# VHL Family Forum

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# Report from Padua

On Thursday we drove into the countryside to a medieval abbey nestled in the rolling green hills, surrounded by wheat fields and lush woodlands. Fifty monks still live in this enormous complex, but one large wing has been renovated to form a modern conference center with all the conveniences. We entered through ancient walls into a stone foyer, and proceeded to a modern auditorium with comfortable chairs and modern audio-visual equipment.

After Dr. Opocher and Joyce Graff welcomed everyone, Dr. William Kaelin of Boston introduced the first session, "New Advancements in VHL Proteomics." Proteomics[1] is the process of annotating the genome. We may know the letter sequences that form the genes, but we don't yet understand just what all this means. We are moving from the VHL gene sequence to the protein it encodes and the functions of this protein in the cell and in the body.

So far we know that VHL combines with elongin B and elongin C, CUL-2 and Rbx1 to form an E3 ubiquitin ligase complex known as VEC, a kind of garbage-collector machine. This machine can attach to any of a number of other proteins in the cell in order to lower their levels in the cell, or "degrading" them, clearing them out, in order to function as an "off" switch for the function of these other proteins. When they are needed they are produced. When they are no longer needed, VHL is supposed to degrade them and turn off their function. If the VHL protein is not there to perform this function, they can continue to function – a normal function but now out of control – and a tumor can ensue.

A number of these proteins are being studied, in hopes of finding a "target" for a drug to work on. Perhaps by manipulating the levels of one of these other proteins we can effectively replace the function of VHL. Three primary angiogenic factors – VEGF, PDGF, and TGF-alpha – are all being studied for other cancers. In addition, it is clear that VHL plays a role in the body's response to changes in the levels of available oxygen and how the cell processes oxygen. It does this through its binding with HIF-1 and other substances. The scientists presented their work with these chemical processes, studying them in the lab as well as in animals.

VHL is highly conserved in evolution. Many animals have a VHL gene quite similar to our own, including the drosophila fruit fly and the worm, as well as guinea pigs and mice. Dr. Tien Hsu of South Carolina and Dr. Harry Drabkin from Denver described their work with drosophila. Smaller animals go through many generations in a short time, allowing us to see effects more rapidly. Dr. Laura Schmidt of the U.S. National Institutes of Health described their

*cont'd on page 2*

1. See Dr. Michels' article on proteomics *VHLFF* Sept 2000 at http://www.vhl.org/newsletter/vhl2000/00cagene.htm

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VHL FAMILY ALLIANCE

After a year's search, the Board adopted this new logo. It was felt that this design best depicts the strength of the VHL Family Alliance as we approach our second decade: the importance of the Unity of Family, Friends, Physicians, and Researchers in helping to diagnose, treat, cope with, and ultimately to cure VHL.

Congratulations to Tim Nielsen and his design staff at Transamerica for their winning submission. Many thanks as well to all the other candidates who helped to shape our thinking and bring us to a strong choice.

***Inside this issue!***


*Giuseppe Opocher, M.D. (left), University of Padua, chaired the meeting. Dr. Maha Kacem came from Tunisia, where she works with two VHL families.*

work in creating a "mouse model" -- a mouse with a kind of VHL sufficiently similar to the human VHL disease that they can use it to test out therapies.

Dr. Kaelin remarked that it takes examination of the same problem from many different perspectives in order to form a complete understanding of a complex issue like pVHL function. There is something unique about the way VHL works that loss of one of the things in the picture does not make the same outcome. There is something special about the VHL protein itself. We need other models – fly, worm, and mouse – to help us see the problem fully.

The VHL protein also seems to have a regulatory effect upon the orderly differentiation and dispersion of cells, the orderly creation of microtubules, and orderly processing of a variety of mechanisms in the cell. In the absence of the VHL protein, these cells proliferate in a haphazard manner.

The development and availability of *in vivo* models for VHL – drosophila, worm, and soon mouse – provide us with greater ability to observe the normal and aberrant processing of these substances by the cell, with and without pVHL.

Dr. Neumann's group presented their findings about the genetic causes of pheochromocytomas. So far there are at least six different genes which can cause a pheo. Why so many? In studying the functions of these various genes we will eventually get to the problem. Dr. Opocher's group found that people with VHL who have pheos often also have a particular change in chromosome 1. Similarly, Dr. Thomas Böhling of Finland showed that in the group he studied, people with VHL who have CNS hemangioblastomas often also had a change at chromosome 6q, and Dr. Hiltrud Brauch of Stuttgart showed that a change in the MDR1 gene raised the risk of having renal cell carcinoma.

There is evidence that some modifier genes exist, influencing the effects of VHL by raising or lowering the odds of getting particular kinds of tumors (e.g. loss of 6q may influence toward CNS tumors, and alteration of MDR1 may influence toward renal tumors). These conditions help to explain why different people in the same family will have entirely different experiences of VHL.

People in VHL Type 2 families (with pheos) tend to be at somewhat higher risk of pancreatic neuroendocrine tumors (PNET). Careful monitoring is needed to ensure that any PNET are detected early and that metastatic disease can be avoided.

Dr. Catherine Stolle of the University of Pennsylvania moderated a session on Genotyping. Genotyping is not easy. Methods vary from one lab to another. Finding known VHL mutations in clinically diagnosed patients is one challenge, finding large-size alterations in people with ambiguous diagnoses is much more challenging. The ability of the diagnostic lab varies considerably. It is clear from studies done in countries with higher rates of detection that there are many people (8-25%) with a single VHL-associated tumor who will likely have a germline mutation. Rates of new mutation are very significant (15-25%) and rates of mosaicism are small but significant (1-2%).

Then came the clinical presentations. Dr. Hartmut Neumann studied the use of PET scanning to find where the pheochromocytoma is hiding in the body. He found that 18F DOPA PET is a highly sensitive and specific procedure for detection of pheochromocytomas and has potential as the functional imaging method of the future. MRI got essentially the same results, but requires more skilled interpretation. PET scanning is still not widely available, but might be sought out in the case of an elusive pheo.

Dr. Edward Oldfield of the U.S. National Institutes of Health showed some compelling data on the natural history, or growth patterns, of CNS hemangioblastomas. It is important to understand that most hemangioblastomas never develop into clinically significant tumors. More symptoms are caused by the cyst than by the tumor itself. The ability to forecast which of these very small tumors might be about to

*Hartmut Neumann, M.D., violin, and Klaus-Martin Kreusel, M.D., piano.*

*Joke Jansen, Naim and Hetty Berisha, from the Netherlands. Dr. Berisha is originally from Kosovo.*

form a cyst would help us select targets for therapy before the damaging "mass effect", the pressure, begins to build. It is also important to advise patients and physicians of the large numbers of small tumors that may be seen on increasingly finer quality scans, in order to sustain hope and work toward appropriate treatment. It's not a matter of how many tumors you have, it's how big they are.

Dr. Alessandra Murgia described her VHL clinical program at the University of Padua. A clinical care center that serves as a resource for differential diagnosis, clinical collaboration and technical support to local physicians can make a tremendous impact on appropriate clinical care for people with VHL.

Dr. Kathlyn Marsot-Dupuch described her studies of ELST in France. Because an ELST can occur even where there is normal hearing function, they are reviewing the 1997 NIH recommendations to use auditory screening as a way of determining who needs to have focused temporal bone imaging study. She feels that ELST should probably be considered as a major clinical criterion for VHL diagnosis in the same way as hemangioblastoma.

Dr. David Gross from Israel presented his encouraging results using halofuginone to inhibit the growth of pheo cells *in vitro*, in a dish in the lab. Dr. Richard talked about the mixed results he received using SU5416 with three patients. While none of the tumors regressed, it did cause edema in the eye to disappear, improving vision. The likelihood is that it will take more than one drug to constrain the growth of VHL tumors because of the multiple influences that promote them.

In the general discussion we talked a bit about some of the key questions for which there should be better answers:

- Should we have a more practical set of screening guidelines? Is it reasonable to recommend an MRI annually, when the reality is that it will not often be economically feasible to do so?

- What is the right age to begin monitoring children? The French now begin regular screening at age 4. They are seeing symptoms earlier because of DNA diagnosis -- they are looking earlier and with better imaging capabilites than ever before.

We will visit these questions in greater depth as we revise the Handbook over the next year.

The German and Spanish affiliates of the VHL Family Alliance described their experiences in creating their groups, deciding what to talk about, getting people together in meetings, in chat rooms, or in e-mail discussions on the internet. There is much energy and organization going on in Europe, much of it driven by Gerhard Alsmeier, our International Volunteer of the Year, and by our energetic new affiliate in Spain.

There were also fifteen poster presentations, with new contributions by teams in Hungary, Spain, and Croatia. Attendees came from six continents!

It was not all hard work. On Friday afternoon we toured the Abbey, an impressive self-supporting community. Later we went to dinner at the Air Museum in San Pelagio, near Padua, where Dr. Neumann gifted us with his traditional violin serenade after dinner, with Dr. Klaus-Martin Kreusel from Berlin accompanying him on the piano.

Lella Guerra, our contact person in Italy, held a meeting for the Italian families on Saturday afternoon where they drafted a constitution for an Italian Affiliate. Sunday fifteen of us met in Abano Terme for a European Leadership meeting of VHLFA, sharing ideas for forming groups and collaborating across Europe and around the globe.

As ever, it was hard to say goodbye. This community and the bonds we have formed among researchers, clinicians, patients, and families is a rich and rewarding group that honors and respects the power of the community as a whole. The most important message we can bring you from Padua is a message of hope. There is a global community of brilliant scientists and doctors working to find the answer to this puzzle and to make life better for all of us. *Arrivederci* -- 'til we meet again -- perhaps in Cleveland in October?

*Richard Harbud, Lone Sunde, and Thomas Rosenberg from Denmark.*

# My Life

*by Alva L., Florida*

As I look back over my life which began over 78 years ago, it's been a long pleasant trip with some detours.

Before I go into the VHL part of my life I'd like to reflect on an incident that occurred in New York City about 1935, when I was 10 or 11 years old.

My friend and I were about to cross a street, but noticed an automobile approaching in the distance. Anyone with any sense would not cross the road in front of an auto, no matter how far away it was. A gentleman came and stood waiting with us. As the auto approached we saw a beautiful black shiny automobile with a pure white convertible top, pulled down. There was a driver and one passenger. The passenger noticed us and was waving as hard as he could. The gentleman asked if we knew who that was. I answered, "No." He said, "That is your president, Franklin Delano Roosevelt." Frankly, I was more impressed with the auto than the President.

The word car did not exist at that time. As I think back the President and driver had no escorts. There were no police or Secret Service. The President seemed quite happy to see us. How things have changed!

I was brought up in an era when we did not take medicine. We never even had an aspirin in our home. To this day I do not take medicine. There were other weapons to take care of problems that came up — natural products. Headaches were helped by putting ice on our head and heat at our feet. Believe it or not, it works! The term von Hippel-Lindau wasn't introduced into my life until June of 1985, when I was 61 years old. I visited an excellent ophthalmologist by the name of Gordon Schwenk in Ocala, Florida. He discovered a hemangioma in my right eye. He treated it, successfully, with laser. More than that, he saved my life.

He asked about my family history and concluded I had von Hippel-Lindau syndrome. I had never heard of this medical condition up to that point. He suggested I go to the best place I could find and he explained the parts of my body that could be affected.

Fortunately I did as he suggested. I went to Boston where I was diagnosed as having renal cell carcinoma on the right side and a pheo on the left side. The surgery was performed successfully by Dr. Libertino. The scar is barely visible and I've had no problems in that area since.

This syndrome is such an insidious disease. How could this happen? Where did it come from?

As I looked back to my visit with Dr. Schwenk it was obvious he knew I had VHL. But I soon came to realize that my son did also.

*Alva L., Florida*

Ed had one pheo surgery at the age of 17 in 1960, successfully removing the tumor and his adrenal gland. Then surgery on the opposite side of his body at the age of 20. This time the surgeon managed to save a piece of the second adrenal gland, so it was never necessary for my son to take hormone replacement medication.

Much later in my son's life he developed kidney cancer in both kidneys. Surgery was successful, but the cancer metastasized. At the age of 53 he passed away in June 1996. How lucky I am to have had such a son! He had so many kind attributes and was loved by so many, because he cared. What a pleasure it was to be his mother. He and his wife, Linda, managed to raise two wonderful, successful children. Neither of the children has VHL.

Now we know we have a cunning, insidious congenital problem. Where did it come from? My mother was from Germany and was one of five children in her family. Four of them died between the ages of 7 and 28. Yet my mother survived to the age of 80 with no apparent problems.

She and my father had eight children and we now know four had VHL. Three of them died at early ages and I am the fourth.

On my father's side nearly everyone lived to a ripe old age.

In our family we can trace this disease through four generations. There are others from the family tree who inherited VHL and yet others who have not.

As I think back, I realize I had symptoms at an early age. I had toxemia during one of my pregnancies. In my 20's for a period of time I had intense headaches. At the same time this was happening I thought I had a tumor because my stomach swelled and I didn't feel well. The doctor said nothing was wrong. He felt I was physically and mentally stressed. He was right, I was stressed at the time, but I am now convinced that there was more going on.

Does that mean we could have VHL eruptions when things aren't going well? Are we sometimes victims of our own personalities or of people we allow to annoy us? Who knows.

For the past thirty years I have taken vitamins and I believe they have contributed to a fairly healthy life

except for the few VHL episodes that I've experienced. I'm also an advocate of healthy eating, exercise, and drinking lots of water. I distill my water.

As a youngster I was quite active in athletics such as swimming, ice skating, roller skating, and other sports. I did the same things with my kids later in life. Did this help? Maybe. Apparently it didn't hurt. But who knows all the answers.

One thing I do know. It does not pay to dwell on this problem. Forget it. Get checkups, but lighten up, have fun, enjoy life. Travel even if it's to the beach or mountains.

Thanks for listening.

-- *Alva*

# Cleveland Meeting, October 11-13, 2002

***Update on VHL: An Integrated Medical Approach to a Multisystem Disorder***

The Cleveland Clinic Foundation and the VHL Family Alliance will sponsor a continuing medical education event for primary care physicians, nurses, and genetic counselors to be held at the Marriott Airport Hotel, October 11-13, 2002. The meeting will be chaired by Dr. David Goldfarb of the Cleveland Clinics and Dr. Robert Uzzo of the Fox Chase Cancer Center. Continuing Medical Education credits will be awarded by Cleveland Clinic to physicians and genetic counselors for the sessions they attend.

Because VHL crosses so very many medical specialties, it is a challenge for any health care professional to follow a patient with VHL. Without the cooperation and close collaboration of the patient and the family, it is practically impossible. For this reason we always work to engender a partnership between the families and their health care professionals.

The agenda includes a survey of the medical issues in VHL, diagnostic techniques and treatments, including legal and insurance issues and stress management. A special session is included on pre-implantation testing for VHL. Because of the expertise of the Cleveland Clinics in kidney issues, the program is particularly strong in kidney.

Families are welcome to attend this meeting. In the nine years since we began holding "patient/provider conferences," we and the physicians who have attended have come to believe strongly that it takes teamwork to manage VHL. The patient has an important role to play, and empowering the patient is good both for the patient and for the physician.

The conference is a wonderful opportunity to meet others with VHL. Andy noticed at his first meeting that other people also had "zippers" peeking out beneath the hairline. Tania noted that "all the women were wearing sensible shoes." Gale bumped into another person and both said in chorus, "Excuse me, that's my blind side." You will learn quickly that you are not alone, and that other people with VHL are just like you! -- nice, normal people with a health challenge to manage.

If you have not previously attended a VHLFA conference, you are encouraged to attend VHL 101, an introductory session with Joyce Graff on Friday morning (9:00 to 12) before the formal start of the conference at 1:00. You will have an opportunity to meet other attendees and VHLFA Board members, and gain an understanding of terms and concepts that may be new to you, especially in parts of the body with which you have not dealt before. The VHL 101 segment is free, but we ask you to register so that we know how many people to plan for.

*David Goldfarb, M.D., Head of Transplantation, Urological Institute, Cleveland Clinics Foundation, Cleveland, Ohio*

For the full draft agenda and registration information, see http://www.vhl.org/conf2002 For hotel reservations, call Marriott at 1-800-228-9290 or (216) 252-5333

"Wow! I'm so glad we went! Next time we're going to bring our family doctor with us! We all feel much more confident now that we know what to watch for, and where to go for coaching in difficult times."

*Robert G. Uzzo, M.D., Urologic Oncology, Fox Chase Cancer Center, and Assistant Professor, Temple University School of Medicine, Philadelphia, Pennsylvania*

# Miracle on Thirty-Fourth Street

*by Joan C., New Jersey*

Perhaps it's prophetic that the Hospital of the University of Pennsylvania is located on 34th Street, because on September 11, 1996, when our family needed a miracle we received one.[1]

Our son Scott walked into that hospital and never left for 53 days. It was his second brain surgery. The first was done on an emergency basis by a local neurosurgeon in 1993 when he was 28. At that time, he was diagnosed with 15 tumors, four of which were removed. Actually, there were 16 because one was hidden behind another. He recovered nicely from that procedure in spite of our fears.

When an MRI indicated a new very large tumor with its own blood supply and one preexisting tumor that had enlarged significantly, in the cerebellum, Scott was sent to a neurosurgeon at the University of Pennsylvania Hospital.

The plan was that an embolization procedure would be done. A team of doctors would pass a tiny tube into the vein in his groin area, pass the tube all the way up to the cerebellum, and inject a kind of glue into the vein feeding the largest tumor, sealing off its blood supply. This would shrink the tumor and reduce the amount of blood in it, making it easier for the surgeon to deal with. Scott would stay overnight in intensive care, and the following morning the neurosurgical team would go in and remove these two tumors that were dangerously close to the brain stem.

Unfortunately, just as the embolization procedure was completed, the tumor ruptured, spilling over 4 pints of blood and crushing Scott's brain stem before they were able to open his skull. The ensuing surgery was a horror. Late that night, when they had done all they could do, the two tumors were removed, but the doctors were unsure whether Scott would wake up from the surgery, or what damage might have been done.

I sat by his bed and spoke to him. Somehow, I knew my words would get through. I told him he was my stubborn child and that this was no longer a vice but a virtue that he needed now to carry him through this difficult time.

He did awaken, but so much was gone. His marvelous intellect was intact but his body was significantly damaged. He was totally paralyzed on one side and his sight, speech, swallowing, and motor skills were gone. He couldn't even blink his eyes – BUT thankfully, he was alive.

In the days, weeks and months that followed, he was often on the edge of death. Unable to swallow, he went into aspiration pneumonia and respiratory failure. Several times we thought we would lose him. Still he fought with all of his strength and survived. The doctors said they had never encountered such a will to live. He simply refused to die.

Each of the many doctors who worked with him took me aside and told me that his survival was miraculous. There was no medical or scientific reason that he should have survived. This was indeed a miracle. My response to all was the same, "This hospital is on Thirty-Fourth street, isn't it?"

Scott came home by ambulance on November 1st. It was now up to his father and me to provide all his nursing care. He was on a feeding tube. He required suction equipment to remove all of the excess secretions that he generated and could not swallow. He needed to be catheterized every four hours.

Therapists came to our home. First he was taught to sit. If you sat him on the bed, he would merely topple over. In time, he learned to crawl on the same living room floor as he had as a baby. He finally stood, and after ten months began to swallow on his own. His eyes quieted down and stopped bouncing all over and the double vision and blurring ceased. He had speech therapy, occupational and physical therapy at home and then later on an outpatient basis.

My husband Charlie turned our den into a gym. He would wheel Scott into the den and then place him on the equipment. He stood him on a stair climber before he could stand on his own and held him until he took one, then two and then ten steps on it. No matter what goal my husband set for him, Scott doubled it. If Charlie said, "Let's do five," Scott would say, "No, ten." Charlie held Scott on a stationery bike, his feet strapped on the pedals, while Scott pedaled the bike. For one year this went on.

One day, my daughter came to me in tears. She said that Scott was crawling through the house, pushing his laundry basket and she didn't know what to do. I told her to go ask him if he would like her to carry the basket to the washer for him. He nodded yes and continued to crawl to the washer, pulled himself up to a standing position, and did his laundry.

At night, I would watch my grown son, much as I had watched him as a little boy, trying to write his name on a sheet of paper. At first, because his motor skills were so poor, he couldn't even fit the letter "S" on the sheet of paper, but he worked and worked and worked. Each and every night, he worked on his speech, his writing, his motor skills.

He finally stood alone and then with assistance took his first step.

There was a song called "Watching Scotty Grow" that came out when Scott was quite young, about the songwriter's son and his learning to walk and talk. My

1. The reference is to the motion picture, "Miracle on Thirty-Fourth Street" 1947, 1994.

*Scott at work.*

husband would sing this song to Scott as a little boy. The words to that song ran through my brain as I watched my son, now an adult of 32, learning for the second time how to do all of those things. I never dreamed that I would see him take his "first step" twice in a lifetime.

Scott is no ordinary human being. He claims to be accomplishing all he has out of spite. Whatever the doctors said he wouldn't or couldn't do, his goal was to prove that he would and he could.

To train his eyes to focus, he re-read the works of William Shakespeare. Each night when I got home from work I would take him up to the Boardwalk in his wheelchair and stand him at the rail. We would count the number of steps he could take in a row and the next night he would increase that number. The next summer we did it without holding on to the rail.

When he was seen by the doctors at Penn, they would just laugh in delight. He had defied all odds. He shouldn't be here, yet here he was and doing the impossible. His determination and the family's teamwork had pulled him through.

It was about this time, that the neurosurgeon told us for the first time that he was sure that Scott had VHL. Charlie and I both come from very large families and no one in either of our families exhibited symptoms of VHL. Nonetheless, the doctor was sure Scott had VHL. He recommended DNA studies, which confirmed the diagnosis. One copy of the VHL gene wasn't just altered, it simply wasn't there – it was totally missing! Charlie and I both underwent DNA studies as well. Both of us have completely normal VHL genes. With our permission, University of Penn's genetics department contacted the U.S. National Institutes of Health, and Scott spent a week there in the VHL research program.

Scott continued to forge ahead with his rehabilitation. He took computer courses to strengthen his motor skills. He started to walk with a walker and subsequently a cane. He started to apply for jobs and met with resistance. He looked great on paper but, believe me, the doors do not open wide to the handicapped. He took a Civil Service test for Probation Officer in the State of New Jersey and came in #60 out of the 2500 who took the test. He was hired by the Superior Court and began work in August of 2000.

Prior to his first surgery, he was pursuing his Master's Degree at Villanova University. He had been writing his thesis when this calamity struck. I wrote to the University explaining his situation, and he was permitted to continue his studies. He completed his Master's degree while working a full day. He submitted his thesis on February 2, 2001, only weeks after he learned that he would soon undergo another brain surgery for the removal of four more tumors and a large cyst in the cerebellum, dangerously close to the brain stem. The doctor warned him that this surgery could set him back again. Scott clenched his jaw and set the date for the surgery. This time, he emerged with no further deficits even though he had two major bleeds during the surgery. At his post-op check up, his first question was, "Okay, when can I go back to work?"

On May 20th, as we stood on the field of Villanova University and "Pomp and Circumstance" began to play, I turned around to see my son, pushing his walker, leading the graduating class. It was the most beautiful sight in the world.

He now walks with a cane, his speech is monotone but distinct and through his exercising daily, his motor skills have greatly improved. He eats everything in sight, and looks like a million bucks. His delightful sense of humor puts people at ease and brightens his days. Scott lives, thanks to the skill of his doctors, but also because of his amazing attitude. I learn from him that every day we have the choice to live fully. Attitude, after all, is everything.

Scott says, "I enjoy my job because every case is different. When people come it to be arraigned, I interview them. I ask them a lot of personal questions, like what type of childhood they had."

Five years ago, a friend asked me, "Don't you ever ask, why me, why my son?" My answer was, no, because that would mean that I would want this to happen to you or to someone else and that would make me less than human. But it's more than that. I truly believe that this handsome, determined, strong willed human being is here to be an inspiration for all who see him. My purpose is to be a voice, not only for him, but for all of those who have VHL. Scott is my joy, my miracle.

# Volunteer of the Year

This year we honor Kelly Heselton, who is retiring from the Board of Directors after six years as Treasurer. She receives this year's Minster Award for Volunteer Service, a beautiful gold pin designed and donated by Minster's Jewelers of Newark, Delaware.

Kelly's Aunt Lois Erickson, who has VHL, served on our first Board in 1993 and still serves on the 800 Line Committee. Lois' sister Audrey Tobin joined the Board as our Treasurer in 1994, and Audrey drafted her daughter Kelly as Assistant Treasurer. Kelly joined our Board in 1996 and has been one of the reliable mainstays of this organization since that time.

In addition to her duties as Treasurer, Kelly organized and chaired our International Symposium in Rochester, Minnesota, in 2000. At home, Kelly is an auditor for Norwest Bank. She lives with her husband Dan and their two daughters. They are expecting their third child in October of this year.

We very much appreciate her many talents and organizational skills, and her strong and steady partnership in this work. ***Thank you, Kelly!***

# Regaining Balance

I have VHL and have undergone 9 craniotomies, all in the cerebellum. I mention the location because this area is a balance center.

Not once did anyone suggest physical therapy because I was doing well: But, I went to see a physical therapist for a knee problem and mentioned in passing that I had had all of that neurosurgery. He offered me a set of simple "exercises" to work my balance. What a great idea!! I was faithful with them and noticed an improvement, even though I had not been at all aware of any deficit.

I have now learned to include in my exercise regime some aspect of balance, be it yoga, or the big inflated balls, called "balance balls." There a wide range of video tapes available on either subject, and the difference is astounding. I was very pleased when a neuro-audiologist (balance specialist) was clearly astounded at my "rock-steady" balance! All that and I currently have 10 tumors still in that area, yet no one can tell that I have had any run-in with neurological issues at all, least of all me.

I believe that there are many folk, who, unaware of these options, have resigned themselves to a life that is less that they can have. Brain elasticity is astounding! My tip for people would be ,"Go for it! and Stretch your limits!" -- *Deb C., Michigan*

Just wanted to thank you again and again for your referral several months ago to Dr. Peter Choyke at NIH. He recently assessed my re-scan of kidneys and provided me with a clear and concise report. It was very good news, indeed: no solid tumors and no further action called for excepting a follow-up scan in one year. I had been so upset about the possibility that the lesions were much worse or more serious. Dr. Choyke's opinion has allayed my fears.

I want you to know that it is precisely this aspect of the von Hippel-Lindau Family Alliance that I appreciate the most. I needed information, and you were there for me. – *David I., California*

# NCI Reports Available

*U.S. Cancer Progress Report, 2001* - This report is the first in a new series to present in one place up-to-date information on the U.S. progress against cancer. The report succinctly describes and illustrates the progress in reducing the cancer burden, from prevention through the impact of deaths from the disease. National cancer data, trends, and progress relative to certain cancer-related targets of the project "Health People 2010" are provided. Measures of progress are presented that are based on scientific evidence and, in most cases, are products of long-term national data collection and analysis. Key measures are included in the areas of prevention (behavioral and environmental), screening, diagnosis, life after cancer, and end of life. Access the executive summary on-line at http://progressreport.cancer.gov

*The Nation's Investment in Cancer Research for Fiscal Year 2003: Plans and Priorities for Cancer Research*. - NCI annually articulates its plans and priorities in this planning and budget document. The document serves as a tool for communicating NCI's vision, goals, opportunities, and challenges for cancer research. It describes "Extraordinary Opportunities for Investment," areas where focused research efforts and increased resources can produce dramatic progress toward reducing the cancer burden: (1) genes and the environment; (2) research on tobacco and tobacco-related cancers; (3) cancer communications; (4) molecular targets of prevention and treatment; (5) cancer imaging; and (6) defining the signatures of cancer cells: detection, diagnosis, and therapy. Access the publication online at http://plan.cancer.gov

Copies of these reports can be requested by calling 1-800-4-CANCER (1-800-422-6237)

# Best to Diagnose Pheo

*by Laurie Barclay, M.D., Medscape Wire, June, 2002*

Plasma free metanephrines is the best single test to diagnose pheochromocytoma, according to a multicenter cohort study reported in the March 20 issue of *The Journal of the American Medical Association*.

"Plasma free metanephrines constitute the best test for excluding or confirming pheochromocytoma and should be the test of first choice for diagnosis of the tumor," write Jacques W.M. Lenders, MD, PhD, of St. Radboud University Medical Center in Nijmegen, Netherlands, and colleagues. "Combining different tests did not improve the diagnostic yield beyond that of a single test of plasma free metanephrines."

The authors compared test results in 214 patients with histologically confirmed or widely metastatic pheochromocytoma and in 644 patients not found to have this tumor on extensive workup despite suggestive signs and symptoms.

Sensitivities were 99% for plasma free metanephrines and 97% for urinary fractionated metanephrines, which were higher than those for plasma catecholamines (84%), urinary catecholamines (86%), urinary total metanephrines (77%), and urinary vanillylmandelic acid (VMA; 64%).

Specificity was highest for urinary VMA (95%) and urinary total metanephrines (93%); intermediate for plasma free metanephrines (89%), urinary catecholamines (88%), and plasma catecholamines (81%); and lowest for urinary fractionated metanephrines (69%).

Using receiver-operating characteristic analysis to consider both sensitivity and specificity, the authors concluded that plasma free metanephrines was the best test for confirming or excluding pheochromocytoma. This test was negative in more than 80% of patients tested, virtually excluding pheochromocytoma and eliminating the need for immediate further tests in these patients.

"In about 80% of patients with pheochromocytoma, the magnitude of increase in plasma free metanephrines is so large that the tumor can be confirmed with close to 100% probability," they write. "In these patients, the immediate task is to locate the tumor."



Calibrations for diagnosing pheos in children have been compiled by Weise, Walther, Eisenhofer et al. "The findings indicate that plasma free metanephrines provide a sensitive tool for detection of pheochromocytoma in children. Age appropriate reference ranges should be used, and gender differences should be considered." *Journal of Clinical Endocrinological Metabolism,* 87(2002): 1955-1960.

# Socializing Helps

*Adapted from an article by Jennifer Warner, reviewed by Dr. Gary Vogin*

Patients that maintain strong social ties to family and friends may be better able to cope with their disease, both mentally and physically. A new study shows limiting social interaction during cancer treatment can increase the risk of depression.

In the study, published in the journal *Psycho-Oncology*, researchers found losses in social functioning and severity of symptoms were most closely related to depression. The greater the losses in social interaction and more serious the symptoms were, the more likely the patient was to suffer from depression.

Depression is a common problem among newly diagnosed patients with cancer or chronic illnesses, and previous research has suggested that a patient's mental health can significantly affect their physical well-being.

"These depressive symptoms can adversely affect a patient in many ways: they can interfere with treatment, increase length of hospital stay, reduce ability to care for oneself, impair quality of life and possibly reduce overall survival time," write the authors of the study.

Researchers interviewed 228 elderly lung cancer patients four times over the course of one year and assessed their symptoms of depression, physical functioning, social functioning, physical symptoms, and related conditions.

At each interview, the study found the best predictors for serious depression were the severity of the patients' symptoms and their reported losses in social functioning.

The number of depressed patients was highest at the start of the study, which is in line with prior studies that show the risk of depression is greatest immediately after diagnosis. Depressive symptoms also declined as the severity of symptoms declined.

Researchers say the findings suggest that healthcare providers should work with their patients to develop a treatment plan that addresses their symptoms while interfering as little as possible with normal social activities.



***VHL Stands For ...***

How about

***Very Hopeful Lives***

After all, we are working to find a cure.

*-- Barbara M., Australia*

# Ask the Experts

### *Dental Anesthesia*

***Question:*** The *Handbook* says we should never go under anesthesia without the healthcare provider knowing of any potential risk of pheochromocytoma. What if you go to a dentist and he has to use local anaesthesia just to numb your mouth for cavity fillings? Should that be a concern for VHL patients?

***Response:*** There are concerns about spinal anesthesia — your anesthesiologist should check and be aware if there are any spinal hemangiomas in the area where they will be inserting needles. Dr. Oldfield gave us a good answer for that one in June 2001. Obviously that is not a concern in the case of dentistry.

There are also concerns about having a pheo incident during anesthesia. A pheo episode can be provoked by lots of things, from a fall or a minor auto accident on up — any kind of stress-provoking incident. It would clearly be best for you to know before the dental procedure whether or not you have a pheo to worry about. You do this through regular check-ups. If you are on a regular check-up schedule and do not have an active pheo, then there should be nothing of concern for your dentist to worry about.

If you have a pheo of any size, even if it is considered "inactive," it would be wise to advise your dentist, just in case. Dental procedures can definitely set off a pheo. Any type of stimulus can set off a pheo. They are very unpredictable. You might say something like "low risk of pheochromocytoma". In the remote case of a crisis, it's the clue that could save your life. *– our thanks to Dr. Gladys M. Glenn & Dr. McClellan Walther of the U.S. National Institutes of Health for their help in preparing this reply.*

See Dr. Oldfield's response in VHLFF June 2001, www.vhl.org/newsletter/vhl2001/01bnaske.htm

### *Rearrangements and Deletions*

***Question:*** As I was getting our papers ready to take to NIH last night, I noticed that my husband's DNA results read that he has a "rearrangement of the VHL gene" and that our 2 sons' results read that they have "a partial deletion in the VHL gene." I am curious if that means that they have a different mutation than their Dad? I am embarrassed by my lack of understanding of the genetics of VHL. In our online discussion group one person expressed interest in finding "others with the same mutation 454 C to T (P81S)." I looked and can't find that sort of info on any of their DNA results and wondered why.
*– Robin K., Texas*

***Response:*** First of all, please don't be embarrassed. Genetic terminology can be very confusing, and sometimes two different names can be used to describe the same effect. For example, a "rearrangement of the VHL gene" often produces a "partial deletion of the VHL gene", so the mutation that your husband has is almost certainly the same mutation that was described for your sons. I'll try to explain in more detail.

A **rearrangement** is a type of mutation that can affect relatively large portions of a gene, and typically the rearranged fragment will move to another part of the chromosome (or to another chromosome), and therefore loses its function. So the fragment that stays in place is now shorter – in genetic terms, the type of mutation that has arisen is called a 'truncation'. The gene is now described as 'truncated'.

Imagine this is the VHL gene:
TTAATGAATAGCTTGGCATTACCATCGGAACCA

If the gene breaks in the middle (and we don't yet understand what can cause it to break)…
TTAATGAATAGCTTGGCATTAC CATCGGAACCA
… then what stays in place is now a truncated (therefore mutated) gene
TTAATGAATAGCTTGGCATTAC

This truncated gene does not work the same as the intact, full-length gene, and can give rise to VHL lesions.

Meanwhile, the other fragment CATCGGAACCA has moved to another
chromosomal location. It has relocated or 'rearranged'. In its new location, this fragment has lost its original function.

By contrast, **point mutations,** such as 454 (C to T) which you mention, are different types of mutations altogether. Here, there are no big breaks and relocations of the VHL gene, but instead, just one 'letter' of the gene is altered. In this type of mutation, the size of the gene remains the same.

The fifth letter is mutated in this hypothetical example. A geneticist would call this a 5 (T to G) mutation.
TTAATGAATAGCTTGGCATTACCATCGGAACCA
TTAAGGAATAGCTTGGCATTACCATCGGAACCA

In families with a 454 (C to T) mutation, the change in letters affects position 454, instead of position 5. A genetic test would not identify such point mutations in your husband or sons, because entire strings of letters are missing.

It may seem surprising that large deletions of the gene and very small point mutations can have similar clinical consequences (that is, they both cause VHL tumors to develop). However, keep in mind that this is not exactly true: families who have large deletions often do not develop pheochromocytomas, while families who have point mutations are more likely to present with pheochromocytomas. This is why it's important to know what mutation one has, because one can then pay more attention to certain types of screening and tests. *– Myriam Gorospe, Ph.D., Director of Research, VHLFA*

# Ask the Family

### *Childbearing Choices:*

**Question:** Would you please reprint the article you wrote some years ago about the varying thoughts that women may have of having children, especially in a VHL family? I remember so vividly, sitting and reading the article and relating completely to each set of thoughts. It is unbelievable how much that article related to me, my thoughts of my kids, and the feelings of being a woman, mother, and having a spouse with VHL. I truly appreciated that article. We made the decision that was right for us, and we will help with the education of family and friends of the disease and to help give our children the road map to continue the journey and pursuit towards a cure. Thank you again! – *G. S., New Mexico*

***Response:*** We are happy to reprint it.

Sally and Tom fell madly in love and married at 19. Knowing that Tom had VHL, and with active pressure from their parents not to have children of their own, they decided to adopt children when the time was right, but in the near term the priority was to finish college. They chose oral contraceptives for now, adoption later.

Jane and Mike at 27 had been married for some years. They wanted to make sure their child would be healthy, but there was then no prenatal test for VHL. They thought about adopting, but also thought a lot about having their own child. Even though there was one gene they really didn't want to pass to this child, they still had a lot of good ones to pass along! They had a child, the "old-fashioned way," and showered that baby with love, good nutrition, and good values.

Margaret at 32 discovered herself pregnant. Her intra-uterine birth control device (IUD) had embedded in the wall of her uterus and become ineffective. She had always wanted lots of children, and wanted to welcome another child, but there were lots of issues. Her husband was very sick with VHL, and moreover had recently had a course of radiation treatment, raising questions whether it might have affected his sperm. She was the sole support of her family: a sick husband and a four-year-old. The gynecologist told her there was also a chance that her uterus could rupture during the pregnancy. She chose to terminate the pregnancy.

Sally, Jane, and Margaret have something in common — they are all me, at different points in my life. Each time I was faced with the childbearing decision, I was a different person, enmeshed in a different set of circumstances. Today, I sometimes look back and say that I probably could have coped with that second child and it would have been okay. But I'm no longer the desperate, over-stressed person now that I was at 32. Just as we should not judge other people for making decisions other than the ones we feel are correct, we should also not second-guess ourselves for the decisions we made at other points in our own lives.

If there had been prenatal testing in 1970, would I have used it? Yes. Would I have terminated the pregnancy for a positive reading? Probably. In those days I knew only two people with VHL — my husband and his father — who both had bad experiences with VHL in an ancient medical era. From all we could see then, VHL was a ferocious disease. Now we know that we were seeing only the tip of the iceberg. Now we know that a change in the VHL gene doesn't necessarily predestine you for terrible things.

Life will happen to us, with or without VHL. Some of us will have better trips than others. VHL is a risk factor, just like the risk factors for breast and colon cancer that you read about in the press. With a change in the VHL gene, you have a greater chance of developing certain kinds of tumors than people in the general population, but nothing is absolute. We still have a chance to change the outcome. With prevention, early detection, and appropriate intervention, people are doing enormously better today than ever before.

I am glad to say that I have a perfectly wonderful son — a fine young man I wouldn't trade for anyone else in the universe. He has VHL. When he and his wife approach this question for themselves, my pledge to them is to allow them to make the right decision for the two of them, without my interference but with my loving support. Their decision will not be absolute, it will be what it is for the time being, and it may change over time. That is their right. This year he's raising two cats.

In the March 1998 issue of *VHLFF* you will find a variety of true stories depicting the choices we can make as we evaluate the extent to which we want to involve children in our lives. Each one of us will make our own choices. There is no "right" or "wrong" here — we present this information to you in the spirit of supporting you in seeking the answer which is right for you and your partner at this point in your lives. Whatever opinions you may hear from individuals, from your relatives and friends, and even from your parents — are *their* opinions — to which they are entitled, and which they have the right to voice — but they need not necessarily shape your own choice. The "right" answer for you is the one in your own heart. – *Joyce G., Massachusetts*

1. See *VHL Family Forum* 6:1, March 1998, http://www.vhl.org/newsletter/vhl1998/98aachld.htm

# Our New Affiliate Group in Spain!

*In Padua we officially welcomed our newest affiliate group, Alianza Española de Familias de von Hippel-Lindau, based in Spain. Dr. Karina Villar of Toledo and President Susi Martinez of Barcelona brought a poster to share at the Symposium. They are off to a very strong start. They have already joined FEDER, an organization of rare diseases in the Spanish-speaking countries, similar to the National Organization for Rare Diseases in the U.S., and Eurordis, a similar organization among the states of the European Union. Dr. Villar shares some of her observations from their first meeting in Madrid.*

After the presentations, one of two shy men who had remained unidentified in the back of the room stood up and suggested that each person in the room say their name and where they were from. This surprised me, but I was even more surprised by the events that followed. One by one, each of the attendees stood up and told the rest what VHL manifestations they had, what health problems, which organs affected, etc, how VHL had been for them... without hesitation or reservations. It was sharing of information as I had never witnessed before. It was so deeply moving ... and particularly for me, because it was all about VHL. I really enjoyed this exchange.

We have made a list of everyone's names and phone numbers - in fact, those shy men were the ones most interested in having these phone numbers as soon as possible - I would have never believed what took place at that meeting if I hadn't been there myself! My sister also attended and she was so glad she did and she had a chance to meet other families with VHL. It was very special, almost magic.

When the presentations were over, nobody moved, everyone stayed there for a long time. I was telling Susi that this was the best proof that everyone enjoyed the experience - they just WOULDN'T LEAVE! For the next meeting, we're planning to request the participation of specialists, so that we can address more complex questions.

*Karina Villar, M.D. (left) and Susi Martinez (right) hanging their poster. Padua, June 6, 2002.*

# Carers Week, U.K.,

Carers are the people who voluntarily take care of a family member or friend who needs a little extra assistance in their daily lives. There are 12 key initiatives taking place during Carers week this year, June 10-16, 2002, to honor these people. Free holidays will be awarded to 1,000 carers, and Carers Week leaflets will be given out, enabling carers to send personal messages to Local Authorities explaining why services are so crucial to their quality of life. For more information or for a carers week pack contact Paul Matz, Carers Week Manager on +44 20 7566 7619 or e-mail: mail@carersweek.org

# Resources

### *healthfinder® español*

Healthfinder® español, a Spanish-language Web site that helps consumers track down reliable health information quickly and easily on the Internet.

Available at http://www.healthfinder.gov/espanol, this new easy-to-use Spanish-language consumer resource offers over 300 topics from 70 government agencies and nonprofit organizations. A unique feature of healthfinder® español is the ease with which users of the site can switch between Spanish and English versions of the same information. English-speaking family members or health professionals can use this feature to search in English for information to share with Spanish-speaking relatives or patients.

### *The Medicine Program.*

There is a "Medicine Program" in the United States that offers assistance to individuals who are regularly required to take prescription medication but who lack adequate income to fill their prescriptions every month. There is a one time $5 filing fee per prescription and then the Medicine Program staff will fill out the paperwork necessary to get the individual into one of the patient assistance programs sponsored by the drug manufacturers. This is available to any U.S. citizen and any age.

For more information go to www.themedicineprogram.com or call 1-573-996-7300. They have brochures available in English and Spanish. -- *submitted by Peggy M., Mississippi*

# Meet the Directors

### *Thomas Lusk, Chicago, Illinois*

Elected to the Board in 2001, Tom Lusk is an Institutional Futures Broker with Carr Futures in Chicago. He has spent the last 20 years working on the floor of the Chicago Mercantile Exchange.

He was first introduced to von Hippel-Lindau when his wife was diagnosed in 1992. He found the information he received from the Alliance very helpful. He would like to help make sure the VHLFA can continue its work and to grow so those that are faced with the challenges of VHL will always have support and a source for the latest in medical information pertaining to VHL.

Tom is a member of the Finance Committee.

## Board Elections 2002

The results of the current ballot are in! Maria has been re-elected for a second term; Matt and Andy add their expertise to the group. We are positioning ourselves for strength and growth in our second decade!

### *Maria Shipton, Philadelphia, Pennsylvania*

Maria has served on the Board as Director of Communication since 1999, and as Chairman of the Board since 2001. She has been Chairman of the Pennsylvania Chapter since 1997. "I feel Pennsylvania and the entire country needs to be more informed about this disease that is not so rare, just under-diagnosed. I would not want anyone else to go through what I did to find information about VHL. I need to let the medical professionals know what VHL is and how to screen for it. I am honored to be part of the VHLFA Board."

### *Mattison Painter, Esq., Brentwood, Tennessee*

Matt is taking over the key role of Treasurer. His wife's family is affected by VHL. A graduate of Vanderbilt School of Law, Matt is a tax attorney in Brentwood, Tennessee, a suburb of Nashville, where he works with many clients in the area of estate planning and charitable giving. Matt has served in various positions with charitable and professional organizations including Miami Valley Housing Opportunities, Inc. (Trustee), the Dayton Art Institute, Kettering Medical Center Foundation, the Dayton Bar Association, the Nashville Bar Association (Treasurer 2000), and the Nashville Bar Foundation (Trustee). He also speaks frequently to lay and professional groups regarding various estate tax and charitable contributions planning topics.

### *Andrew Lax, San Francisco, California*

Andy Lax brings exceptional corporate, messaging and issues experience through his nearly 20 years as a senior business journalist, producer and publisher. Andy graduated from Swarthmore College in Pennsylvania. He is a public relations account executive in San Francisco. He brings his considerable media relations talent to the team. During his 17 years in broadcast news he help cover major news stories for ABC and NBC Television operating stations. Andy also helped developed Ziff-Davis Television in association with MSNBC Television. He has won Columbia University's George Peabody Award for Distinguished Journalism with ABC News, and the Telly Award for Corporate Communications.

This community is strong because of its many willing hands and hearts

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Toll-free in the United States and Canada: 1-800-767-4VHL
Editor: Joyce Wilcox Graff, 1-617-232-5946 (eve)
Adviser: Debra L. Collins, M.S., U. Kansas Med. Center, 1-913-588-6043
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# VHL in Brazil!

*by Joyce Graff, Massachusetts*

Our first ever VHL meeting in Brazil, in Portuguese language, occurred April 25 in Saõ Paulo, chaired by Dr. José Claudio da Rocha of the Ludwig Institute. Because I was in Saõ Paulo to speak at a high-tech Security conference for Gartner, I was privileged to attend the meeting.

I arrived in Brazil Sunday at 5 am. Boston to Miami was 3.5 hours, and Miami to Saõ Paulo was another 8 hours. I spent Sunday afternoon touring with Dr. Rocha. From Sunday evening through Tuesday evening I had a very full schedule of meetings for the Security Conference, which was very successful. I met with interesting Brazilian clients, and learned a lot about local issues and local laws.

Saõ Paulo is the financial center of Latin America. It is also one of the five largest cities in the world, with 18.5 million people. Mexico City is even larger, with 20 million. To give you a point of reference 20 million is the population of the entire continent of Australia. The shoes from Brazil are among the most fashionable in the world, and the clothes are vibrant and sexy.

Saõ Paulo is also the medical research center of Latin America. The Hospital do Cancer here is a partner in the genome project, and has all the most modern equipment. The Ludwig Institute conducts a great deal of research. Dr. Rocha has created an excellent clinical care center for VHL.

Thursday was VHL day! We met in a conference room at the Hospital do Cancer with thirty-one patients and family members. Dr. Rocha and his colleagues made presentations in Portuguese about VHL, about DNA testing, and about clinical care for

*Brazilian meeting, April 25, 2002, Saõ Paulo*

CNS and kidney lesions. Then I spoke, sharing with them our experiences in forming the VHL Family Alliance, and the benefits we have gained from being together these past nine years. We have learned so much from each other, and found comfort in knowing we don't have to go through this alone.

Most of all, we welcome the participation of groups from other parts of the world. It makes the world smaller, and increases the size of the community of families. It also gives us a broader perspective on the disease. In only three years of his project, Dr. Rocha has identified 21 distinct families with VHL. In fact eight of these families have mutations we have not seen before among families in North America, Europe, the Middle East, nor Japan. I used slides in Portuguese, and Dr. Maria Isabel Achatz was kind enough to translate my remarks into Portuguese.

We shared our stories, we laughed, cried, and hugged, and took lots of photos. Dr. Rocha's clinical screening program has already made a positive impact in the course of the disease in these Brazilian families. Now that they have found each other, I am sure that the families will work to form a family support organization in Brazil. We look forward to working with our neighbors in South America!

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