the first histomorphological and chemical description of pheochromocytoma, was his first and last in this field. His subsequent major work concentrated on hygiene, that is, infectious diseases and public health. His Institute of Hygiene at the University of Freiburg was opened the same year as the equivalent institute of Dr. Max von Pettenkofer in Munich, the latter regarded as the first such institute in Germany. On becoming chief of this institute, Max Schottelius initiated the separation of pathology as a discipline distinct from hygiene, microbiology, and public health. This innovation was adopted throughout Germany and many countries worldwide, but not in neighboring Austria.

Works of Max Schottelius

- Sectionstafeln mit erläuterndem Text (Sectional plates for autopsy with explanatory text), 1878
- Untersuchungen über physiologische und pathologische Texturveränderungen der Kehlkopfknorpel (Investigations regarding physiological and pathological alterations of laryngeal cartilage), 1879
- Ueber einseitige Hydronephrose (On unilateral hydronephrosis), 1877

- Ueber Inhalationspneumonie (On pneumonia by inhalation), 1878
- Zur Aetiologie einfacher Kehlkopfgeschwüre und deren Verhältniss zur Tuberkulose (On the etiology of simple laryngeal ulcers and their relation to tuberculosis), 1880
- Ueber Tuberkulose (On tuberculosis), 1883
- Zum mikroscopischen Nachweis von Cholerabacillen in Dejectionen (About the microscopic detection of cholera bacilli), 1885
- Biologische Untersuchungen über den Mikrococcus prodigiosus (Biological investigations on *Micrococcus prodigiosus*), 1887
- Untersuchungen über die desinfizierende Wirkung der Teerprodukte (Investigations of the disinfecting effects of tar products), 1890
- Die Aufgaben der öffentlichen Gesundheitspflege (The tasks of public health), 1891
- Denkschrift zur Einweihung des neuen hygienischen Instituts der Universität Freiburg im Breisgau (Memorandum for the inauguration of the new institute of hygiene at the University of Freiburg im Breisgau), 1897
- Die Bedeutung der Darmbacterien für die Ernährung (The importance of enterocolic bacteria for nutrition), 1898
- Bakterien, Infektionskrankheiten und deren Bekämpfung (Bacteria, infectious diseases and their control), 1909 (2. Auflage)
- Land- und Verkehrshygiene (Land and travel hygiene) 1914

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