My Life for Pheochromocytoma

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Introduction

The fascination of hereditary tumor diseases, especially von Hippel-Lindau disease (VHL) and pheochromocytoma, has dominated my academic life for three decades. My background was the warm and rich atmosphere which gave me my parents, Colonel Joachim Neumann and Mechtild Zuckschwerdt, PhD, MA, descendent of an industrial family from Magdeburg. Together with 3 sisters and a brother, I spent my youth in Brunswick, Hamburg and Bonn with a classical education including Latin and Greek. I served 2 years in the artillery of the German army. From 1969 until 1974, I studied medicine at the Universities of Bonn and Heidelberg.

After examination, I felt unprepared for an university career. I started in internal medicine in a country hospital, but decided after some months to go to the roots, to pathology in the large city hospital of Ludwigshafen/Rhein, the city of the BASF company. The five-year training with 500 autopsies and 20 000 biopsies and operation specimens, dominated by the cultured personality of the head Kurt Wegener gave me a solid background. But returning to the wards at the University Clinics of Freiburg at age 34 was not promising: in this country, I was considered too old.

The early years until 1993 at the University of Freiburg

The year was 1983: as a member of a nephrology department, I realized that the causes of diseases, especially glomerulonephritis, were unlikely to be clarified soon (still not done even today!). The key event happened after less than 2 months, when I had charge of a patient with pheochromocytoma. His sister informed me that she had been operated for a brain tumor, an hemangioblastoma. Overnight, I realized the diagnosis must have been VHL. The gene was neither mapped nor identified at that
time, and I had secondary hypertension with a defined cause – heredity – in hand, the basis for clinical and basic research for years. Fascinating were the many aspects of clinical relevance, mainly diagnosis and treatment of pheochromocytoma and hemangioblastoma of the central nervous system (CNS), but also the other components of VHL, retinal (hem)angio(blasto)ma, clear cell renal cancer and pancreatic neuroendocrine tumor. However, I was in a section of nephrology and my proposed clinical and research platform encompassed multidisciplines, resulting in lack of support in my own department. In other words, I wanted to study a unicorn: too rare, too many disciplines, hence, hopeless. I therefore respectfully requested joint appointments with the chiefs of the eye, neurosurgery and visceral surgery departments. I then was able to review the patients belonging to all 3 departments and made 3 lists. I noticed some identical family names across the 3 lists, some identical living in venues with small populations. I contacted these patients, and with their permission, I drove after work through the Black Forest to meet the families, to collect information and blood samples. The number of VHL patients grew.

After revising the diagnostic criteria for VHL (1) and its prognosis (2), I started my publications in international scientific journals with a report on sporadic and VHL associated CNS hemangioblastomas (3). After disappointing ventures with distinguished international research groups to help identify the VHL gene, I joined the Bostonian group who lost – and the RET gene – I joined the Cambridge/UK group and achieved only an acknowledgement in the Nature publication (4) - I decided to try on my own a major manuscript without molecular genetic data. The breakthrough was in 1991 with the Lancet publication on epidemiology and classification of VHL (5) which is used until now as VHL type 1 and type 2 (6). The other major project from this period still remains the only prospective study for clinical diagnosis of pheochromocytoma published in 1993 in the New England Journal of Medicine (7). In
36 out of 79 investigated at risk persons from 24 families with this tumor, we found 42 new pheochromocytomas. We were able to compare the sensitivity and specificity of ultrasonography, computerized tomography, magnetic resonance tomography, metaiodobenzylguanidin scintigraphy and biochemical methods to detect pheochromocytoma. For this publication, I received the highest award of the German Society of Nephrology, the Franz-Volhard Prize in 1994.

**Academic career**

Although I was initially deemed too old, I completed specialization in Internal Medicine (1988), Nephrology (1990) and Endocrinology (1994) at the University Medical Center of Freiburg, and was appointed Privatdocent (1988) and subsequently Extraordinary Professor (1994). Around that time, I established a molecular genetic laboratory for both research and clinical genetic diagnostics. In 1996, I won the competition for the chief position of the Department of Nephrology at the University of Innsbruck. But finally I declined that position due to terms which would have doomed me to failure. This ended in the tragedy that my laboratory staff departed thinking that I would accept the position at Innsbruck, and I never was invited again for a chief position. But all things in life happen for a good reason.

**Scientific fruits**

In 1996 and 1997, I reorganized my laboratory with successful grant applications and a staff of up to 10 postdocs, technicians and students based on projects for pheochromocytoma and associated syndromes, hemolytic uremic syndrome and autosomal dominant polycystic kidney disease, funded by the German Cancer Foundation, the German Research Foundation and the Else Kroener-Fresenius-Foundation. The research group was formally incepted in 2006 as the Section for
Preventive Medicine. In fact, the focus of our activities was the work “at the edge” of molecular classification of tumors and diseases by identification of germline mutations in the blood of patients in order to establish programs for best treatment and follow up and to archive optimal long term outcome. For this objective, it turned out that outstanding large registries are essential. And we established these registries for all component tumors of VHL and sporadic counterparts, e.g., retinal angiomas, CNS hemangioblastomas, renal clear cell cancer and neuroendocrine tumors. One of our most unique initiatives comprises the 2000-registrant strong European-American-Pheochromocytoma-Paraganglioma-Registry based in Freiburg. This Registry contains all forms of hereditary and sporadic pheochromocytomas and paragangliomas including those of the skull base, neck, and thoracic and pelvic locations. In parallel, we have established similar registries in Freiburg for hemolytic uremic syndrome, autosomal dominant polycystic kidney disease and Fabry disease.

**The Freiburg Warsaw Columbus Pheochromocytoma Study**

The pheochromocytoma registry started with a local collection gained by systematic offers to endocrinologists, pediatricians and visceral surgeons in Germany, but also to colleagues abroad. Unique was a meeting in Berlin in 1996 with Andrzej Januszewicz whose father, Wlodzimierz Januszewicz, head of the Department of Hypertension at the Medical Academy of Warsaw, admired our above mentioned 1993 paper. I was conferred honorary membership of the Polish Society of Hypertension. The registry was dramatically enlarged by Polish patients including blood samples from all cases. When in 2000 mutations of the *SDHB* and *SDHD* genes were shown in patients with paraganglioma syndromes type 1 and type 4, Birke Bausch, then a medical student in my laboratory, completed molecular genetic testing analyses in 271 patients with apparently sporadic pheochromocytomas. The
design, interpretation and manuscript elaborated together with Charis Eng, then in Columbus/Ohio, was published in 2002 in the New England Journal of Medicine (8). The editorial summarized the message as “The death of an axiom” (9). Indeed the anticipated 10% heredity in pheochromocytomas exploded to 24%, all 4 genes contributed considerably. Until today, this publication has more than 900 citations in peer reviewed journals.

The grant of the European Union

Soon after this publication, I was contacted by the Finnish geneticist Lauri Aaltonen and invited to apply in a group of 6 for a grant to be submitted to the European Union on Defects in the Tricarboxylic Acid (Krebs) Cycle Genes in Tumourigenesis, EU-Project No. LSHC-CT-2005-518200. The application was fully granted and gave an optimal basis for the coming years. We extended our activities to head and neck paragangliomas and reported on the spectrum of germline mutations and clinical manifestations for SDHB and SDHD in 2004 and for SDHC in 2005, both in JAMA (10, 11). Subsequently we elaborated guidelines for selection of candidate genes to be tested in patients with pheochromocytoma in Clinical Cancer Research (12) and patients with head and neck paragangliomas in Cancer Research (13).

Felix Fraenkel’s report from 1886 on Minna Roll: First Description of an Heritable Pheochromocytoma

The keynote speaker at the 1st International Symposium on Pheochromocytoma in Bethesda/Maryland in 2005, William M Manger, at that time President of the American Society of Hypertension, gave credit to the report of Fraenkel, widely regarded as the first description of pheochromocytoma (14). It was a patient treated in Freiburg and thus a new challenge for me. In fact, this report which had been
translated to English before (15) has remarkable features: a 19 year old patient, bilateral adrenal tumors, histological diagnoses of a “sarcoma” in one adrenal and “angiosarcoma” in the contralateral side and no affected relatives. Unlike the current regulatory environment, the Fraenkel report names his patient Minna Roll, and the village where she lived, Wittenweier, 50 km north of Freiburg. Anticipating potential heredity based on young age and multifocal tumors, we estimated based on our registry with patients up to 19 years, more than one tumor and the ZIP codes of places of living. In all estimates, Minna Roll should have a high likelihood of a \textit{VHL} germline mutation. Once I returned from the meeting, I started an in-depth survey for records or other documents in the medical clinic, the institute of pathology and the university library. I found a handwritten macroscopic autopsy report, no drawings, no slides. I asked Alexander Vortmeyer from the NIH to check the extensive histological description in the publication. He agreed with a final diagnosis according to the actual tumor classification as bilateral pheochromocytomas. But was there remaining uncertainty? I decided to contact by mail 20 individuals carrying the same family name (Roll) from the Wittenweier telephone directory. I received positive answers and invitations for visits. Thus, I learned that all inhabitants of the village and interested persons like me had access to a book with pedigrees of all families of the village. This and information provided by the families gave evidence that descendents of two of the six brothers of Minna Roll had been recently operated for pheochromocytomas. We had access to blood from these patients, and to our tremendous surprise, we did not find a \textit{VHL} mutation. The mutation detected was in the \textit{RET} gene (p.Cys634Trp). Thus we had evidence that the classical report on pheochromocytoma was a patient with multiple endocrine neoplasia type 2 (16).

\textbf{The fight for adrenal sparing and endoscopic surgery in hereditary pheochromocytoma}
Present in the operating theater for my first patient with bilateral and hereditary pheochromocytoma in 1983 and asking why complete removal of both adrenals is indicated, the response was “You will do the surgery for the recurrent tumor” and bilateral complete removal was done. This spurred me to create the concept of adrenal sparing surgery in hereditary pheochromocytoma. My vision was that recurrence, if at all, would happen many years later, that malignancy is unlikely, that considerably many hereditary pheochromocytomas are diagnosed in an asymptomatic stage after family screening or (only years later available) molecular genetic testing. With this concept, one major burden to the patients, e.g. lifelong steroid replacement for postoperative Addison disease, could be avoided. Since 1985, all my patients were operated accordingly, in the first years by Helmut Kirste in an open procedure (17). The extended concept was Endoscopic Adrenal Sparing Surgery. Thanks to the surgeon Martin Walz in Essen, this concept is now the gold standard, and I am happy to say that all my 150 pheochromocytoma patients operated by Martin Walz had endoscopic tumor removal, all with retroperitoneal access with minimal scars, all were discharged after 2-4 days, and all preserved sufficient adrenal cortical tissue with no recurrence after a mean of 7 years. This series also includes an additional 30 patients with extraadrenal pheochromocytomas, some of whom had difficult to reach or tenous locations within the thorax or pelvis, all successfully removed endoscopically (Figure 1).

A dream come true: author in Harrison´s Textbook of Internal Medicine

In 2007, I received an email by the editorial team of Harrison´s Textbook of Internal Medicine. I was asked to write the chapter pheochromocytoma. My response was that such a chapter would lie best in the hands of Lewis Landsberg. But it was Lew that had suggested me as he wanted to “retire” from this chapter. What a challenge!
With the excellent mentorship of Larry Jameson, I presented the generally accepted genetic classification with new colour coded graphs as the core of the chapter. This 17th edition was published in 2008 followed by invitations for the 18th edition (2011) and 19th edition (in press) (18-19). I realized that moderate verbal strategies are successful and strengthened the indication for endoscopic tumor removal, organ sparing procedures as well as for molecular genetic diagnosis and its clinical relevance.

**For the patients: labor of love and a necessity**

The research from projects on diseases with lifelong and next generation relevance, especially with multi-organ involvement should be made available to all patients. Thus, we give back, in part, what we learnt from the patients providing them with gene-specific risk profiles and best management. Starting in the mid-1980s, I invited patients with such hereditary tumors and also those with their sporadic counterparts for informational evenings. This was followed by information booklets. But all this was incomplete if there are no standard user-friendly means for patient-to-patient communication. In this regard, I was visited by Ms. Joyce Graff from the United States and who lost her husband to VHL and whose affected son received too aggressive recommendations for kidney tumor surgery. Her amazing personality was able to change the situation completely. She organized with me the first patient-provider conference in 1994 in Kansas City. She founded and established the American VHL Self Support Group. In this context, she created a periodical for information for the patients; she organized the conferences year by year in different states of the US and later also in other countries, and she was always ready to be on call. Thus, in 1998 with Joyce’s inspiration, a German VHL Self Support group was founded by Gerhard Alsmeier.
In contrast to VHL, such activities have no parallel for pheochromocytoma in general, but the pressure rose. So I decided to write an informational booklet for patients with pheochromocytoma, paraganglioma and associated diseases. It became a book of 150 pages with many figures, graphs and tables and included also general information how to understand the terminology of the mutations. The response of the German patients was encouraging, and I decided to make the information accessible worldwide free of charge and in the country-specific languages in the internet. At present, there are 13 translations including Hungarian, Russian, Bulgarian, Turkish, Persian and Arabic and more are planned (www.uniklinik-freiburg.de/nephrologie/live/.../PheoBookDeutsch.pdf).

**School of Freiburg**

Thanks to our many patients and the many colleagues in different fields of medicine, the University Medical Center of Freiburg has developed into a center of excellence for the management of VHL and pheochromocytoma-associated diseases and similar other diseases. Corner stones have been and remain Vera van Velthoven in neurosurgery, Dieter Schmidt in ophthalmology, Irina Mader in neuroradiology, Arnd-Oliver Schaefer in radiology, Damian Wild and Philipp Meyer in nuclear medicine, and Wolfgang Schultze-Seemann and Christian Leiber in urology. Many students wrote their thesis in medicine on molecular and clinical aspects in the broad field of various diseases. International collaborations were set up with the universities and cancer centers in Warsaw, Padova, Salamanca, Rome, Shanghai and Madrid and included visits and stays of guests in the laboratory and outdoor clinic in Freiburg. Common projects resulted in best ranked theses by Zoran Erlic in Padova and Ioana Milos in Timisoara/Romania. Thus the preventive medicine center became a model, and similar structures have been established as satellites abroad. In-house
collaborations led to 7 professorial theses, among these those based on longterm collaborations with Sven Glaesker, neurosurgery, and Carsten Boedeker, otorhinolaryngology. In 1994, I organized a first scientific symposium on VHL in Freiburg, attended among others by Alfred Knudson jr. This became a self-running international meeting of researchers and affiliated self support groups every two years rotating through all parts of the world.

In 1998, I was honored by the Hufeland Prize, the German award for Preventive Medicine (Figure 2). Later, VHL patients sent a letter to the President of Germany, Mr. Horst Koehler, who awarded me with the Cross-of-Merit of the Federal Republic of Germany in 2008. For long lasting partnership with Tivadar Tulassay and Karoly Rács, the Semmelweis University of Budapest honored me with the degree of a doctor honoris causa in 2010.

**Outside medicine**

In 1985, I married Henriette Baroness von Krane – von Ficker. We have two daughters, Fanny and Luise. Words cannot express how grateful I am for the endless patience and support of my beloved wife. All collaborators and guests are invited to our home, meaning mainly her wonderful house where I always had and have the privilege for daily lunch. My passion is music (Figure 3). Having been taught how to play violin from childhood, I spend abundant time in string quartets and amateur orchestras such as the Orchestra of the German Pediatricians. Since 2003, I have been a member of the Order of St. John the Baptist.

**Admiration and partnership with the Grand Lady, Charis Eng**

Charis Eng (MD and PhD), Director of the Genomic Medicine Institute at the Cleveland Clinic, before that as a postdoctoral trainee in Cambridge/UK,
subsequently in faculty positions in Boston and Columbus/Ohio, with whom I have initiated many projects over the past 20 years. My admiration of her is sky-high. To date, we have 37 publications together, all in peer review journals (8, 10-13, 16, 20-50). I deeply regret that the distance has widely hindered personal meetings. But in early 2011, we had, after a very long while, a festive reunion in Cleveland (Figure 4). In honor of her, I gave a violin recital in the Miller Pavillon of the Cleveland Clinic accompanied by pianist Shuai Wang with Bach, Mozart, Beethoven, Massenet and as an encore, the Tango by Boulanger “Avant de Mourir”.

I officially retired October 1, 2013 and spent my last working day, September 30, in Nancy, where after many years of collaboration with my friend Georges Weryha, I was awarded a doctor honoris causa of the Université de Lorraine.

With “retirement,” I am looking forward to focusing more on science and my collaborations, always with my patients and the many colleagues who supported me in the past three decades in mind.

**Word Count:** 2898

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Tables and Figures

Table 1

Von Hippel-Lindau disease: Major manifestations and clinical classification

Retinal Angiomas
Hemangioblastomas of the central nervous system
Clear cell renal carcinomas
Pheochromocytomas
Pancreatic neuroendocrine tumors
Epididymal cystadenomas / Cystadenomas of the broad ligament

VHL type 1 shows predominantly renal carcinomas but very rarely pheochromocytomas.

VHL type 2 shows predominantly pheochromocytomas but very rarely renal carcinomas. Especially in VHL type 2A kidney tumors are exceptions, but not in VHL type 2B, whereas in VHL type 2C, as a rule, only pheochromocytomas are present.

Table 2

Pheochromocytomas and Paragangliomas: Molecular genetic classification

Multiple endocrine neoplasia type 2 associated with mutation in RET
Von Hippel-Lindau disease associated with mutations in VHL
Paraganglioma syndrome type 1 associated with mutations in SDHD
Paraganglioma syndrome type 2 associated with mutations in SDHAF1
Paraganglioma syndrome type 3 associated with mutations in SDHC
Paraganglioma syndrome type 4 associated with mutations in SDHB
Paraganglial tumors associated with mutations of TMEM127
Paraganglial tumors associated with mutations in MAX
Paraganglial tumors associated with mutations in SDHA

The nomenclature is not always the same. According to the WHO classification the term pheochromocytoma is restricted to adrenal tumors. Most clinicians say pheochromocytoma when the tumor is vasoactive with attacks of hypertension, sweating and headaches, and reserve paraganglioma to those of skull base and neck locations.

Figure 1

Pheochromocytomas and paragangliomas

A Bilateral adrenal tumors in multiple endocrine neoplasia type 2. Image: Courtesy Martin K Walz, Huyssens Hospital, Essen, MD

B Extraadrenal retroperitoneal pheochromocytoma, CT. This giant tumor was endoscopically resected in 8.5 hours by Martin Walz, Essen, by an bilateral retroperitoneal access and minimal scars. The tumor was after dissection in situ cut in pieces and removed. Image: Courtesy Schu-Ren Yang, MD, University Medical Center, Freiburg

C Paravesical pheochromocytoma (paraganglioma) with postural catecholamine attacks. Resected endoscopically by Martin Walz. Image: Courtesy Schu-Ren Yang, MD, University Medical Center, Freiburg

D Thoracic left sided pheochromocytoma (paraganglioma) resected endoscopically after intubation of the right lung and collaps of the left lung. Image: Courtesy Schu-Ren Yang, MD, University Medical Center, Freiburg

E Scars after conventional and endoscopic surgery for pheochromocytoma

Figure 2
Hartmut Neumann when awarded by the Hufeland Prize in 1998

Figure 3

Hartmut Neumann with Joyce Graff at the 3rd International Symposium on VHL in Paris 1998

Figure 4

Hartmut Neumann and Charis Eng at the Symposium for MEN 2 in Grand Rapids, Michigan, 2002
Fig. 1E
Results after Endoscopic and Conventional Surgery