



VHL Family Forum



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The Structural Biology of VHL

*Reporting a series of articles in Science, Molecular and Cellular Biology, and the Proceedings of the National Academy of Sciences*¹

A series of breakthroughs have been made in the last several months, increasing our knowledge about the structural and functional biology of the VHL protein (pVHL), and helping to advance our knowledge of how pVHL operates in the cell. While there is still a great deal more to learn, some key findings have been published in a series of articles in the journals *Science* and *Molecular and Cellular Biology*, and the *Proceedings of the National Academy of Sciences*. As this issue goes to press, more articles are appearing that we will report in the September issue.

The technology reported in these papers is truly amazing. Unless you too are a molecular biologist, it is an advanced technology completely outside our experience. We are at the dawn of a new era in medicine, so incredibly different from what we have known before that it boggles the mind. In reading these articles and speaking with several of the authors, we have tried to glean the parts of greatest interest to affected families, and to put together some analogies to help us grasp the important messages.

This quest brought to mind Rube Goldberg's wonderful cartoons of fantastic labor-saving devices at the beginning of the machine age. When Goldberg was born, "the horse and the boat were the principal forms of transportation. There were no automobiles, no superhighways, no airplanes, no radios of television sets, and only a few commercial telephones." Beginning in the 1920's he hypothesized some modern labor-saving devices, "depicting technology in disarmingly humorous terms. He lived in the midst of the greatest technological revolution that man had ever seen. Electricity and atomic energy were captured and tamed during his eighty-seven years. He lived to see men step on the moon, juggle human hearts from the dead to the living, and send moving pictures through thin air. It was an age of social invention, a time when new machines were being

standardized, mass-produced, and marketed for everyone."²

Imagine that you are similarly standing in the 1920's, looking into the future, at the prospects of all that was ahead. Advances in medical technology, similar to those of machines in the 20th century, await us in the 21st century. Just as Goldberg's cartoons imagine fanciful and humorous machines (see Figure 1), let us imagine some of the incredible machines that exist in the human body. Picture that we are standing in 1920 with a 1999 radio in our hands. We know that if we turn the knob, music comes out. But how? We take it apart, but we don't find the simple internals of a music box, instead we find little bits and pieces assembled on a board, with silver lines connecting them. We can see the structure and map it, but we don't yet understand the function of each of these bits and pieces in bending electrical impulses, taming them to do the job. Little by little we test and deduce the function of each component. Imagine that VHL is one portion of one transistor. From this perspective,

continued on page 2

Inside this issue!

VHL Tissue Bank	Interview with Jay Platt
Anti-Cancer Therapies	England, Australia, Canada
Symposium 2000	Chat Sundays
Origins of Cancer	Keep up the Good Work!
Up for the Fight	Churchill Hospital joins
Report from Bonn	CCC Program
Thanks for the Miracles	Clinical Care Centers
Tree for Hungary	Listing
	Prevention and VHL

let's take a look at understanding the structure of the VHL protein, map its relationship to the other bits and pieces, and see what is being learned about the probable function of the protein.

Why is this important? It is important so that we can learn what happens when the VHL protein is present and fully functional, and what goes on when the VHL protein is missing or not quite right. It is important for us to find out what we can do to intervene at some point along the chain and make a difference in the outcome. If, for example, in Goldber's machine (Figure 1) the bread dough (E) doesn't rise as high as expected, and the monkey continues to snooze, none of the actions G through P will occur. Might there be some other way to wake up the monkey? Or if we simply do something entirely different to entice the monkey to grab the rings (N) we would still get the same result. Where else could we intervene and make a difference in the outcome?

The VHL gene encodes a protein essential to the normal functioning of the cell. A protein is a long string of amino acids that folds into a 3-dimensional structure with a specific shape, depicted as a ribbon diagram (see Figure 2). The shape is important to its ability to connect with other proteins and enzymes and therefore for its function.

When there is a change in one of the amino acids in the chain, one of two things may happen: (1) the change may cause it to unravel, or (2) other changes on the surface of the protein may interfere with its

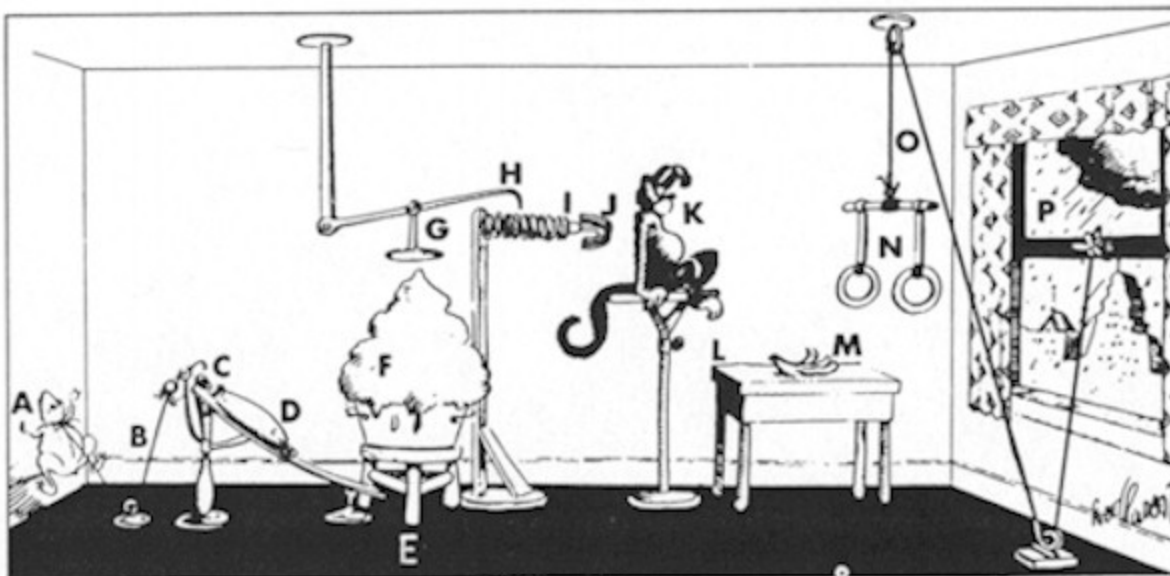
ability to form at least one important connection. Picture a set of electronic components that have to fit together in a specific way in order for the larger complex to do its larger job. If the coupler is damaged, or one of the pins on the transistor is broken off, the two parts don't fit together properly.

The shape of the VHL protein is published for the first time this month in *Science*.³ (See Figure 2.) In addition, two other proteins that bind closely with VHL are identified and their shapes described as well. The ribbon diagram shows the physical shape of these proteins, and the way they fit together. A "binding region" has been identified along the VHL gene, which serves as the connection point where ElonginC binds to VHL. ElonginC in turn binds to ElonginB, forming a three-part VCB complex. A second area along the VHL gene forms a second binding site. The current hypothesis is that this second site is used to attach one of several proteins to the VCB complex.

Interestingly, when we look at the locations of the point mutations found in people who have the condition we call VHL, we find that those mutations generally occur at these binding sites. Therefore the hypothesis is that when the binding site is disrupted and the connection with Elongins C and B cannot be made correctly, a change occurs in the cell's life cycle.

"The structure of VHL allows sense to be made of the rich database of known VHL mutations in tumors."⁴ One group of mutations clusters in an area where they probably disrupt binding to ElonginC, whereas another group clusters in an area which

Figure 1: Closing the Window



RUBE GOLDBERG™ and copyright of Rube Goldberg Inc., Distributed by United Media. Reprinted with permission.

The professor takes a pill and dopes out a device for closing the window if it starts to rain while you're away.

Pet bullfrog (A), homesick for water, hears rain storm and jumps for joy, pulling string (B), which opens catch (C) and releases hot water bag (D), allowing it to slide under chair (E). Heat raises yeast (F), lifting disk (G) which causes

hook (H) to release spring (I). Toy automobile-bumper (J) socks monkey (K) in the neck putting him down for the count on table (L). He staggers to his feet and slips on banana peel (M). He instinctively reaches for flying rings (N) to avoid further disaster and his weight pulls rope (O) closing window (P), stopping the rain from leaking through on the family downstairs and thinning their soup.

appears to define a binding surface for an as yet unidentified protein, suggesting that VHL serves as a kind of adapter, attaching one or more proteins on one end to the Elongins on the other end. This structure and function looks very similar to another complex, the SCF⁵ complex, which seems to play a role in regulating the levels of certain cellular proteins in the cell by targeting them for destruction, a process called proteolysis. There is reason to believe that VHL plays a similar regulatory role, taking certain cellular proteins from the cytoplasm of the cell and targeting them for destruction.

Scientists also reported discovery of a new protein, Rbx1, that is a part of the VHL tumor suppressor complex or machinery. Remarkably, Rbx1 is also found as a critical component of the machinery that controls cell growth and division by targeting important regulatory proteins for destruction.

"An exciting hypothesis is that, in its normal form, VHL works together with Rbx1 to prevent the cell from accumulating proteins that trigger uncontrolled cell proliferation. But a mutation in the gene that produces VHL can cause cancer by interfering with the cell's ability to destroy the trigger proteins, leading to runaway cell growth," said Joan Conaway, Howard Hughes Medical Institute investigator at OMRF.

Notes Ron Conaway, "Not surprisingly, the mechanisms that regulate protein destruction are turning out to be every bit as complicated and every bit as important as those that regulate protein synthesis. The discovery of the link between VHL, Rbx1, and the protein destruction machinery should help

researchers identify the specific trigger proteins targeted by VHL and may lead to new approaches to cancer prevention and treatment."

In 1993 the Conaways discovered and isolated the Elongins as proteins that help to control the mechanism that turns genes, including cancer genes, "on" or "off." In 1995 they collaborated with Drs. Richard Klausner and Marston Linehan of the National Institutes of Health (NIH) to demonstrate that the Elongins function in cells with the VHL tumor suppressor protein to prevent cancer.

"These findings represent a significant advance in our understanding of the function of the VHL gene and how damage to this gene leads to the manifestations in patients that we know of as cancer," said W. Marston Linehan, M.D., Chief of the Urologic Oncology Branch at the National Cancer Institute. "We strongly feel that it is work such as this that will one day play a major role in the development of effective forms of therapy for patients with kidney cancer."

What's Next? How Can We Help?

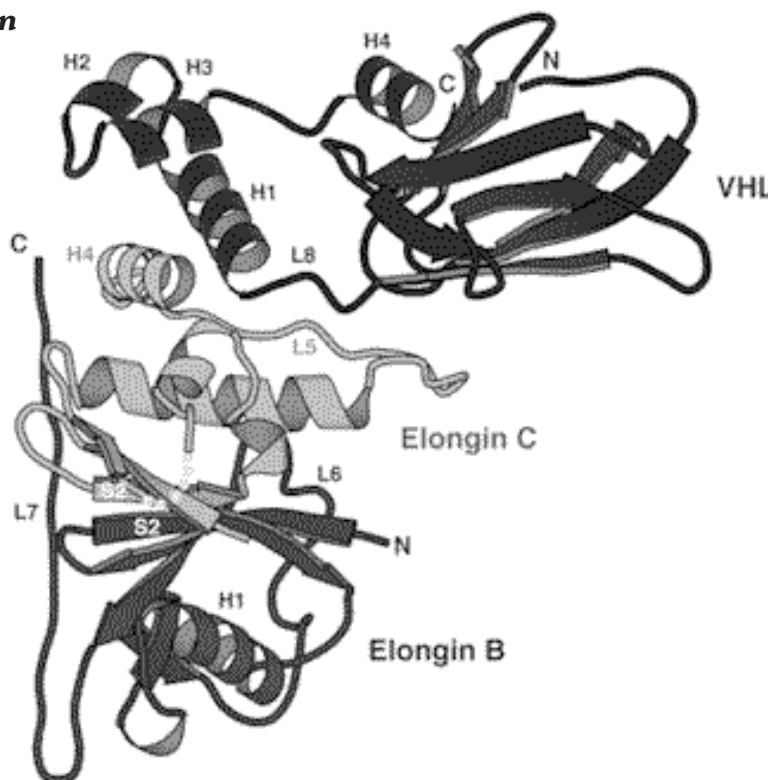
Based on these new understandings, additional research teams will form new conjectures about the effects of VHL on various cell functions, and will set out to prove or disprove them in the lab. This will lead to new therapies for VHL and other cancers.

The VHL families can assist by continuing to donate tumor tissue to the VHL Tissue Bank⁶, and by participating in research studies whenever they are appropriate. It takes all of us -- families, clinicians, research scientists, and donors of research money -- to make the kind of progress we are seeing. It also takes

Figure 2: Structure of VHL Protein

The VCB 3-part complex consists of two interfaces, one between VHL and ElonginC and the other between ElonginC and ElonginB. This ribbon diagram illustrates the secondary structure of the VCB complex. The H4 helix of ElonginC, which bulges out from the side of the concave surface, fits into an extended groove formed by the H1, H2, and H3 helices of the VHL alpha domain. The H1 helix of the VHL alpha domain fits into the concave surface of ElonginC and is important for ElonginC binding. About half of VHL missense mutations occur in these critical binding areas. VHL Type II mutations (with pheochromocytoma) frequently occur in the ElonginC binding area or the secondary protein-binding site. VHL Type I mutations frequently occur in the beta domain core, causing a more complete unraveling of the VHL structure. Thus Type II mutations more often cause partial loss of function. (C marks the COOH terminus (the end); N marks the NH2-terminus (the beginning of the numbering sequence).

Stebbins et al, *Science*, 284:455. Reprinted with permission of the author.



work to ensure that society uses this new information responsibly for good, not as a new tool for discrimination. We look forward to the scale of advances in genetics and medicine that Rube Goldberg saw in machines in his lifetime. The human body is the ultimate incredible machine.

1. Stebbins et al, "Structure of the VHL-ElonginC-ElonginB Complex: Implications for VHL Tumor Suppressor Function," *Science*, 284:455, 16 April 1999; Tyers and Willems, "One Ring to Rule a Superfamily of E3 Ubiquitin Ligases," *Science*, 284:601, 23 April 1999; Skowrya, Conaway, et al., "Reconstitution of G₁ Cyclin Ubiquitination with Complexes Containing SCF^{G₁} and Rbx1," *Science*, 284:662, 23 April 1999; Kamura, Iliopoulos, Kaelin, Conaway et al, "Rbx1, a Component of the VHL Tumor Suppressor Complex and SCF Ubiquitin Ligase," *Science* 284:657, 23 April 1999; Lee, Pause, Klausner et al, "Transcription-Dependent Nuclear-Cytoplasmic Trafficking Is Required for the Function of the von Hippel-Lindau Tumor Suppressor Protein," *Mol. Cell. Biol.* 19:1486, 1999; Gorospe, Zbar, Lerman et al, "Protective Function of von Hippel-Lindau Protein against Impaired Protein Processing in Renal Carcinoma Cells," *Mol. Cell. Biol.* 19:1289, 1999; Liakopoulos, Pause, et al., "Conjugation of the ubiquitin-like protein NEDD8 to cullin-2 is linked to von Hippel-Lindau tumor suppressor function", *PNAS*, May 1999. Our thanks to Myriam Gorospe, Charles Stebbins, Othon Iliopoulos, and Joan and Ron Conaway for their assistance in preparing this article.
2. Marzio, *Goldberg*, p. 145.
3. C. Stebbins, W. Kaelin, and N. Pavletich, "Structure", *Science* 284:455.
4. Tyers and Willems, "Ring," *Science*, 284:601
5. Skp1-Cdc53/CUL1-F-box protein. Another similar structure, APC, has also been identified as a possible ubiquitin ligase

complex. It is believed that each of these three complexes mediate the targeted degradation of many cellular proteins. Targeting proteins for degradation requires ubiquitin, a small protein that can be attached to other proteins, thereby 'marking' them for deletion, in much the same way that a forester marks trees to be cut down. Skowrya et al., provide a relevant example of the importance of this protein degradation pathway (*Science* 284, 23). Cyclins are proteins that trigger cell division, and their elimination was shown to be mediated by the SCF complex, which is very homologous to the VHL complex. If the degradation complex (SCF or VHL) is disrupted due to mutations or due to the absence of certain complex components, these cyclins cannot be eliminated, and the cell division cycle continues uncontrolled, as in tumors. Therefore, protein destruction is a very important way of 'keeping in check' cellular growth and keeping tissues and organs healthy.

6. The VHL Tissue Bank keeps surgically removed tumor tissue on file so that researchers will have the cells they need to study. As the level of VHL research increases, the need for VHL tissue for research also increases. It is here that we can help. If you have been diagnosed with VHL, and are contemplating surgery, you can help the research community by donating any surgically removed tissue to the VHL Tissue Bank. All cost and arrangements for recovery and transfer of tissue will be taken care of by the Tissue Bank. If you would like to help the VHL research effort, please fill out the Donor Registration Form below and mail it today. All information will be treated in the strictest confidence. Pre-registration makes the process simple in the event of surgery. Simply contact the tissue bank, give them the name and contact information for the surgeon and the date of surgery, and the Tissue Bank will make all the necessary arrangements. Even if you are not already pre-registered, arrangements can be made by contacting the Tissue Bank. Outside the U.S., please call the nearest Affiliate for similar programs near you.

Donor Registration Form -- Tissue Bank for VHL Research

I, _____, wish to register myself (or a dependent minor) as a VHL tissue donor with the Brain and Tissue Banks for Developmental Disorders at the University of Maryland at Baltimore. This donation grants permission for the Brain and Tissue Bank to make every attempt within its means to coordinate recovery of surgically removed tissue of the above named donor. Further, if death should occur, I (do or do not) hereby grant permission for recovery of brain and other tissues. All tissue is donated for the expressed purpose of furthering the research of von Hippel-Lindau disease.

Donor name _____	Next of Kin _____
Address _____	Address _____
City _____	City _____
State _____ Zip _____	State _____ Zip _____
Phone Evening _____	Phone Evening _____
Phone Day _____	Phone Day _____

Donor's Date of Birth _____ Sex _____ Ethnic Group _____

If the Donor was diagnosed with VHL: When? _____ By whom? _____

Brief Medical/Family History (add paper as necessary):

If you (the Donor) are not diagnosed with VHL, are you the parent/relative of someone who is?

Yes, No Describe relationship

Signature of Donor or Legal Guardian: _____ Date _____

Feel free to include any further relevant information.

Please mail to: Brain and Tissue Banks for Developmental Disorders
University of Maryland at Baltimore, Department of Pediatrics
655 West Baltimore Street, Room 10-009 BRB
Baltimore, Maryland 21201

Questions?
Call Sally Wisniewski
800-847-1539
btumab@umabnet.ab.umd.edu

Anticancer Therapies

Adapted from a review in JournalClub Review by P\S\L Consulting Group, Inc. (www.pslgroup.com)

Recent advances in the understanding of tumor angiogenesis suggest that anti-angiogenesis therapy may offer a novel approach to controlling tumor growth in cancer patients. In particular, the rapidly accumulating information about endothelial growth factors suggests that they may well offer new targets for antiangiogenesis.

Angiogenesis, or the growth of new blood vessels, has been shown to be important in feeding a variety of tumors, including cancer of the breast, kidney, prostate, colon, and brain, as well as melanoma. But not all anti-angiogenesis drugs are appropriate to all types of cancers. As we read articles in the press, it is somewhat difficult to tell which ones may potentially be helpful against the tumors of VHL.

There are also drugs that help with epithelial cells (e.g. lung). These are unlikely to be useful with VHL, which involves endothelial cell growth.

Endothelial growth factors appear to be tumor specific. Therefore, it is important to understand the role of each endothelial growth factor in human tumors.

Basic fibroblast growth factor (bFGF), of which at least eight different versions have been identified, is the most potent promoter of division of the cell nucleus. bFGF appears to be fully involved in new vessel formation and is able to induce several processes. It is localized in neural cells, keratinocytes, macrophages, and endothelial cells, and has been found in tumors associated with cancers of the brain, pancreas, bladder, and prostate. It is not common in other types of tumors such as breast and gastrointestinal cancer or VHL.

Vascular endothelial growth factor (VEGF), which is characterized as a vascular permeability factor with a potency some 50,000 times higher than that of histamine, is frequently and markedly up-regulated (that is, in abundant supply), in a wide variety of tumor cells, including kidney, breast, ovary, stomach, lung, bladder, head and neck cancers and glioblastoma cells. Data strongly suggest that VEGF may directly promote the growth of new blood vessels in tumor tissues. Studies have also demonstrated a possible synergy between VEGF and bFGF. The majority of work on VHL is around VEGF and related mechanisms in the cell.

Platelet-derived endothelial cell-growth factor (PD-ECGF) is increased in breast, stomach, colon, head and neck tumors. Studies have suggested a cooperative function of PD-ECGF and VEGF for new vessel formation.

Hepatocyte growth factor (HGF) can act not only on hepatocyte growth, but also on the growth of other

types of cells, including endothelial cells. Few data have been published on the relationship between HGF and microvessel formation in tumor tissues.

Antiangiogenesis therapy, first suggested more than two decades ago, offers a number of benefits over conventional anticancer therapies: tumor specificity, easy accessibility, less possibility of resistance, effectiveness in combination with conventional treatments, and possible use as a way of preventing tumors.

There are two anti-angiogenic drugs currently in early stages of clinical trials for use with VHL. Progress will be reported here and on the VHL website.

VHL Symposium 2000 Call for Papers

The Fourth Biennial VHL Symposium will be held in conjunction with the Annual Patient/Provider Meeting at the Mayo Clinic in Rochester, Minnesota, co-sponsored by the Mayo Clinic.

July 20-23, 2000

Phillips Hall, Mayo Clinic
Rochester, Minnesota

Please note that the date has changed.

Blocks of rooms have been reserved at the Kahler Grand Hotel and the Rochester Marriott.

The conference will be co-chaired by Dr. Virginia Michels, Chairman of the Department of Medical Genetics, Mayo Clinic, and Kelly Heselson, Treasurer of the VHL Family Alliance. Continuing Medical Education credits will be awarded by the Mayo Clinic to specially registered attendees for the sessions they attend.

For further information, please contact VHL2000 by September 1, 1999, and indicate whether you intend to submit an abstract. The official announcement brochures will be mailed out in October 1999 and will include a call for abstracts, registration and hotel information, and additional details.

Show Us Your Stuff!

Photos - Drawings - Paintings

We are seeking art work for the Year 2000 VHL Calendar! They can be any photograph, drawing, or painting done by a member of our community. Please send *only copies*, as the submission cannot be returned.

Please send by 30 June to: Pierre & Lisa Bonneau, 1761 W. Waterbuck Drive, Phoenix, Arizona 85742

Twelve winners will be chosen, and will be notified by September 1. Winners will be featured in the Year 2000 VHL Calendar. See page 15 for ordering information.

Report Bonn, Germany

By Gerhard Alsmeier, Florian Hoffman, Joyce Graff, and translator Gerlint Bansberg.

On March 17 Prof. Hartmut P.H. Neumann (University Hospital Freiburg) invited families from the German-speaking countries to join him for a meeting in a charming little inn "Zum Wilden Schwein" ("Under the sign of the Wild Board") in the village of Duisdorf near Bonn, Germany. This site was chosen for its proximity to Dr. Neumann's parents' home, and to the cathedral city of Cologne (Köln). In addition to Dr. Hartmut Neumann, Dr. Luitgard Neumann (his sister, a geneticist at Charité Hospital, Berlin) and Joyce Graff (VHL Family Alliance, USA) were in attendance. Approximately 25 patients came from Germany, Austria, and Switzerland, filling the room quite completely.

Initially Prof. Neumann stressed the importance of adequately informing everybody concerned with VHL. He referred to a brochure for patients written by him. It is not a direct translation of the VHL Handbook used worldwide, but a similar undertaking in German language which includes explanations appropriate to the German health care system. It is of essential help both for patients and also for the attending physicians.

Dr. Neumann spoke about his vision of a family group in Germany, the possible goals of such an organization, particularly in supporting research on VHL, its organization, publications, and so on. Over

the past 15 years his group has developed a good system of surveillance and preventive care. Nonetheless, what is really needed for the next generation are ways to prevent tumors from occurring and to shrink them without surgery. To achieve this vision money is needed for research.

Most important, what is needed now is to enroll additional family members in a program of DNA analysis to determine whether they are in fact at risk, and if so, to engage them in a program of regular screening to identify problems early when they are most easily treated.

He envisions a central German institute with an office that could assist families in doing the necessary screening, making the necessary appointments, with a lab and an information service. His dream is to have a foundation which would address research, diagnosis, and treatment of VHL. He asked those present to begin thinking of sources of funding for such an institute. For example, it currently takes 8-12 weeks to do a simple direct DNA test of family members in a family where the DNA alteration has been found. Finding the mutation in the first person to be tested in a family can take considerably longer. Technology exists now in other countries to improve these times (U.S., Italy), but it requires investment to improve this service in Germany.

The most important initial concern of a family support organization is to help people know that they are not alone. Because VHL is a rare illness, it is difficult to find good information. People may have had no information, or wrong information, from their local doctors, and many have significant fears they may not want to share with doctors. Joyce Graff presented the model used in the U.S. and other countries. The family organization can assist with these fears and concerns, and help connect people with competent help, such as is available through Dr. Neumann's program in Freiburg or at the Charité in Berlin. VHLFA in the U.S. has a central information service (1-800-767-4845 or info@vhl.org) and contact people in most U.S. states. VHL France also has a system of regional contact persons, to minimize telephone costs for callers. A well-organized German-speaking group, with good connections to the English-language group in the U.S., would serve the German-speaking families very well.

At the moment there are two small German groups, one in Berlin under Peter Zeitmann and Florian Hoffman and one being organized in the Northwest of Germany under Gerhard Alsmeier. Erika Trutmann also expressed interest in starting a support group in Switzerland. Contact names were shared



Bonn, March 1999



Cologne Cathedral, March 1999

with the group so that they could begin working together to create a structure that works. Before the group can begin to raise money for its own expenses or to support research, it will need to obtain official registration as a charity in each country. The German group has recently applied for charity status.

Joyce Graff said that the VHL Family Alliance would welcome an affiliate group in Germany, such as already exist in Australia, Canada, France, Ireland, Italy, Japan, New Zealand, and the United Kingdom. Help is needed in bridging the language barrier. Members who are bilingual and on the internet can assist with translating occasional correspondence between the English-speaking group and other language groups worldwide.

Dr. Luitgard Neumann mentioned that there is a genetic disease registry at the Verein Mosaik-Medico in Berlin. It was suggested that a registry of people with VHL in Germany could be very informative for research. The French registry project has resulted in a number of very enlightening articles.

People interested in finding a self-help group can do so by contacting one of the university hospitals, or by contacting the VHL Family Alliance at <http://www.vhl.org>. In Germany the numbers to call are Gerhard Alsmeier +49 (59) 3192 9552, Florian Hoffman +49 (30) 6119057 or Peter Zeitmann +49 (30) 472-9593 or in Belgium Chris Hendrickx at +32 (3) 658-0158. E-mail addresses are listed on the VHL website under international contacts. Erika in Switzerland is best reached by e-mail; voice messages for her will be taken in German by Chris Hendrickx.

Topics for future meetings were discussed: The most essential problem for the patients is how to find competent local medical care. Competent medical

care implies too that the possible future development of symptoms is taken into consideration. Only as long as the patients find a physician who also plans for the future, can they deal with their anxiety and the mistakes that result from this anxiety. In addition, patients feel threatened by stigmatization and prejudices resulting from the lack of information about genetic disease among the general population. As in every country, the expansion of genetic information provides powerful tools for medical advancement, but also powerful tools that can be misused for discrimination. We all need to get involved in the ethical and legal discussions in our own countries.

Participants thanked Prof. Neumann for the organisation of the gathering, and for his work during the past years. After the meeting the patients whose mother tongue was German had dinner together. Many stayed for the following day's Hufeland Prize ceremony in Cologne, lunch with Joyce Graff, and visits to the delicate gothic cathedral of Cologne.

In Cologne on Thursday Prof. Neumann was awarded the 1998 Hufeland Prize for Preventive Medicine. (See also page 16.) Professor Neumann's award-winning thesis, "Von Hippel-Lindau Krankheit, Prävention und Prophylaxe bei einem hereditären Tumorsyndrom: Ein Modellprojekt" (VHL: A model project of prevention and preventive intervention in a hereditary tumor syndrome, German only). It contains many photographs, and is a good supplement to Dr. Neumann's German-language Information Handbook. It costs 50 DM (\$35 USD) plus shipping and can be ordered from Dr. Neumann's address, Dr. Hartmut P.H. Neumann Medizinisch Universitätsklinik; Hugstetter Strasse 55; Freiberg im Breisgau; D-7800 GERMANY Fax: +49 (761) 270-3778; E-mail: neumann@mm41.ukl.uni-freiburg.de



Bonn, March 1999

Up for the Fight

by Peggy Marshall, Mississippi

The doctor looks at your MRI and says, "You need surgery." Oh, no! Not again! I'm tired, I just can't go through another one! Familiar words, feelings or thoughts for us with VHL?

We all have choices to make, serious decisions that only the individuals can make for themselves. Many times we've heard a loved one say, "Well, that's it for me, no more surgeries!" We can certainly empathize with that person. You watch them stop going for check-ups and tests though you encourage them to go. There are symptoms, something is wrong, and it needs medical attention. But we can't make someone go to the doctor if they have decided "no more."

We try to respect and accept our loved one's right to choose their fate. But is it fair to all of those family members and friends who care so much?

A dear friend who does not have VHL shared her experience with me. She was having chest pains, racing heart, and other signs of a possible heart condition. She did not tell her family what was wrong, but they knew she was ill. Her daughter asked her to see a doctor. She refused, saying she had taken care of sick relations for several years and felt the pain of watching them die. She didn't want to put her kids through that. Her daughter asked if she had felt that was really the fair thing to do. "But Mom, what if you have a stroke, can't move, and you don't die? Is that fair?" My friend thought about the other side of what she felt was the best decision for all, and decided to go to the doctor. The diagnosis was better than she had once feared. Her story really touches on a delicate issue.

We reach a point of giving up sometimes, and decide no more check-ups, tests, or surgeries. "I'm going to take whatever time I have left and enjoy it." Those words came across on the 800 line one day while talking to a VHL patient. But, does that work?

For a moment, let's take a look at the other side of that decision. Tumors eventually cause deficits if left unattended: loss of vision, inability to walk, talk or even swallow. Are you getting the picture? Death isn't always the quick end one might expect. You may live much longer than you thought, and be in need of constant medical care.

Von Hippel-Lindau is a manageable disease and one can live a long life if the proper screenings are followed. I've lived with VHL for 37 years since my diagnosis. You cannot ignore it. The condition is chronic and it will not go away.

My plan is to face VHL head-on and not ever give up! I hope every one of you can find the strength to do the same.

Thanks for the Miracles

by Joyce Graff, Massachusetts

Many thanks to everyone who sent good wishes to me and my son, through his recent kidney surgery. He did very well through the surgery and is recovering well. Unfortunately, the kidney did not survive the surgery. Damon is settling into dialysis, and we are hoping to proceed to a transplant, probably in the fall.

It's hard, but it's not a tragedy. I don't think anyone would say dialysis is fun, but these days the centers are very professional and well set up, and there are lots of centers available worldwide. He has a very good attitude, and is integrating the three dialysis treatments of four hours each into his "real life." Some people spend 3-4 hours at the gym three times a week, he needs to invest the time in dialysis to maintain his health.

There are lots worse alternatives he could be facing. He did very well in his surgery. He is young and otherwise quite healthy. He has strong support from family and friends. The doctors recommended dialysis and transplant thirteen years ago, when he was 15, in 1986. Instead, he got through puberty, through high school and college, and is well established in his career. The technology is much improved. They have learned how to prevent anemia and keep people much healthier on dialysis. Transplant methods are better today than they were, and improving at a fast pace. Every extra year one can stay on their own kidney power is to the good. He worked hard with his doctors to keep this kidney as long as he could. It's no one's fault, no one did anything wrong, he just had a particularly nasty case of VHL in the kidney.

We like to say that we want to make VHL stand for "Very Happy Life." People sometimes think we are being flippant in saying that. But in fact, it's intended as a transformational statement: "when life gives you lemons, make lemonade." Take those lemons, and deal with the reality, even if they are not your first choice of fruit.

In 35 years of dealing with VHL I have learned that we don't always get the answers we ask for, but sometimes we get a different answer that can turn out to be as good if not better. Miracles don't usually come made-to-order. If we are stuck on watching for a miracle of a particular size and shape, we may not realize that a different one has arrived.

Here are the blessings I am counting this month:

1. He has a very positive attitude.
2. He is strong and healthy, and recovering well from the surgery.
3. He has muscle strain in his back from ten hours of surgery in a contortionist position. But the good news is that he's complaining only about his back

muscles, not about anything with more medical significance!

4. They got all the cancer out, with no metastatic sites, and clear lymph nodes.

Hooray!

5. Because he is cancer-free, they say that he is eligible for transplant in only four months, as soon as he is completely healed from this surgery and stable on dialysis.

6. He has a good vein for the best kind of trouble-free dialysis access fistula. It is installed and maturing well.

7. My sister-in-law Susan flew in to give both of us an extra dose of Tender Loving Care.

8. There are two family donor candidates (Susan and me) going through testing. If all goes well, we should have one good kidney for him by the end of summer.

The miracles in my life are the people and the supportive events that occur around me to help me in times of trouble. When we got back to Boston the first thing I did was to call my regular chiropractor and see if he had an opening to work with Damon to heal his back. I explained that he has no kidneys, and is on dialysis, which adds a number of complexities in dealing with herbs, medications, and fluids. I expected him to be wary of the situation, but he said "Fine" with confidence. On the day of the appointment we learned what I had never known after working with this chiropractor for more than five years – he lost all kidney function 20 years ago in his young 20's, and is now on his second transplant.

Chance? What is the statistical probability of finding a chiropractor with a kidney transplant? And what a gift to someone embarking on this voyage to happen across a healthy and successful professional who has been living this way for 20 years!

Is the glass half full? Or half empty? Everyone has down days for reasons that are sometimes frivolous and sometimes very serious. We all have days when we must consciously choose to smile, to get up, to get back to our real lives. Many of us go through serious life transitions, where we have to learn to live with a new set of abilities and impediments. We can choose to rebel against the new reality, or embrace it and integrate it into our lives. I am thankful for a wonderful son with a strong spirit. I am thankful for the many good people whose thoughts and prayers and good wishes, and their willingness to share themselves, sustain us.



Origins of Cancer

Racing to the Beginning of the Road is a look at the methods and outcomes of cancer research, designed to appeal to readers without a scientific background -- those familiar with the subject, however, will be riveted by the author's knowledge of the men and women who have devoted their careers to it. In this updated paperback edition of the Harmony Books hardcover, award-winning researcher Robert A. Weinberg explains the amazing advances in the field of cancer research, from just a few decades ago up to the fast-paced present. Inviting readers into the hallways and laboratories of some of the field's greatest thinkers, Weinberg describes discoveries such as the oncogene and the tumor-suppressing gene, and other important events in the field, in a clear, easy-to-understand tone. The VHL gene is a tumor-suppressor gene.

"A nontechnical and exhilarating description of how this field has evolved." (*Nature*)

"An authentic, informative, and thoroughly enjoyable book about the momentous scientific developments to which Weinberg has so richly contributed." (*Science*)

"The next time one of my research friends asks me to recommend a book that will imbue his son or daughter with the true excitement of biomedical investigation, I'll tell him to buy a copy of *Racing to the Beginning of the Road*." (*New York Times Book Review*)

Robert A. Weinberg is a founding member of the Whitehead Institute for Biomedical Research and professor of biology at the Massachusetts Institute of Technology. He has been awarded the National Medal of Science and the Keio Medical Science Foundation Prize in 1997.

Tree for Hungary

Dr Gyorgy Pfliegler, professor for internal diseases in Debrecen (Hungary) and vice president of the Hungarian VHL Society has translated to Hungarian "Your Family Health Tree" by Myra Vanderpool Gormley and Joyce Graff, 1993. It is adapted to the medical system and culture of Hungary, without the data concerning the U.S. Copies in English and Spanish are also available through the VHLFA publications office. Call 1-800-767-4VHL or +1 617 277-5667 (US and Canada) or +44 (0)20 7681-1796 (London), or write to info@vhl.org

"Your Family Health Tree" is up for revision in 1999. Your suggestions for modifications will help us make it even more helpful. Please send comments and suggestions to Joyce Graff, Editor, joyceg@pipeline.com.

Interview with Jay Platt

Following is an interview conducted on April 28, 1999 between Maria Shipton, VHLFA National Public Relations Committee Member and Jay Platt about his soon to be released book, *A Time To Walk: Life Lessons Learned On The Appalachian Trail*.

Maria: With us today is Jay Platt who recently completed a southbound "thru-hike" of the 2,160-mile Appalachian Trail. Welcome Jay.

Jay: Thanks, it's great to be here.

Maria: So what have you been up to since completing your hike?

Jay: After taking some time off to rest, I began working in earnest on my book as well as doing some motivational speaking.

Maria: The name of your book, *A Time to Walk: Life Lessons Learned On The Appalachian Trail* is intriguing. How'd you come up with the name?

Jay: From the beginning, I wanted this to be much more than just another book on hiking in which the author simply publishes his journal and calls it a book. Although it discusses my hiking experiences, that's not the main focus of it.

Maria: Please go on.

Jay: Well, I firmly believe that everyone can benefit from this book's message. No matter what your struggle, you can persevere. Not everyone can hike the Appalachian Trail (or wants too) whether it be due to physical limitations, not having the time or whatever. But, everyone must eventually "hike" his or her own trail in life.

Maria: What do you mean?

Jay: Life can be difficult at times. And you know what? It doesn't matter who you are. Eventually, you'll go through some hard times. How you respond will determine your success or failure. Winning in life is a matter of attitude. I love what Henry Ford said, "If you think you can or think you can't, you're right."

Maria: What can you tell us about the contents of the book?

Jay: Well for starters, it's not some thick novel or something. It's around 150 pages or so. I intentionally wrote it in an easy reading fashion. It's divided into four sections.

Maria: Which are?

Jay: The first section, entitled "Tales from the Trail," consists of stories that happened to me while I was on the trail. Most of them are humorous in nature. However, at the same time they also teach the reader values that are important to a successful life. There are 10 chapters in this section with titles that include Moon Over Mt. Washington, Hurricane at 5,000 feet, and The Giant Rat Attack, to name a few.

Maria: Sounds great!

Jay: Section two, entitled "Winning the Game Called Life" also has ten chapters. Each chapter here reflects certain principles that have helped me

throughout the years, not only during my Appalachian Trail experience, but also in dealing with VHL and other various ups and downs in my life. I truly believe everyone can benefit from the principles listed here. A few of them discussed are The Power of Commitment, The Importance of Discipline, and Life is an Attitude.

Maria: Fantastic!

Jay: The third section, which I call "So You Want to Be A Hiker," contains essentially my journal as recorded on the VHL web site. I had to think long and hard before I decided to include this part. All in all, though, I feel it really adds to the book by allowing the reader to experience my thoughts as I felt them while I was actually on the trail.

Maria: I think readers will enjoy that.

Jay: The final section, called "Thoughts to Ponder" consist of quotes, short stories, etc. which have served me well over the years.

Maria: The book sounds wonderful. When it will be available and where can we get it?

Jay: It will be available as of August 1st of this year. It can be purchased on this web site as well as Amazon.com. I'm also working on other outlets. I will announce further information as soon as I get it. Anyone with questions can contact me by email at Ucan2online@excite.com.

Maria: Do you have any closing thoughts?

Jay: In closing, I'd like to say again to everyone who's helped me along the way how truly grateful I am for your support. I could never express how much it really means to me. More than ever I believe in our cause. On that note, I want everyone to know that I

Patient Advocate Foundation

In Althea's article on Managed Care on page 6 of the December 1998 newsletter, the telephone number listed for the Patient Advocate Foundation is incorrect. Our apologies for any inconvenience.

Helpful numbers:

Patient Advocate Foundation
1-800-532-5274

England, Australia, Canada

Due to a change in the regional telephone codes in England, our phone/fax number in London has changed. Please correct your records. Instead of 171, the new code is 207. Our new number is thus +44 (20) 7681-1796 (London).

Telephone Numbers

The convention we use in writing international telephone numbers is +country-city/area-number. The + indicates that you need to add the access code for reaching the international dialing system. In the U.S., you would dial 011-country-city-number. Thus from the U.S. you would dial 011-44-20-7681-1796 to reach the London number.

If you are already in the target country, they you need to dial whatever prefix normally comes before the city code or area code. For calls within the U.S. and Canada, it's 1-area-number. For calls within England or Australia, dial 0-city-number. Callers from inside the U.K. dial 020 7681-1796 to reach London.

New Phone in Sydney

There is also a new central telephone number in Sydney, Australia, that receives voicemail and fax: +61 (2) 9473-1441. We now have three regional contact persons in Australia: Jennifer Kingston in Queensland, Paul and Gay Verco in New South Wales, and Michael Walker in Western Australia. They will share monitoring of this central service. We would welcome a volunteer in Victoria.

VHL Canada an official charity

Tania Durand reports that VHL Canada has been awarded official charity status by the Canadian government. Canadians who donate to VHL Canada can now get a tax credit for their donations. Tania (Ottawa) and Paul Bonneau (Quebec) are co-chairs of VHL Canada. Tania is recovering from surgery and doing well. Canadians can call the hotline 1 (800) 767-4VHL without charge with questions or referrals to Paul and Tania.

No Response?

Please note that you can reach all the VHL Family Alliance information from your local country contact point, as we stay in close touch with one another to serve you, and will forward your query worldwide to get you the best information. However all of us are volunteers, so if you don't hear back within the timeframe you need it may be that someone is on holiday or dealing with a family obligation. Please feel free to contact the U.S. numbers which are staffed by a committee of volunteers and are most consistently available.

1 (800) 767-4845, info@vhl.org, <http://www.vhl.org>

Chat Sundays!

We are inaugurating a series of online "chat" sessions (a group typing fest) under the sponsorship of two health network sites. We will meet on the last Sunday of the month for the next three months to give it a try.

All sessions will be held twice:

- 10 am EDT (Eastern U.S. Daylight Time, that's 3 pm in the U.K., British Summer Time)
- and 8 pm EDT (that's 2 pm in Hawaii, or 10 am on Monday morning in Sydney)

We hope that one of these will be a reasonable hour for everyone.

June 27: 10 am and 8 pm EDT. Gale Lugo and Joyce Graff will be there to share information from the Atlanta meeting, or talk about other topics as the group wishes.

July 25: 10 am and 8 pm EDT

August 29: 10 am and 8 pm EDT

September 26: 10 am and 8 pm EDT

Free registration at Dr. Koop's site is required.

Please see www.drkoop.com or www.vhl.org for more information.

Watch the VHL website for announcement of additional chat sessions. Please submit additional ideas for future chats. Also, please provide your feedback on your experience in these chat sessions. How did it go registering and logging on? Do you have concerns about the registration or logon process? Our intention is to provide a layer of confidentiality, but if it is too hard to deal with, we don't want people to give up. If you had a frustrating experience for any reason, we need to know that.

How was the session? Did it meet your needs? Would you come to another session? What concerns do you want to share?

If you did not attend a session, what kept you away? Did you forget the date? Were the dates and times inconvenient? Are the sessions too far apart? What suggestions would you make to help you attend another one in the future?

There are other more open sites where we could hold a chat. What would you think of attending a chat session in a place without password access?

Send comments to webmaster@vhl.org

Air Miles

Do you have air miles about to expire? Delta miles can be donated to VHLFA! If you wish to donate miles, please send your request in writing to Delta Airlines, Inc., Dept 745, Skymiles Award Travel, P.O. Box 20543, Atlanta, Georgia 30320-2543. VHLFA uses miles to send volunteer representatives to speak at large conferences, or to bring special speakers to VHLFA meetings.

Keep Up the Good Work

-- Dawn Cerf, Chapter Chair, California

As the California Chapter Chair, I have had my share of rewards for doing this work, and the rewards come from seeing others benefit tremendously from the help provided by the VHL Family Alliance.

Just yesterday I received a follow-up telephone call from the sister of a man fighting for his life in a hospital. In her first telephone call, the sister related that the doctor was not able to determine the exact cause of her brother's current and dire problem. I referred her to the 800 telephone line (1-800-767-4VHL) because they would have more experience understanding the symptoms her brother was experiencing. In the follow-up call, I learned that it took just two symptoms for the VHLFA 800 line volunteer to suggest that the brother might have intracranial pressure, which suggested a different area of the body than the doctor had been investigating.

The doctor then took a CT-scan of the brain and immediately had his patient transferred to Stanford University for a shunt insertion and future surgery. Needless to say, the sister was so grateful and deserves tremendous praise for aggressively helping her brother. And what a wonderful job the 800 line volunteers are doing.

“

I dilly-dallied about taking the tests and didn't really push it since I felt so good and didn't manifest any symptoms. [My doctor] was just as surprised at the test results as I was.

”

I would like to relate one more instance of help someone received from the VHLFA. In this case a woman attending our California Chapter meeting last April at Stanford University related in a roundtable discussion that although VHL runs in her family and DNA testing revealed she did carry the defective VHL gene, she has been lucky to have no symptoms. After careful inquiry, it was revealed that she had not been undergoing the recommended screening. It was strongly suggested by many others at the meeting that she have an abdominal CT-scan for possible kidney lesions whose presence often does not provide symptoms until an advanced stage.

In a letter to me this grandmother wrote, "I know it was meant to be that our family was at the Family Alliance seminar at Stanford so I would be encouraged to take my tests more seriously and not procrastinate. I dilly-dallied about taking the tests and didn't really push it since I felt so good and didn't manifest any symptoms. I truly believed my cardiologist/internist didn't believe there was anything like VHL bothering my health, and he was just as surprised at the test results as I was. I had my surgery and I'm doing fine.

I'm glad the tumors in my kidneys were found now and we were able to take care of the matter before really serious problems developed. Anyway, thank you for organizing the local VHL meetings whereby I was able to contact Derrick, Bruce and Patti and speak to each one before going in to speak to my urologist and making the decision to operate."

I am proud to be a cog in the wheel of the VHLFA that is doing so much to help people have an easier time in dealing with VHL. This is what life is all about, helping each other, as these two cases reveal. Keep up the good work and support for family members and others with VHL who can benefit from the experience and effort you can provide.

Many hands make light work! We can always use some additional hands and ears and mouths. Please call and volunteer your help. 1-800-767-4VHL or your local chapter or affiliate; info@vhl.org or via paper mail.

Churchill Hospital joins CCC program

by Dr. Susan Huson, Oxford, England

I am honoured that you have asked me to become a member of your clinical care programme. The appropriate contact name at the present time is myself and the details are as follows:

Dr Susan M Huson
Consultant Clinical Geneticist
Department of Clinical Genetics
The Churchill Hospital
Old Road
Headington, Oxford, OX3 7LJ
Telephone: +44 (0)1865 226024
Fax: +44 (0)1865 226011
E-mail: shuson@immsvr.jr2.ox.ac.uk

I would be happy to be contacted by anyone in the UK with VHL queries, but we usually recommend that patients go to their nearest genetic centre as a lot of the UK genetic centres have taken on the role of co-ordination of the VHL family care in their areas. The areas we specifically cover are Northamptonshire, Oxfordshire, Buckinghamshire, Berkshire and Wiltshire.

We run a VHL clinic day about five times a year, when people with the condition or at risk of it can have co-ordinated screening on the same day. They have a clinical assessment with myself or one of my team, indirect ophthalmological examination with Dr. Peggy Frith, our Consultant Ophthalmologist, and MRI scans as appropriate.

The VHL Family Alliance welcomes Churchill Hospital to the Clinical Care Centers Program.

We are grateful for the many contributions from...

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that you can write in VHL
 Family Alliance as your preferred
 charity in a United Way campaign?
 that VHLFA gets 100% if you
 donate directly.

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I just wanted to express my
 gratitude to the VHLFA for
 putting together this homepage.
 It has helped me tremendously
 in gaining knowledge about
 VHL, which has recently
 become part of my family's life.
 It is empowering to know that
 we are not the only people
 living with this disease. I'm
 sending my donation in today to
 become a member, and to
 support Jay in his quest for a
 cure. Thanks so much! --
Laurie A., Connecticut

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Prevention and VHL

In March Dr. Hartmut P.H. Neumann received the Hufeland Prize for Preventive Medicine for his work in VHL over the past 15 years. (See also pages 6-7). Joyce Graff attended the award ceremony, and combined this trip to Germany with a trip to Poland and Belgium.

"The contrast between the previously Socialist East (East Germany and Poland) and the Democratic West of Europe is striking. Where in the West there has been money to rebuild both the town and the sense of civic pride, in the East resources were taken away to the Soviet Union and the reconstruction, if any, is of gray concrete block buildings covered with the soot that belches from uncontrolled smokestacks." Throughout east and western Europe there has been "health care for all" throughout this time, but in the East few hospitals had imaging equipment until the last five years, and there was little visibility of VHL. Most people got no preventive care. While there are many expert and caring physicians, the lack of diagnosis and preventive care has left a large number of people with VHL in the woeful physical state that was common worldwide until 20 years ago. Dr. Karol Krzystolik and the team of doctors at the Hereditary Cancer Center in Szczecin are working to identify family members at risk for VHL throughout Poland, and begin now a program of preventive care like the one which Dr. Neumann has helped to pioneer.

The Hufeland Prize Committee were very impressed with the progress Dr. Neumann has been able to make in keeping people with VHL healthy over the last 15 years. The previous evening I had spoken with one of his first patients, a woman in her 50's



Professor Hilger, Dr. Neumann, and Dr. Geitner presenting the Hufeland Prize, named for Christoph W. Hufeland, a famous German physician (1762-1836).

with children and grandchildren. She and her brother both have VHL. She said that previously the people in her family died mysteriously in their 30's of heart disease or stroke or an occasional brain tumor. Dr. Neumann finally diagnosed VHL and worked with them to remove adrenal tumors and screen for other problems. She and her brother are now grandparents, and their children and grandchildren are healthy. They are thrilled with the difference his research and care have made in their lives.

Living in developed countries and in an age of relatively routine preventive care, it is easy to forget what a difference it has made. In the last 20 years, the life expectancy of people with VHL has increased at least 20 years. It takes vigilance, but it's worth it. Many thanks to Dr. Neumann and the thousands of other physicians worldwide who have made it possible for us to enjoy these advances. It is up to us to implement them, and to build upon them.

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