Introduction

A fascination with hereditary tumor diseases, especially Von Hippel–Lindau (VHL) disease and pheochromocytoma, has dominated my academic life for three decades (Table 1, Fig. 1). My background was the warm and rich atmosphere created by my parents Colonel Joachim Neumann and Mechtild Zuckschwerdt, PhD, MA, descendant of an industrial family from Magdeburg. Together with three 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 to 1974, I studied medicine at the Universities of Bonn and Heidelberg.

After examination, I felt unprepared for a university career. I started in internal medicine in a country hospital, but decided after some months to move into pathology in the large city hospital of Ludwigshafen/Rhein, the city of the BASF company. The 5-year training programme of 500 autopsies, 20 000 biopsies and operation specimens, dominated by the cultured personality of the head Kurt Wegener, gave me a solid background. However, returning to the wards at the University Clinics of Freiburg at the age of 34 years was not promising: in this country, I was considered too old.

The early years 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 achieved even today!). The key event happened within 2 months, when I had charge of a patient with pheochromocytoma (Table 1). His sister informed me that she had been operated on for a brain tumor, a hemangioblastoma. Overnight, I realized that 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 (inheritance) to consider, the basis for clinical and basic research for years. The many aspects of clinical relevance were fascinating: diagnosis and treatment of pheochromocytoma and hemangioblastoma of the CNS, and the other components of VHL, retinal (hem)angio(blasto)ma, clear-cell renal cancer, and pancreatic neuroendocrine tumors. However, I was in a section of nephrology and my proposed clinical and research platform encompassed multiple disciplines, resulting in a lack of support from 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 was then able to review the patients belonging to all three departments and made three lists. I noticed some identical family names across the three lists, while others all lived in the same small locations. 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 (Neumann 1987a) and its prognosis (Neumann 1987b), I started publishing in international scientific journals with a report on sporadic and VHL-associated CNS hemangioblastomas (Neumann et al. 1989). After disappointing ventures with distinguished international research groups to help identify the VHL gene, I joined the Bostonian group and later the Cambridge, UK group, achieving only an acknowledgment in the Nature publication (Mulligan 1993), I decided to try on my own a major manuscript without molecular genetic data.

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Endocrine-Related Cancer

Correspondence
should be addressed
to H P H Neumann
Email
hartmut.neumann@
uniklinik-freiburg.de
Table 1  Von Hippel–Lindau disease: major manifestations and clinical classification

<table>
<thead>
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<th>Manifestation</th>
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<tr>
<td>Retinal angiomas</td>
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<tr>
<td>Hemangioblastomas of the CNS</td>
</tr>
<tr>
<td>Clear-cell renal carcinomas</td>
</tr>
<tr>
<td>Pheochromocytomas</td>
</tr>
<tr>
<td>Pancreatic neuroendocrine tumors</td>
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<tr>
<td>Epididymal cystadenomas/cystadenomas of the broad ligament</td>
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</table>

In VHL type 1, renal carcinomas are predominantly present, but pheochromocytomas are very rarely present. In VHL type 2, pheochromocytomas are predominantly present, but renal carcinomas are very rarely present. 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.

The breakthrough was in 1991 with the *Lancet* publication on the epidemiology and classification of VHL (Neumann & Wiestler 1991), which is still being used now to distinguish between VHL types 1 and 2 (Plate et al. 2007) (Table 2). The other major project from this period still remains as the only prospective study for the clinical diagnosis of pheochromocytoma, and was published in 1993 in the *New England Journal of Medicine* (Neumann et al. 1993). In 36 of the 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, metiodobenzylguanidine 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 Privatdozent (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. I had to decline that position due to terms that would have doomed me to failure. This ended in the tragedy of my laboratory staff departing, thinking that I would accept the position at Innsbruck, and I was never invited again for a chief position. However, 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 ten postdocs, technicians, and students based on projects for break as 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 the 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 outcomes. For this objective, it turned out that outstanding large registries are essential. 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 not only to

**Table 2  Pheochromocytomas and paragangliomas: molecular genetic classification**

<table>
<thead>
<tr>
<th>Syndrome Type</th>
<th>Gene(s)</th>
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<tbody>
<tr>
<td>Multiple endocrine neoplasia type 2</td>
<td><em>RET</em></td>
</tr>
<tr>
<td>Von Hippel–Lindau disease associated with mutations in VHL</td>
<td><em>SDHD</em></td>
</tr>
<tr>
<td>Paraganglioma syndrome type 1 with mutations in <em>SDHC</em></td>
<td><em>SDHAF1</em></td>
</tr>
<tr>
<td>Paraganglioma syndrome type 2 with mutations in <em>SDHD</em></td>
<td><em>SDHC</em></td>
</tr>
<tr>
<td>Paraganglioma syndrome type 4 with mutations in <em>SDHB</em></td>
<td><em>TMEM127</em></td>
</tr>
<tr>
<td>Paraganglioma tumors associated with mutations in MAX</td>
<td><em>MAX</em></td>
</tr>
<tr>
<td>Paraganglioma tumors associated with mutations in SDHA</td>
<td><em>SDHAF2</em></td>
</tr>
</tbody>
</table>

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.
endocrinologists, pediatricians, and visceral surgeons in Germany, but also to colleagues abroad. Wlodzimierz Januszewicz, Head of the Department of Hypertension at the Medical Academy of Warsaw, admired our above-mentioned 1993 paper. At a meeting in Berlin in 1996 I was conferred honorary membership of the Polish Society of Hypertension by his son, Andrzej Januszewski. The registry was dramatically enlarged by Polish patients including blood samples from all cases. When mutations of the SDHB and SDHD genes were shown in patients with paraganglioma syndrome types 1 and 4 in 2000, 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 together with Charis Eng, then in Columbus, Ohio, were published in 2002 in the *New England Journal of Medicine* (Neumann et al. 2002). The editorial summarized the message as ‘The death of an axiom’ (Dluhy 2002). Indeed, the anticipated 10% heredity in pheochromocytomas exploded to 24%; all four genes contributed considerably. This publication now 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 six 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 provided an optimal basis for the coming years. We extended our activities to head-and-neck paragangliomas and reported on the 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 the *Journal of the American Medical Association* (Neumann et al. 2004, Schiavi et al. 2005). Subsequently, we elaborated guidelines for the selection of candidate genes to be tested in patients with pheochromocytoma in *Clinical Cancer Research* (Erlic et al. 2009) and patients with head-and-neck paragangliomas in *Cancer Research* (Neumann et al. 2009).

Felix Fränkel’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 Fränkel, widely regarded as the first description of pheochromocytoma (Fränkel 1886). 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 (Fränkel 1984), has remarkable features: a 19-year-old patient, bilateral adrenal tumors, histological diagnoses of a ‘sarcoma’ in one adrenal gland and ‘angiosarcoma’ in the contralateral side, with no affected relatives. Unlike the current regulatory environment, the Fränkel report names his patient as Minna Roll and the village where she lived as 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 residence. In all estimates, Minna Roll should have a high likelihood of having a 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, and 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. 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 descendants of two of the six brothers of Minna Roll had been recently operated on for pheochromocytomas. We had access to blood collected from these patients, and to our tremendous surprise, we did not find a VHL mutation. The mutation detected was in the RET gene (p.Cys634Trp), a common pathogenic RET mutation. Thus, we had evidence that the classical report on pheochromocytoma was a patient with multiple endocrine neoplasia type 2. We were happy and proud that again the *New England Journal of Medicine* published this work (Neumann et al. 2007).

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, and that a considerable number of hereditary pheochromocytomas are diagnosed at an asymptomatic stage after family screening or (only available many years later) molecular genetic testing. With this concept, one major burden to the patients, e.g. lifelong steroid replacement for postoperative Addison’s disease, could be avoided. Since 1985, all my patients have been operated on accordingly, in the first few years by Helmut Kirste in an open procedure (Neumann et al. 1999). 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 on 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 extra-adrenal pheochromocytomas, some of whom had difficult-to-reach or tenuous locations within the thorax or pelvis, all successfully removed endoscopically (Fig. 1).

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

In 2007, I received an email from 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 who 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 color-coded graphs as the core of the chapter. This 17th edition was published in 2008, followed by invitations for the 18th edition (2011) (Neumann 2008, 2011). I realized that moderate verbal strategies are successful and strengthened the indication for endoscopic tumor removal and 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 learned 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 to information evenings. This was followed by information booklets. But all this was incomplete if there were no standard user-friendly means for patient-to-patient communication. In this regard, I was visited by Ms Joyce Graff from the USA, who lost her husband to VHL and whose affected son received recommendations for overly aggressive 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 USA 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 information booklet for patients with pheochromocytoma, paraganglioma, and associated diseases. It became a book of 150 pages with many figures, graphs, and tables and also included general information on 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 other languages on the Internet. At present, there are over 13 translations and more are planned.

School of Freiburg

Thanks to our many patients and to our 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, pheochromocytoma-associated diseases and similar diseases. Cornerstones 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 the molecular and clinical aspects of a broad selection 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 by guests in the laboratory and outdoor clinic in Freiburg. Common projects resulted in best-ranked theses by Zoran Erlic in Padova, Italy 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 seven professorial theses; among these are those based on long-term 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 2 years rotating through all parts of the world.

In 1998, I was honored by the Hufeland Prize, the German award for Preventive Medicine (Fig. 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 of daily lunch. My passion is music (Fig. 3). Having been taught how to play violin from childhood, I spend much 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

in the Miller Pavilion 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 on 1st October 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 over the past three decades in mind.

References


Mulligan LM 1993 Germ-line mutations of the RET proto-oncogene in multiple endocrine neoplasia type 2A. Nature 363 458–460. (doi:10.1038/363458a0)

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