

15 YEARS OF PARAGANGLIOMA

Pheochromocytoma, paraganglioma and genetic syndromes: a historical perspective

Tobias Else

Metabolism, Endocrinology and Diabetes, Department of Internal Medicine, University of Michigan, 2560E MSRB2, 1150 West Medical Center Drive, Ann Arbor, Michigan 48109-5674, USA

Correspondence should be addressed to T Else
Email
telse@umich.edu

Abstract

The last decades have elucidated the genetic basis of pheochromocytoma (PC) and paraganglioma (PGL) (PCPGL)-associated hereditary syndromes. However, the history of these syndromes dates back at least another 150 years. Detailed descriptions by clinicians and pathologists in the 19th and 20th centuries led to the recognition of the PCPGL-associated syndromes von Hippel-Lindau disease, neurofibromatosis type 1, and multiple endocrine neoplasia type 2. In the beginning of the current millennium the molecular basis of the hereditary PGL syndrome was elucidated by the discovery of mutations in genes encoding enzymes of the Krebs cycle, such as succinate dehydrogenase genes (*SDHx*) and other mutations, causing 'pseudo-hypoxia' signaling. These recent developments also marked a paradigm shift. It reversed the traditional order of genetic research that historically aimed to define the genetic basis of a known hereditary syndrome but now is challenged with defining the full clinical phenotype associated with a newly defined genetic basis. This challenge underscores the importance to learn from medical history, continue providing support for clinical research, and train physicians with regards to their skills to identify patients with PCPGL-associated syndromes to extend our knowledge of the associated phenotype. This historical overview provides details on the history of the paraganglial system and PCPGL-associated syndromes. As such, it hopefully will not only be an interesting reading for the physician with a historical interest but also emphasize the necessity of ongoing astute individual clinical observations and clinical registries to increase our knowledge regarding the full phenotypic spectrum of these conditions.

Key Words

- ▶ medical history
- ▶ pheochromocytoma
- ▶ paraganglioma
- ▶ neurofibromatosis type 1
- ▶ multiple endocrine neoplasia type 2
- ▶ von Hippel-Lindau disease
- ▶ hereditary paraganglioma syndrome

Endocrine-Related Cancer
(2015) 22, T147–T159

Introduction

The last 15 years have brought significant advances in our understanding of the genetic basis of hereditary syndromes with a predisposition to pheochromocytoma (PC) and paraganglioma (PGL) (PCPGL) development. In the 1990s the genetic causes for three classic cancer

syndromes for which PC is a well-recognized clinical feature were identified: neurofibromatosis type 1 (*NF1*), von Hippel-Lindau (*VHL*) disease, and multiple endocrine neoplasia type 2 (*RET*) (Cawthon *et al.* 1990, Xu *et al.* 1990, Latif *et al.* 1993, Mulligan *et al.* 1993, Crossey *et al.* 1994).

In the early 2000s mutations in succinate dehydrogenase subunits (*SDHA*, *SDHB*, *SDHC*, *SDHD*) and related genes (*SDHAF2*) were discovered to cause hereditary PGL syndromes (PGL1–5) (Baysal *et al.* 2000, Niemann & Muller 2000, Astuti *et al.* 2001, Hao *et al.* 2009, Burnichon *et al.* 2010). More recently, PCPGLs have been suggested to be part of other syndromes, such as hereditary leiomyomatosis and renal cell cancer (*HLRCC*) caused by mutations in *fumarate hydratase* (*FH*) (Clark *et al.* 2014). For some gene mutations, PCPGL is currently the only known phenotypic expression (e.g., *TMEM127* or *MAX*) (Qin *et al.* 2010, Comino-Mendez *et al.* 2011). Lastly, PCs also occur in patients with mosaicism for activating *HIF2 α* mutations (Zhuang *et al.* 2012).

However, the history of uncovering the hereditary basis of PCPGL dates back at least another 150 years. Our current knowledge was only made possible through the observations of astute clinicians in realizing the association of PCPGL with other syndromic features. There is still an ongoing need for clinical observations to further define PCPGL syndrome associations; therefore, it is important to understand the historic advances that led to our current knowledge of PCPGL-associated syndromes. This review will not only highlight historic exciting events but also hopefully spark the interest of physicians and scientists to keep detailed clinical observations of patients with PCPGL to better define the associated syndromes to improve patient care.

From the discovery of the adrenal gland to the detailed understanding of the paraganglial system

It is still a matter of debate whether Galen actually encountered the adrenal gland in his studies. It is safe to say that he certainly did not appreciate it as a distinct organ. The only suggestion of Galen finding the adrenal gland is the comment on some 'loose flesh' ('lockeres Fleisch,' translation by Simon) at the end of a blood vessel originating from the left renal vein, likely representing the left adrenal vein (Simon 1906). On the contralateral side, he appreciated small venous blood vessels, but no distinct organ. The first definitive description of the adrenal glands was by Eustachius in 1563, and he termed them 'glandulae renibus incumbentes' (glands adjacent to the kidney; Eustachi 1714) (Fig. 1). For the next two centuries there was the common notion that the adrenal glands were hollow organs with diverse proposed functions, such as the secretion of a lithotryptic agent into the kidneys or fetal meconium into the gut or filtration of the intestinal

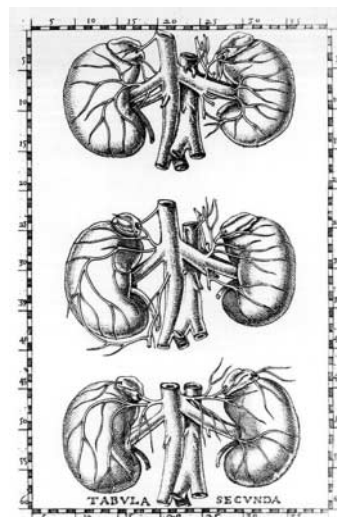
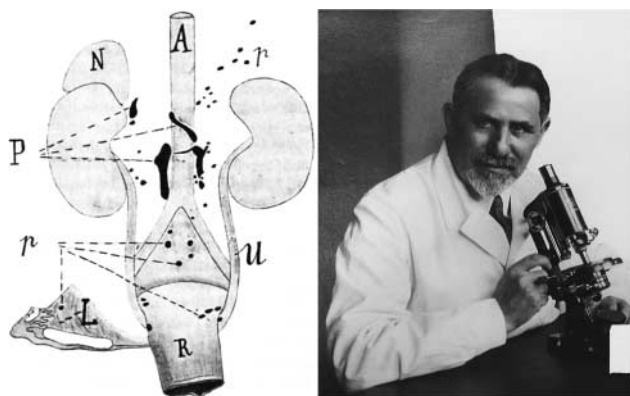


Figure 1

Illustration (Tabula Secunda) from Bartolomeo Eustachi's first description of the adrenal gland (Eustachi 1714).

lymphatic fluids (Carmichael & Rochester 1989). Some authors even reported on excretory ducts of the adrenal glands. The central cavity, which was observed by anatomists in the early ages of modern medical sciences, was likely caused by the large central vein and the post-mortem autolytic fragility of the organ. Nagel (1836) was first to appreciate the two parts of the adrenal gland using the term 'medulla' (Mark) and 'cortex' (Rinde). He described the adrenal glands of multiple species in detail, including the less distinct separation of cortical and medullary cells in birds and reptiles.

The distinct color reaction of the adrenal medulla when exposed to chromium salts was first described by Werner (1857) and further explored by Henle (1865) (Carmichael 1989). Later, Kohn employed the chromium staining method to systematically explore the developmental distribution of what he called 'chromaffin tissue.' Kohn (1903) published a detailed report on the abdominal paraganglial tissue, which he found closely related to the adrenal medulla and sympathetic nervous system (Fig. 2). A main focus of Kohn's manuscript is on the embryological description of the 'organ of Zuckerkandl.' This paired organ had been initially described by the anatomist Zuckerkandl in 1898 as part of the abdominal sympathetic nervous system that was particularly prominent in fetuses and newborn children (Fig. 3) (Zuckerkandl 1901). Kohn also gives the first detailed insight into the embryology of the carotid body ('Carotidruese'), which had originally been described in 1743 by Taube and Berckelmann, both mentees

**Figure 2**

Original drawing about the locations of paraganglial tissue in the abdomen (Kohn 1903). Paraganglial tissue is shown in black. Left: N, adrenal gland; A, aorta; U, ureter; P, paraganglia; R, rectum (reproduced from Kohn A (1903) *Die Paraganglien*, *Archiv für Mikroskopische Anatomie*, 62, 263–367, with kind permission from Springer Science and Business Media). Right: Portrait of Alfred Kohn (reproduced, with permission, from Naňka OGM (2008) *Alfred Kohn, profesor histologie na Německé univerzitě v praze. Casopis lékařů českých* 147 240–244).

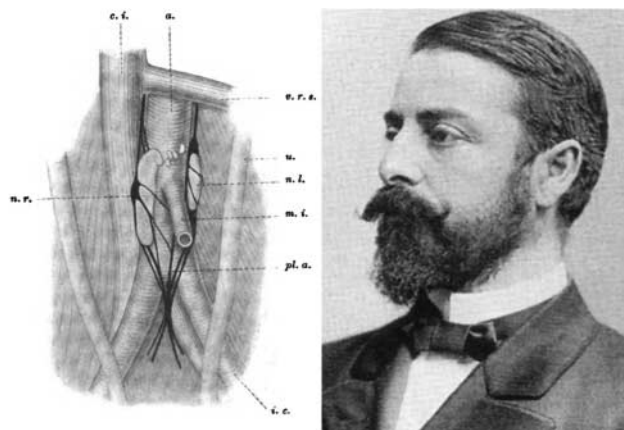
of von Haller (Fig. 4) (Taube 1743, Berckelmann 1744). Although Kohn insisted the carotid body was part of the same system as the other paraganglia, he glossed over the fact that the chromium stain may not be as strong in this gland as it was in the abdominal sympathetic paraganglia.

In parallel to the exploration of the anatomic distribution of autonomic ganglia and paraganglia, there was an interest in defining the physiology of the autonomous system. The largely anatomically inspired term ‘sympathetic nervous system’ was initially coined by the Danish anatomist Winslow (1776), but a further detailed physiological description of the autonomous system and the division of sympathetic and parasympathetic nervous system was introduced by Langley at the turn of the 19th century (Nozdrachev 1995). Because Kohn’s main methodology for identifying paraganglia was based on staining with chromium salts, he failed to identify other non-chromaffin paraganglial tissue in the head and neck area. However, there were ample publications before and after his time describing the thickening of the vagal nerve and its branches (Cock 1837). The glomus jugulare, a conglomerate of cells analogous to the carotid body but of smaller size, was definitively described by Guild (1941). Although since the early 1800s there were descriptions of small areas and conglomerates of paraganglion-like cells, there is still to this day controversy on the number, function, and anatomy of these cells (Cock 1837, Maranillo *et al.* 2008).

The emergence of PCs and PGLs as distinct tumor entities

In the 1800s and early 1900s, there was a lot of confusion and discussion regarding the origin of adrenal tumors. This confusion was caused by the fact that the embryological origin of the adrenal gland was not yet determined and the histological difference between the medulla and the cortex had not become general knowledge. Furthermore, there was minimal to no understanding of the different functions of the two parts of the gland.

The first case report of a PC including the first description of the typical clinical presentation is accredited to Fraenkel (1886) (Fig. 5). Fraenkel found bilateral adrenal tumors in an 18-year-old female patient who suffered from reoccurring episodic symptoms of palpitations, headaches, dizziness, and anxiety for 1 year. These episodes lasted minutes and, for the last 4 weeks prior to hospitalization, became constant. On examination the patient had tachycardia and retinal hemorrhages in accordance with long-standing hypertension. Unfortunately, the patient passed away. Fraenkel hypothesized that the patient had some kind of kidney disease, but to his surprise, on autopsy he identified bilateral adrenal tumors, which microscopically seemed to originate from the adrenal medulla. Fraenkel diagnosed the tumors as likely being a spindle-cell sarcoma on one side and an

**Figure 3**

(left) Original drawing of the organs of Zuckerkindl (n.r. and n.l. ‘Nebenorgan des Sympathicus’) (reproduced, with permission, from Zuckerkindl E (1901) *Ueber Nebenorgane des Sympathicus im Retroperitonealraum des Menschen. Verhandlungen der Anatomischen Gesellschaft* 14 95–107), and (right) portrait of Emil Zuckerkindl (reprinted from *Annals of Anatomy*, 190; Shoja MM, Tubbs RS, Loukas M, Shokouhi G & Jerry Oakes W; Emil Zuckerkindl (1849–1910): anatomist and pathologist; pages 33–36; Copyright 2008, with permission from Elsevier).



Figure 4

Front page of original dissertation by Hartwig Taube (Taube 1743), mentee of Albrecht von Haller (portrait reproduced, with permission, from Peiper HJ (2008) Albrecht von Haller. An illustrious ancestor. *Chirurg* 79 486–493, with kind permission from Springer Science and Business Media).

angiosarcoma on the other side. Therefore, although Fraenkel is accredited with the first description of a PC, he did not identify it as a unique tumor entity. It is noteworthy that the discussions on adrenal tumors in the literature for the following decades fail to mention or cite Fraenkel's observation, suggesting that subsequent researchers were not aware of his initial description of adrenal tumors.

Manasse (1893) reported on tumorous and hyperplastic changes in the adrenal medulla. He mentioned four cases of adrenocortical tumors, likely adenomas, which he referred to as 'struma suprarenalis.' He also described adrenal medullary tumors seen on autopsy of a female patient with the incidental finding of a chicken egg-sized encapsulated brown-black medullary tumor, which was not reported to cause any symptoms at any time of her life. The adrenal cortex in this case was completely pushed to the periphery of this tumor. Another largely cystic medullary tumor was described by Hedinger (1911) as 'Struma medullaris cystica.' The term 'PC' was finally introduced by Pick in 1912 in his manuscript 'Das Ganglioma embryonale sympathicum (Sympathoma embryonale).' The main focus was dedicated to tumors, which are now called neuroblastomas, but he also acknowledged a class of more differentiated adrenal tumors, either originating from the chromaffin cells of the medulla or consisting of tumor cells that differentiate to the stage of chromaffin or 'phaeochrome' cells. To describe these tumors, he coined the term 'PC' (Pick 1912a,b).

Carotid body tumors were well described prior to Kohn's detailed description of the association of the

carotid body/carotid gland with the sympathetic nervous system. Possibly the first such tumor was mentioned by Morgagni (Fig. 6) in 1761 when he described two cases: one encountered by himself, another one seen with his mentor Valsalva.

'A woman of about 50 years of age had been suffering for 3 months from a tumor in the right side of her neck that was hard, oblong, and equal to a turkey egg in size; its base was on the carotid artery in the same side (of the neck), from which it extended all the way to the division of that artery. Sometimes this would hurt, sometimes it brought no pain whatsoever. Ultimately, about twenty days before her death, it began to bother her more frequently, especially in the region of the larynx, such that it forced her to breathe with a certain peculiar stertor, accompanied by a particular sensation of heat in her throat. And so it killed the woman' (Morgagni 1779)

Although no further histological or anatomical description is available, the typical localization and appearance are highly suggestive of a carotid body tumor. In 1891 two seminal manuscripts appeared discussing the origin and existence of tumors of the carotid body. In the first manuscript, Paltauf (1891) gives a detailed description of four cases of carotid body tumors (Fig. 7). He was startled by their histological appearance and therefore suggested that the tumors must have arisen from the carotid body itself and termed them 'endo-(peri-)thelioma of the glandula intercarotica.' In the same year Marchand (1891) also described a carotid body tumor. The

Ein Fall von doppelseitigem, völlig latent verlaufenen Nebennierentumor und gleichzeitiger Nephritis mit Veränderungen am Circulationsapparat und Retinitis').

(Aus der med. Klinik und dem pathol. Institut zu Freiburg i. Br.)

Von Dr. Felix Fränkel,
approb. Arzt aus Ratibor i. Schl.

Figure 5

Title of Fraenkel's initial description of bilateral pheochromocytoma (with kind permission from Springer Science + Business Media: *Virchows Archiv. A, Pathological Anatomy and Histology*, Ein Fall von doppelseitigem voellig latent verlaufenden Nebennierentumor und gleichzeitiger Nephritis mit Veraenedungen am Circulationsapparat und Retinitis, 103, 1886, 244–263, Fraenkel F). Particularly remarkable is the clinical description: 'One night at 9 o'clock the patient had severe palpitations, accompanied by anxiety, dizziness and headaches. This spell lasted several minutes. The patient felt back to normal afterwards and reports to have pursued her work on the farmland. About 4 months later she had a second episode, and a third one later that summer. Since then symptoms worsened: she suffered from headaches and vomiting'.



Figure 6

Front page of 'De Sedibus, et Causis Morborum' (Morgagni 1779) in which Morgagni (right) presents the first case of a carotid body tumor (reprinted from *Journal of Pediatric Surgery*, 43, Zani A & Cozzi DA, Giovanni Battista Morgagni and his contribution to pediatric surgery, 729–733, Copyright 2008, with permission from Elsevier).

author is probably best known for the description of the accessory adrenal glands ('adrenal glands of Marchand') that he had found in one particular case, which in retrospect likely was a woman with congenital adrenal hyperplasia (Marchand 1883).

In the decades to follow there was significant confusion regarding the terminology of tumors of the PC and PGL spectrum. Alezais and Pyron finally suggested using the term 'PGL' (*paragangliome*) for all chromaffin tumors (Alezais 1908). More recently, the nomenclature changed to call chromaffin tumors of the adrenal gland 'PCs' and tumors arising from all other paraganglial tissues PGLs, abandoning the unfortunate nomenclature of, e.g., 'extra-adrenal PC.' Another confusing nomenclature is to reference all adrenomedullary or paraganglial tumors as chromaffin tumors. Chromaffin staining is mainly present in the adrenal medulla and sympathetic abdominal paraganglia and generally absent in head and neck PGL, which are often derived from parasympathetic ganglia. Therefore, the term chromaffin is misleading when used for all paraganglial tissue and should best be avoided.

In the 1890s and early 1900s, there was emerging literature describing surgical attempts and successful surgeries of PCPGL. Marchand (1891) described a 32-year-old woman with a 5.5 cm carotid body tumor that had grown over the course of 4.5 years, encasing the carotid artery. During the surgical attempt, the carotid artery and the jugular vein had to be ligated. He described that the patient postoperatively developed tachycardia and high fevers and died 3 days after surgery. Paltauf (1891)

described probably the first case of a successful surgery of a carotid tumor. A 28-year-old physician was admitted in March 1886 with a growth in the suprahyoid area over the course of 6 months. Because of tumor invasion, the carotis interna and externa were removed, leading to transient hemiplegia, facial and hypoglossal nerve palsy, and aphasia (Fig. 7). Nevertheless, the patient recovered and was without a recurrence 4 years later. Paltauf reported on three additional cases of which two survived and one died as a result of the surgery. Most impressively, he reported that the surgeries for both surviving patients necessitated the removal of the carotid artery. One of the surviving patients was without recurrence, and there was no additional information about the second patient. Moenckeberg (1905) described 12 cases of head and neck PGL: three cases of his own practice and nine additional cases identified in the literature. Three patients died as a result of the surgery; of the nine patients who survived, some had significant neurological deficits and two had a reoccurrence of the tumor. For at least one case, he gives details of the intraoperative course with great fluctuations in the heart rate due to the manipulation of the vagal nerve and carotid sinus or, in retrospect, possibly due to catecholamine excess. Moenckeberg's publication also holds the first case report of a malignant carotid body tumor with metastasis to local lymph nodes. Moenckeberg additionally comments on three 'submastoid potatoe tumors' described by Gilford (1904), but he raises doubt that these tumors were true carotid body tumors as they were only immediately adjacent to the carotid artery rather than involving the artery itself. These tumors might have arisen from different paraganglia. Rosenwasser (1945)

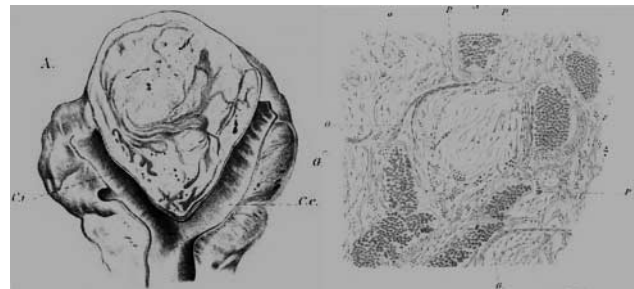


Figure 7

Original drawing of a carotid body tumor in 28-year-old Dr Ferencz. The patient underwent surgery with transient neurological deficits, including transient hemiplegia, aphasia, and facial and hypoglossal paresis. The patient recovered overall remarkably well (reproduced, with permission, from Paltauf R (1891) Ueber Geschwuelste der Glandula carotica. *Beitraege zur Pathologischen Anatomie und Allgemeinen Pathologie* 11 260–301). Left: carotid body tumor shown in the typical location splaying the carotid artery. Right: histology.

**Figure 8**

Anton Freiherr von Eiselsberg (left) performed the first surgery for an abdominal paraganglioma as reported by Stangl (1903). Both Cesar Roux (middle) and Charles Horace Mayo (right) conducted the first surgeries for a pheochromocytoma on European and American continents respectively (left: reproduced from the Wellcome Library, London, UK. Published under the terms of the CC BY 4.0 licence; middle: reproduced, with permission, from Dhayat S, Renggli JC, Dhayat N & Merlini M (2007) On the 150th birthday of Cesar Roux (1857–1918). *Memories of the life and work of an important pupil of Kocher, Chirurg* 78 155–160, with kind permission from Springer Science and Business Media; right: reproduced, with permission, from Mayo CH (1982) Charles Horace Mayo (1865–1939). *Diseases of the Colon & Rectum* 25 734–739, with kind permission from Springer Science and Business Media. Photograph courtesy of the Mayo Clinic).

reports on the successful surgery of a 36-year-old man with a carotid body-like tumor of the middle ear, and he concludes that this tumor likely arose from the glomus jugulare, which had been recently described by Guild (1941). There were reports prior to Rosenwasser's publications describing what in retrospect likely were glomus jugulare tumors, such as the report by Goekopp (1932) (see below).

Surgical reports from the early 1900s describe attempts to remove adrenal PCs and extra-adrenal PGLs. The first documented surgery for an abdominal PGL of the organ of Zuckerkandl was reported by Stangl (1903) (Fig. 8). A 32-year-old farm worker was found to have a walnut-sized tumor on palpation in the umbilical area. The patient underwent laparotomy by von Eiselsberg, and a tumor located at the bifurcation of the aorta, likely arising from the organ of Zuckerkandl, was removed. The patient recovered well and left the hospital 3 weeks later. The history of the surgery for PCs was reviewed in detail by Welbourn (1987). The first successful surgeries were carried out by Roux in Switzerland and shortly thereafter by Mayo in Rochester, Minnesota in 1926 (Mayo 1927, Welbourn 1987). Interestingly, the first description of unexpected, deleterious effects of anesthetic agents precedes the reports on surgery for PCs. In 1910 Kolisko described a case of a 43-year-old patient undergoing tooth extraction with the use of cocaine as a local anesthetic who died a couple of hours after the procedure (Neusser 1910). The autopsy

shows cardiac hypertrophy and a cystic adrenal tumor. The tumor was proven to consist of chromaffin tissue, and the aspirate from the cystic part was shown to induce a blood pressure surge in animals (Hedinger 1911).

Association of PC and PGL with hereditary syndromes

Although it took several decades from the early descriptions of PCPGL to connect PCPGL to the now known predisposition syndromes, there were some characteristics suggestive for a hereditary predisposition even in the late 1890s and early 1900s. Most of the initially described patients were fairly young (20–40 years) when afflicted with these tumors, which we now know often suggests an inherited syndrome. Some reports suggested a possible hereditary component such as the case described by Marchand (1891) of a 20-year-old woman with an adrenal tumor and a family history of a large retroperitoneal tumor in her mother. The knowledge of an association of PCs with classic syndromes – NF1, VHL disease, and multiple endocrine neoplasia type 2 (MEN2) – emerged slowly from detailed case reports starting in the early 1900s and was fully defined by several systematic reviews of the literature and case series in the 1940s to 1960s.

Although not per se a genetic predisposition, there is the peculiar finding of an association of PCPGL development in chronic hypoxic states. This represents a clinical link to other often genetic conditions, such as cyanotic congenital heart disease, and a biological link, as there is a close connection between hypoxia-like signaling changes caused by genetic mutations in *VHL*- and *SDHx*-associated tumors. An association of PCPGL and hypoxia as well as mitochondrial abnormalities was first suggested in the 1970s (Cornog *et al.* 1970, Arias-Stella & Valcarcel 1973, Watanabe *et al.* 1976). Saldana *et al.* (1973) showed a higher prevalence of carotid body tumors in Peruvians who live at high altitudes than those living at sea level. Of note, most patients in this publication also had lung or heart disease, aggravating the hypoxia. One might also criticize that there is a possibility of a genetic influence because these patients are likely from different populations and gene pools. However, there is good evidence that chronic hypoxia due to medical conditions is a growth stimulus for the carotid body. Patients with either cystic fibrosis or cyanotic heart disease have significantly enlarged carotid bodies (Lack 1978).

In the following sections, there will be a short discussion of the history of PCPGL-associated syndromes. Rather than describing every syndrome in minute detail, there will be a focus on historical pertinent events, particularly as it pertains to the association of PCs with these syndromes (Table 1).

Table 1 Timeline of discoveries and events regarding the adrenal gland and pheochromocytomas and paragangliomas

Pheochromocytoma/ adrenal gland	Paraganglioma/ Paraganglia	Neurofibromatosis type 1	von Hippel-Lindau disease	Multiple endocrine neoplasia type 2	Hereditary paraganglioma syndrome
~AD 200 Galen describes 'loose flesh,' likely the right adrenal gland		~1300 Depictions resembling neurofibromatosis			
1563 Eustachi discovers the adrenal gland	1743 von Haller discovers the carotid body 1761 Morgagni describes a tumor at the carotid bifurcation	1768 Akenside com- ments on familial nature of NF1			
1857 Wener describes chromium salt staining 1886 Fraenkel describes bilateral pheochro- mocyoma	1891 First detailed descrip- tions of carotid body tumors by Paltauf and Marchand 1898 Description of the organ of Zuckerkandl	1882 von Recklinghau- sen describes NF1 in detail	1894 Collins describes retinal angiomatosis in two siblings 1895 von Hippel's first description of retinal angiomatosis	1886 Retrospectively, first patient with MEN2	
1912 Pick introduces the term 'pheochromocytoma'	1903 Detailed description of the paraganglial system by Kohn 1904 Stangl describes first surgery for an abdominal paraganglioma	1910 Suzuki describes first patient with a PC and NF1	1915 First description of a patient with classical visceral manifestations 1926 Autosomal domi- nant inheritance of VHL 1927 Lindau describes the syndrome in detail		
1926 First successful surgeries for pheochromocytoma by Roux and Mayo					1937 Goekopp describes three siblings with glomus jugulare tumors

Table 1 Continued

Pheochromocytoma/ adrenal bland	Paraganglioma/ Paraganglia	Neurofibromatosis type 1	von Hippel-Lindau disease	Multiple endocrine neoplasia type 2	Hereditary paraganglioma syndrome
	1941 Description of the glomus jugulare 1945 First surgery and identification of glomus jugulare tumors	1990 Cloning of <i>NF1</i>	1993 Cloning of <i>VHL</i>	1961 Initial description of MEN2 (Sipple syn- drome) 1962 Recognition of autosomal dominant inheritance 1993 Identifications of mutations in <i>RET</i>	2000s Identification of mutations in <i>SDHA</i> , <i>SDHB</i> , <i>SDHC</i> , <i>SDHD</i> , and <i>SHAF2</i>

Neurofibromatosis type 1

Over the course of the 18th and 19th century there were several case reports on patients with a clinical description that matches our current definition of NF1. Descriptions of typical lesions resembling plexiform neurofibromas date back to the early 14th century (Brosius 2010). Even early reports comment on the familial occurrence of cases and suggest a hereditary nature (Akenside 1768, Virchow 1863, Brosius 2010). The first tumor of the adrenal medulla in a patient with neurofibromatosis was mentioned by Suzuki (1910). He described the autopsy of a 60-year-old woman with a diagnosis of neurofibromatosis and bilateral adrenal tumors measuring roughly half a centimeter, of which the right one had a caseating appearance, suggesting the presence of tuberculosis in the gland. The left tumor had a typical appearance of an adrenomedullary PC (Suzuki 1910). Suzuki's patient may well not have been the first report of neurofibromatosis and a PC. Interestingly, von Recklinghausen himself may retrospectively be accredited for the initial description of a patient with neurofibromatosis and a PC. Von Recklinghausen describes the symptoms of 47-year-old Michel Bur (Fig. 9) in his initial description of neurofibromatosis as follows:

'Mr. B. denies any rheumatic pains. He, however, reports that at times of heavy sweating he develops a tension headache originating in the neck and then extending to the forehead. In general he describes to have a tendency to sweat' (von Recklinghausen 1882)

Therefore, it is certainly possible that this young man might have had an undiagnosed PC. Following Recklinghausen's initial monograph and Suzuki's initial case report, many additional reports of patients with neurofibromatosis and a PC emerged. These reports on the association of a PC with neurofibromatosis were summarized by MacKeith *et al.*, Glushien *et al.* and Chapman *et al.* in the 1940s and 1950s. Taken together it was estimated that roughly 5% of reported PCs were associated with NF1 (MacKeith 1944, Glushien *et al.* 1953, Chapman *et al.* 1959).

Multiple endocrine neoplasia type 2

In the early 1890s, there were several reports of patients with PCs in conjunction with calcified tumors of the thyroid gland (e.g., case 9; Winkler 1909). The classic description of MEN2 was initially given by Sipple (1961)

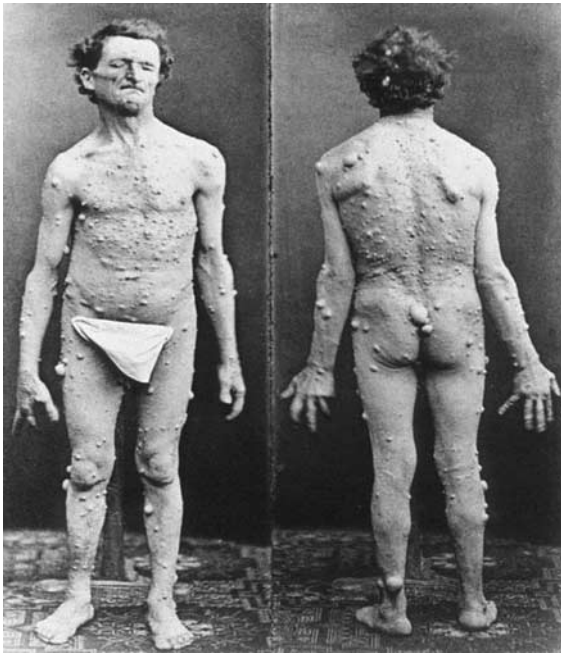


Figure 9

Michel Bur might have had a pheochromocytoma. He was one of von Recklinghausen's initial neurofibromatosis patients who reported headaches and heavy perspiration (reproduced, with permission, from von Recklinghausen F (1882) *Ueber die multiplen Fibrome der Haut und ihre Beziehung zu den multiplen Neuomen*, pp138. Berlin, Germany: A. Hirschfeld).

and is still occasionally termed 'Sipple's disease.' Sipple described a patient affected with all core tumors of MEN2. The 33-year-old patient had bilateral adrenal tumors, a parathyroid adenoma, and a thyroid tumor. Sipple also cited another six cases of PCs with thyroid adenocarcinomas. The distinct pathological entity of medullary thyroid cancer was described in the year following his initial publication (Hazard *et al.* 1959). Williams reviewed several cases of PCs with thyroid cancer and he was able to clarify the medullary histology of the thyroid cancers in all reviewed cases (Williams 1965). The hereditary nature of MEN2 became evident shortly after Sipple's initial publication, when several families with MEN2-associated manifestations were reported (Cushman 1962). Of note, the initial patient with bilateral adrenal tumors described by Fraenkel (1886) had an enlarged thyroid as well, and interestingly, it turned out that she was part of a family that was later diagnosed with MEN2 based on having a *RET* p.Cys634Trp mutation (Neumann *et al.* 2007). The term multiple endocrine neoplasia type 2 was introduced in 1968 to differentiate this syndrome from MEN1, which was until that point largely known as 'multiple endocrine adenomatosis' (Steiner *et al.* 1968).

VHL disease

Collins (1894) published a manuscript that ultimately received little attention in the medical community, describing a pair of siblings affected with angiomatous tumors of the retina. A patient described by Harbitz (1915) is likely the first patient in which the visceral manifestations of VHL disease were present. At autopsy of the patient who had died at age 47 due to a large kidney tumor, a chromaffin tumor of the adrenal medulla, cystic pancreas changes, and kidney tumors were found. In 1885, von Hippel first reported on a case of the clinical syndrome, which later took his name. He presented a patient with unusual retinal findings in 1895 and later in 1904 published a follow-up report, 'Ueber eine sehr seltene Erkrankung der Netzhaut' ('About a very rare disease of the retina'), on two cases of retinal angiomas (von Hippel 1895, 1904). Von Hippel believed the physical findings were likely due to an infectious agent. One year later Czermak (1905) was able to identify the lesions on a surgical specimen as retinal angiomas. Von Hippel (1911) was able to confirm the pathology on one of his own initial cases after enucleation of the eye. The Swedish pathologist Arvid Lindau was the first one to analyze several patients with VHL disease systematically (Lindau 1926). He put the angiomatous changes of the retina in relation to the often observed cystic changes of the cerebellum. In addition he describes almost all of the currently known manifestations of VHL disease. Lindau reviewed 15 cases, nine of which were his own. He found angiomas of the retina in four cases, the cerebellum in nine, the medulla oblongata in five, the spinal cord in four, and the skin in two. Eight patients had cystic pancreatic changes, six patients had renal cell cancer, and two patients had adrenal tumors. Glushien *et al.* (1953) gave a thorough review of the literature providing evidence for an association of VHL disease and PCs. The hereditary nature of VHL disease could have already been suspected from the description of affected siblings by Collins and two affected brothers described by Seidel – interestingly, both professional tightrope dancers with repeated falls, possibly due to retinal and cerebral angiomas (Collins 1894, Seidel 1912). The focus on patient family pedigrees and the finding of autosomal dominant inheritance were proposed in two publications at the end of the 1920s by RoCHAT (1927) and Moeller (1929). Interestingly, several family members of von Hippel's initial proband had been described independently in the medical literature. The whole pedigree and the clinical history of affected family members were

finally summarized in a publication by Piotrowski and Rohrborn (1965).

Hereditary PGL syndrome

Although for the previously discussed syndromes PCs were recognized after the initial description of other syndromic core manifestations, elucidation of the genetic and clinical basis of hereditary PGL syndromes (PGL1–5) was exclusively based on the familial occurrence of PCPGL. Only after the genetic basis was determined, pituitary tumors, gastrointestinal stroma tumors, and renal cell cancer were recognized as part of the full tumor spectrum, albeit with lower penetrance than PCPGL. The first possible descriptions of familial cases of PCPGL were by Marchand (1891) of a patient with a PC and a family history of a mother with a large retroperitoneal tumor. In the 1930s to 1950s more detailed reports by Chase on familial carotid body tumors and by Cook *et al.* on familial malignant PGLs of the organ of Zuckerkandl followed (Chase 1933, Cook *et al.* 1960). In 1932 Goekopp reports on three sisters with ‘fibro-hemangiomas of the middle ear and petrosal bone,’ likely representing glomus jugulare tumors as described 8 years later by Rosenwasser (Goekopp 1932, Rosenwasser 1945).

Since defining the genetic basis of hereditary PGL syndromes in the early 2000s, a growing number of families with mutations in the succinate dehydrogenase subunits (*SDHx*) and associated genes have been identified (Baysal *et al.* 2000, Niemann & Muller 2000, Astuti *et al.* 2001, Hao *et al.* 2009, Burnichon *et al.* 2010). Importantly, there is the common notion that the syndrome is not entirely understood and that there are likely other associations, such as a relative risk increase for other rare tumors and possibly other non-neoplastic manifestations. Therefore the *SDHx*-associated syndromes still provide ample opportunity for systematic clinical research to complete our understanding of risk associations, which is necessary to provide the right genetic counseling and offer the correct and most cost-effective surveillance to these patients.

Recently there have been some descriptions of mutations in *FH*, another enzyme of the Krebs cycle known to cause hereditary leiomyomatosis and renal cell cancer, in patients with PC (Clark *et al.* 2014). There is accumulating evidence that mutations in Krebs cycle enzymes as well as *VHL* mutations cause hypoxia-signaling (‘pseudo-hypoxia’) in adrenomedullary and paraganglial cells, contributing to tumor development (Favier & Gimenez-Roqueplo 2010). In addition, in rare

instances, tumors of the paraganglial system (as well as erythrocytosis) may also arise in patients with germline mutations in *EGLN1* or somatic gain of function mutations in *HIF2A*, further underscoring the importance of the hypoxia signaling pathway (Ladroue *et al.* 2008, Zhuang *et al.* 2012).

Lessons learned from history

Over the last 150 years our knowledge about PCPGL and associated hereditary conditions has significantly broadened. This acquisition of knowledge started with the definition of the origins of the adrenal medulla and its connection to other chromaffin tissues, followed by the description of the paraganglial tissue as its own tissue entity and finally led to the definition of the genetic basis of hereditary syndromes associated with PCPGL. The general principle of this research historically always used the same approach: initially, there were some emerging case reports and, finally, a systematic analysis identifying a new clinical syndrome. Often the discovery of a syndrome is accredited to the first researcher taking the systematic approach in combining cases from the literature with the researcher’s own observations. But it is important to note that the final ‘syndrome discoveries’ were generally based on accumulating bits of small data emerging in medical sciences, which in itself represented important steps forward. Along the way astute physicians and researchers detailed the clinical observations and continued to further define these clinical phenotypes, including associations with other tumors, and described the epidemiology of these conditions.

Over the last two decades, however, there has been a paradigm shift. The initial recognition of rare genetic syndromes nowadays is often preceded by genetic findings lacking a complete knowledge of the clinical phenotype. Nowadays, molecular genetic findings are often evident prior to a fully clinically defined phenotype. It seems almost that thorough clinical descriptions are often ignored. Therefore, continuation (or maybe resurrection) of the ability to obtain detailed clinical observations has become more important than ever before. It is imperative to continue teaching and improving the clinical skills of future generations to provide the data for describing the clinical phenotype for genetic syndromes. In addition, systematic clinical efforts are needed to complete our knowledge about the entire associated tumor spectrum, the age of onset of these tumors, and the penetrance of phenotypes in hereditary syndromes, especially those associated with PCPGL. On the molecular level, attention to clinical detail will also allow for a streamlined approach to identify modifying circumstances,

such as environmental exposures or modifier genes. This knowledge will be necessary to make the right decisions in the clinical care of affected patients. For example, there are still pertinent questions that remain unanswered, such as to what is the right imaging frequency for *SDHx* mutation carriers and whether the risk is truly the same over the course of the lifetime of a patient. Our current assumptions regarding penetrance of the *SDHx*-associated phenotypes is still strongly biased by the analysis of the initial descriptions of high penetrance families. The actual absolute risk for PCPGL development, therefore, remains undetermined. With regards to the risk of tumor development over a mutation carrier's lifetime, it is interesting to note that most patients with head and neck PGLs in historical descriptions were fairly young at diagnosis and often described a time of accelerated tumor growth followed by minimal or no growth. This suggests that the very initial events of tumorigenesis might fall into fetal life, childhood, or adolescence, and there may be less risk of tumor development in adulthood. Only the definition of age-associated risks will allow for establishing evidence-based screening guidelines. Furthermore, it will be important to understand the full clinical spectrum of predisposition caused by mutations in genes that were only recently described, such as *TMEM127* and *MAX*, possibly identifying other associated tumors. It also remains necessary to analyze larger cohorts to prove the causative relationship between PCPGL and genetic mutations that have so far only been found in a single patient or family. Therefore, there is no doubt that future clinical and genetic findings will be as exciting and unexpected as the seminal findings over the last centuries and will most importantly improve preventive care in gene mutation carriers.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

Funding

T Else is funded by the American Heart Association (AHA14SDG17990000).

Acknowledgements

I would like to thank Benjamin Fortson for the Latin-English translation of the manuscripts by Haller and Morgagni. I thank Lauren Fishbein for the careful reading of this manuscript. I am particularly indebted to the current efforts of many libraries and enterprises to make historic manuscripts available to the public (e.g., Google, Hathi Trust). Without these resources a meaningful research on the discussed topic would not have been possible. For further reading, I would like to hint the reader to some detailed and more in-depth reading on the exciting history of the adrenal medulla and neurofibromatosis: Brosius (2010), Carmichael (1989).

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Received in final form 9 June 2015

Accepted 18 June 2015

Made available online as an Accepted Preprint

25 June 2015