VHL FAMILY FORUM

Membership Renewal Issue!

Family, Friends, Physicians, & Researchers dedicated to improving diagnosis, treatment, and quality of life for people affected by von Hippel-Lindau.

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24 April 2007

Dear Friends:

May is VHL Awareness Month. It is time once again to renew our memberships in the Alliance and our commitment to finding answers to VHL. This year for the first time VHL appears widely in the press. While the characterization of VHL is not always what we would wish, we can all work to balance it. In this issue of the newsletter you will see some of the ways the worldwide VHL community is rallying to this opportunity. May we send you a press kit to use locally?

The world is also becoming aware of the many risks hiding in our genes. Ten years ago Dr. Francis Colllins, head of the Human Genome Institute at the U.S. National Institutes of Health projected that within ten years the Human Genome Project would disclose that everyone has at least one significant genetic risk factor. I asked him recently how many people in the general population are carrying some genetic risk factor for cancer. He thought about it, and gave me a rough estimate that one person in 300 carries one of the highly heritable genetic risk factors for cancer. Add to that the more weakley inherited genetic risk factors for other diseases that we are seeing each day in the press, and it's already nearly 100%. As he predicted years ago, the knowledge we have gained through the Human Genome Project is giving us information that is going to be difficult to deal with -- foreknowledge of medical risks that must be managed or they could seriously harm us. We are all wrestling with the ethical, legal, and social implications of that knowledge.

But for us in the VHL community, it is comforting to know that we are not alone. Those of us with VHL have been doing what countless others will now be called up to do -- living with the knowledge that cancer may try to come into our lives. It is up to us to manage it. And we are managing it with ever greater success, living with cancer as a chronic illness. I believe we can be justly proud of what we have accomplished.

All the progress we have made is due to a coalition of effort: to you and all those who contribute dollars, to all the many volunteers worldwide who contribute so much of their time and talent, and of course to the expertise and care of the many physicians and researchers throughout the world.

This year we have received another eight research proposals. We are delighted to see this continuing level of interest in working on VHL. We are excited at the opportunity to encourage more young researchers to undertake VHL research. We have a challenge gift to meet by June 30. Please help to support VHL research and education by paying your dues of $25 per year, which covers the mailings we send you. If everyone pays their dues, we will be able to fund one more grant. ***Anything additional goes to meet the challenge!*** Please help us meet this challenge, and perhaps fund one more additional grant.

It is only through the generosity of our supporters and our volunteers that we exist. We have new opportunities to keep people healthier longer. The Handbook is helping patients and their local doctors do better routine screening and have more constructive discussions about optimal treatment. Through new research discoveries we hope to see within the coming decade ways to keep new tumors from ever forming. ***Please Act Now! See Page 15***

And it's exactly because we have achieved so much already together that we ask you to continue your support, and to help us to reach new donors. If every family would help us raise at least $100, we would more than meet our goal.

Many thanks and all best wishes for a happy, healthy year ahead,

Inside this issue!

Ballots and Challenge due June 20

We Need Your Vote! - See Ballot, p. 15

The Nominating Committee submits this slate of candidates for your approval.

Your vote counts! To be confirmed, each candidate needs the votes of 10% of the members.

❑ LINDA S. BERK, MOUNT LAUREL, NEW JERSEY

Diagnosed with VHL in 2003, Linda is now volunteering her time to various institutions. She is an Activities Leader with Caring Canines, a Club with The Seeing Eye, a Room Mom and your basic chauffeur for her two children, one of whom also has VHL. Previously, she worked for a Philadelphia law firm as a Paralegal. She has over 20 years of legal experience. "Being on the Board will enable me to ensure that diagnosis is done early and treatment/ monitoring are received in a quick fashion, especially for kids. I also hope that with my background I can bring VHL to light. With my legal experience, I hope that I can streamline grants and paperwork to get things done faster with government and local agencies. I also hope to lend an ear to those who need an impartial listener."

☐ ROBERT R. LYDON, CHICAGO, ILLINOIS

Bob attended Loras College in Dubuque Iowa, where he majored in Business Administration. He is CEO of the National Tax Review Service (NTRS), helping to ensure that clients have taken all legally allowable deductions. He is very active in the Chicago Southland Chamber of Commerce and other business councils, as well as his church. In 1987 Bob had 6 hemangioblastomas removed from his cerebellum. Bob inherited VHL from his mother's side and since has had multiple surgeries and procedures on his brain, spine, eye, liver, kidney, pancreas, bone, and lung. Bob's favorite past time is spending time with his wife Ellen and daughter Cristine.

☐ JEANNE McCOY, GREENVILLE, SOUTH CAROLINA

Jeanne McCoy is an active community volunteer, serving the Junior League, the American Cancer Society, the Greenville County Legal Auxiliary, and her children's school. A former French teacher with degrees from Wake Forest and the University of Georgia, Jeanne is now a stay-at-home mother to her three children. Her husband, Ellison, is a labor and employment law attorney. Jeanne was diagnosed with VHL in 2003, less than a year after her mother's diagnosis. Her grandmother lived to the age of 82 despite suffering blindness and other ill effects of VHL. Since her diagnosis, Jeanne has had two neurosurgeries and two kidney surgeries. Jeanne's personal and family experience with VHL have led her to be a vocal advocate for those whose lives have been impacted by VHL and cancer in general. Jeanne intends to use her board membership as an opportunity to develop additional outreach programs regarding VHL.

☐ BILL B. SCHEITLER, LeMARS, IOWA

Bill and his wife Judy, a registered nurse at Floyd Valley Hospital in LeMars, have three children. Son Bill and his wife Jane live on the family farm with their three children; Richard and his wife Jennifer live in Sterling, Virginia; Jodi and her husband Matt live in LeMars, Iowa with their two children. Bill is president and CEO of S&H Marketing in Remsen, Iowa, an agricultural consulting firm. Bill has traveled throughout this country and approximately 16 other countries representing the United States, the State of Iowa, and the Cattle industry. "Communication, education and research are the three areas of focus that I believe are extremely important to the VHL Family Alliance. These areas of interest need to be addressed throughout this country and the world community."

☐ CHRISTOL SORRELL, PERU, NEW YORK

Christol Sorrell is an Accountant and an Adjunct Professor in Business Administration. She has a BA in Business Management and a minor in Accounting. She will be receiving her Master's in Adult Education with a concentration in Human Resources in the Spring of 2009. Diagnosed with von Hippel-Lindau (VHL) in 1994. She has had several surgeries to remove tumors from her spine and brain stem. Her kidneys and pancreas must be monitored regularly to watch the tumors that are present. Her current tumors have pushed her need to explore more options and to see what can be done to help her and others with this disorder.

VHL Awareness in the Mainstream

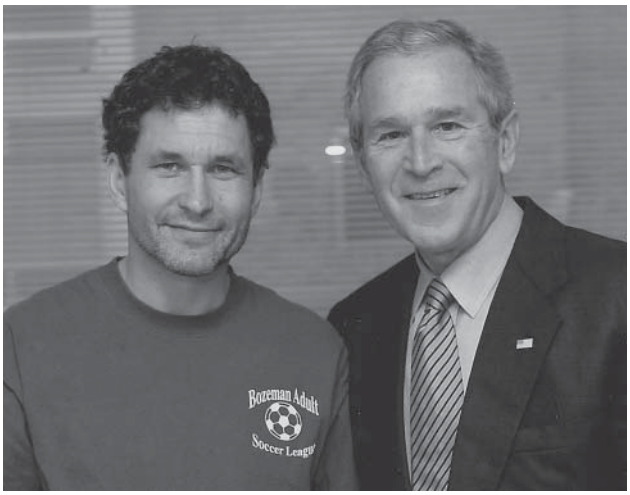
By Dale M., Montana

When I was diagnosed with VHL 21 years ago, in 1986, the urologist that had taken a biopsy of my epididymis (the coiled tubular feature attached to the testicle) said, "you have VHL, a rare disease I've never heard of. Based on a research paper I found, the disease has some serious implications for other issues." No kidding.

Seven years later, in 1993, he went on to remove my left kidney, as multiple cysts had grown to the size that intervention was recommended to prevent the spread of cancer. By then, VHL was still considered rare, but it was also understood to be a complicated, systemic disease that evidenced itself in numerous organs throughout the body.

Last January, 2007, I underwent surgery on my right kidney for a cyst that had grown to a size where intervention was recommended. This time, I underwent a 6-hour laparoscopic surgery in which the tumor was removed while the remainder of my kidney was spared. My surgery was performed at the National Institutes of Health (NIH), where I have been a participant in two study protocols for the last 6 years. So I am functioning on a partial kidney, I have that large tumor in my pancreas, and I have all those littler hemangioblastomas in my brain and spinal cord. But they are all something to watch, not to worry about.

On January 17, 2007, the President visited NIH. He visited only one cancer laboratory, that of Dr. W. Marston Linehan, Chief of Urologic Oncology at the National Cancer Institute, and head for 25 years of one of the largest VHL research projects in the world. Dr. Linehan told him about VHL, about the genetics of cancer, about the VHL families, their many manifestations, about finding the gene and targeting the gene with new therapies. When this picture was taken, the President of the United States was looking at a slide of a kidney cancer from a VHL patient. The President was very interested in Dr. Linehan's efforts to target the gene. He then spent about 20 minutes with two VHL patients in the clinical center, one of whom was Dale. Afterward he participated in had a round-table discussion on cancer prevention, where he came out strongly in favor of the Genetic Information Nondiscrimination Act.



Dale M. and George W. Bush, President of the U.S.A.

While the good news for me is that I am still here for my daughter and that I can play soccer again this summer (a lifelong passion), the news of interest to everyone else is that VHL awareness has entered the mainstream. While I was at the NIH, it so happened that President Bush was also there supporting funding for the NIH, promoting a bill before Congress that would prohibit genetic discrimination (see accompanying article), and giving accolades to Dr. Marston Linehan and his colleagues for their groundbreaking genetic work on the hereditary VHL and papillary renal cell carcinoma kidney cancer genes. That VHL was on the presidential agenda, and that a genetic anti-discrimination bill was a potential reality, seemed a long way from my first introduction to the disease two decades ago.

To add to the feeling of altered reality, it also turned out that President Bush wanted to meet with a couple of VHL patients. I was asked if I was willing. "Oh my. Really? What does one talk about with the President," I pondered, considering the many national and international issues that ran through my mind. I decided I would focus on my support for those at the NIH working on VHL and other diseases. And after it finally happened, I found I had spent almost 10 minutes chatting with the President as we sat on my hospital bed. Chatting. About VHL. Not so rare any more, it seems. Oh, and at the end, when the President was commenting about the odd weather in Texas, I reminded him that climate change might be a consideration. During his State of the Union address to the nation just a few days later, he brought up the important issue of climate change. I was almost sure that he was going to mention VHL too.

The Legendary McCoys

by Joyce Graff

In early April 2007 a story came out from the Associated Press suggesting that the infamous feud between the Hatfields and the McCoys might have been fueled in part by a rare disease that runs in the McCoy family – von Hippel-Lindau disease. In March we were lamenting how little visibility VHL had in the mainstream press. In April we got more than we wanted. We gained not only visibility, one might say we gained a certain notoriety. While the original article as issued from the Associated Press was pretty carefully crafted, as it was reprinted, cut for size, and commented upon by others, it lost much of the balance and fairness until VHL was being characterized as "a rage disease," and commentators were suggesting that this was a weak attempt to propose a medical "excuse" for bad behavior.

On the good side, we have been contacted now by over 100 people who have recognized symptoms in themselves or family members that might be a pheochromocytoma.

What is depicted in the McCoy article is the experience of one family. VHL is different in each person, and varies considerably from one family to another. VHL occurs in one person in every 32,000, worldwide, in every ethnic group. Twenty percent of the people who have VHL are the first person in their family ever to have VHL. Fewer than 20% of people with VHL experience a pheo.

While the article associated VHL with "rage" as a factor in the Hatfield-McCoy feud, VHL is NOT a rage-causing condition. It is important for everyone to understand that a sudden change in behavior, or any unprovoked outbursts, might in fact be a symptom of an underlying medical issue. Families who know they may be at risk for a pheo, should pay special attention. But it is also important to understand that rage is not the usual reaction to this type of tumor.

Most people living with VHL are doing so with humor and grace and carrying on their daily lives like everyone else. As one leading VHL researcher said to me, "People with VHL are bank managers, financial analysts, active duty members of the military, lawyers, business people, physicians -- people from all walks of life who are affected by VHL -- brave, accomplished people functioning at the highest levels of society."

VHL is a disease that may lead to the development of one of six different kinds of tumors, only one of which causes hormonal issues. A "pheo", a tumor of the adrenal gland, can cause surges of hormones like adrenaline -- that fight-or-flight response. They give you extra speed and strength in an emergency. But having these hormones injected into your body at random intervals can give one a feeling like a panic attack or palpitations – or sometimes rage.

Pheos occur in the general population, not just in people with VHL. They may be inherited. A flaw in any one of six different genes may lead to a pheo. VHL is the leading hereditary cause of pheos, but not the only one. 76% of pheos are sporadic, 24% are hereditary. Only two-fifths of the hereditary pheos are related to VHL. (See Figure 1).

Might a pheo have been a factor in the feud? Possibly. But don't forget that the Hatfields of that time did not have pheos and they participated just as wholeheartedly in the feuding. It was a remote region and a lawless time. There was a very strong component of culture and environment operating here in addition to the undiagnosed medical issue.

The article implied that having VHL might be a cause for bad behavior. Having a medical problem is NOT an excuse for bad behavior. Everyone occasionally has bad days, or feelings of rage. Fortunately, few of us act on them. We are all still responsible for our actions.

If you have unfounded feelings of anxiety, rage, or palpitations, or if you have heavy sweating, or uncontrolled high blood pressure, then the best test to determine whether these symptoms might be caused by a pheo is a blood test called "plasma free metanephrines." This test is the most specific for the products of a pheo, and is the most accurate in determining the presence of a pheo. It is not done in every hospital lab, but your hospital can send it for analysis to the laboratory services at the Mayo Clinic. Information about this test and other helpful information for doctors and patients can be found at http://www.vhl.org/pheo

Untreated, pheos are very dangerous. They can cause heart disease or stroke. Having an accident, a baby, or any surgery or dental procedure can be life-threatening. But once the pheo has been removed, all those dangers go away.

The University of Virginia has been working with more than six generations of the McCoy lineage for 20 years. Contact them toll-free at 800-251-3627

Take Action Now!
Before June 20...

...Please return your ballot
.....and pay your dues
.....and ask for a press kit
.....and register for Boston!

Mom Lives with Rare Genetic Condition

By Vikki Hopes, copyright 2007, Abbotsford News, Abbotsford, British Columbia, Canada

Editor's note: Concerned about the McCoy articles, Julie contacted her local newspaper.

Julie D., British Columbia, is cuddling her four-month-old daughter – her third-born child – when she coughs.

The otherwise-normal action sends searing pain through her head. Julie has been having progressively worse headaches since her daughter's birth, but now the pain is so intense that she almost drops her baby.

It's time to have her symptoms checked out. What she doesn't expect to hear, after the appropriate medical tests are conducted, is that she is suffering from the hereditary condition that, years before, she was ruled out as having.

Julie is told she has a benign tumour on her brain and that a fist-sized cyst has grown around it.

The symptoms are all-too-familiar. Her grandmother, mother and an uncle had all experienced tumour growth – the result of a rare genetic illness called Von Hippel-Lindau (VHL) syndrome. In their case, the condition was fatal, as malignant tumours developed on their kidneys.

It is soon confirmed that Julie has inherited the condition. The news couldn't come as more of a shock.

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Her family never talked much about the disease that had ravaged them, but Julie grew up knowing its devastation. She had been told that her mom,

Julie D. relaxes with her daughters (from left) Samantha, Trinity and Katarina. She wants to increase awareness about a rare condition called Von Hippel-Lindau, with which she was diagnosed in 2005. Photo: John Van Putten

Darlene, first displayed symptoms at the age of 12, when she developed eye tumours.

By the age of 38, Darlene developed malignant tumours in her kidneys and had both of them removed. About 10 months later, she required brain surgery.

Julie was 16 at the time of her mom's kidney surgery, and she became pregnant with her first daughter, Samantha, who turns 11 next week. Julie had never displayed any symptoms of VHL but her parents were worried that she might have it or that she would pass it on to any children she might have.

Her teen pregnancy meant they had to face the situation earlier than they had expected. A test, called "linkage analysis," was conducted, and Julie was told she did not have the condition nor was she a carrier. In a horrible twist of events, she later discovered that the test is unreliable.

Darlene endured nine years of dialysis before dying on Sept. 11, 2004, at the age of 46. At the time of her death, the kidney cancer had spread to her lungs.

Darlene's mother had died at 49 and a brother perished at 29.

It is 2005 when Julie is told she could face the same fate, except that things are different with her.

Her years of watching her mother suffer means Julie has learned much about the condition. One thing she has learned is that immediate and ongoing treatment is crucial. Her family had difficulty dealing

with the issues surrounding their illness, and treatment was not sought as readily as it could have been.

Julie decides she will take a pro-active approach, backed by the support of her husband Chris, whom she has been with for eight years. He is adamant that VHL "is not a death sentence."

But the diagnosis brings a heavy burden for the couple. "The first thing that came to my mind was, 'Oh my God, I've given it to my girls,' " Julie says.

Believing that Julie did not have the condition, the couple had two children together – Katarina, now 6, and Trinity, 22 months. (Samantha was born before Julie met Chris.)

But before tests can be conducted, Julie must undergo brain surgery to remove the tumour. This takes place on Jan. 5, 2006, and it takes about four months for her to recover from the procedure and the complications that follow.

At this time, testing is more precise than it was when Julie was told she did not have VHL. All three daughters test positive for the condition.

The couple are devastated by the news, but vow to stay positive and do everything they can to educate their daughters and ensure they live long happy lives.

"You hope things change," Julie says of medical advancements that could lead to a cure.

Chris reassures her: "Don't hope. It will change."

Julie has just now recovered from her last procedure – the removal four months ago of a portion of her left kidney, which had developed a cancerous tumour.

She is currently being monitored for tumours on her brain – she had two that seem to have disappeared – and one on her spine, but she doesn't dwell on the repercussions.

"Pretty much now, when something pops up, it gets taken out," she laughs.

Julie wants to break the code of silence surrounding the condition and dispense of myths – such as that VHL is a "rage disease," as suggested in recent media reports.

"This disease does not make you rage. People make themselves rage," she says.

Her own family's silence about VHL has already been broken. Samantha recently competed in a French immersion speech contest in which she talked about the condition.

She reached the semi-finals.

Editor's Note: Anyone who was tested using linkage analysis, especially before 2000, may wish to consider having the test done again. There is about a 15% room for error in such tests, and a few cases have been reported each way -- both false negatives, like Julie's, and false positives.

Michigan members mourn the passing of Dr. Hoff

by Stephen Sullivan, M.D., Neurosurgery, University of Michigan

Editor's Note: The author, Dr. Stephen Sullivan, was selected by Dr. Hoff to take over the care of the large number of VHL patients in his practice. Dr. Sullivan is a graduate of the University of Chicago, who did his neurosurgical residency at the University of Michigan under Dr. Hoff.

It is with nearly unbearable sadness that we report the death of Julian "Buz" Hoff, M.D. on April 16, 2007 after a courageous battle with cancer. He died with great dignity at home with his loving family. His passing leaves a great wound in our lives.

Dr. Hoff was born September 22, 1936 in Boise Idaho. He attended college at Stanford on a baseball scholarship and attended Cornell Medical School. He served as a Captain in the U.S. Army based in Japan and completed his neurosurgical training at New York Hospital.

The University of California, San Francisco, recruited Dr. Hoff to join their faculty and his talent was quickly realized. He rose to the rank of full professor before accepting the position of Chairman of Neurosurgery at the University of Michigan. The Department thrived under his leadership to become one of the premier training programs in the field of Neurosurgery.

Dr. Hoff is one of the true giants of neurosurgery. He published extensively and was a recognized authority on a diverse array of neurosurgical conditions including brain injury and edema, Von Hippel-Lindau syndrome, acoustic neuroma and cervical spondylosis. He was a great leader of organized neurosurgery at the national and international level and has received numerous awards including the Cushing medal and election to the Institute of Medicine.

None of these honors meant more to Dr. Hoff than did his patients and the resident physicians under his tutelage. His kindness and generosity belied his greatness. His down to earth manner, humility and humor are rare in a man of his stature. He taught physicians to be human first. He had an innate understanding of the frailty of the human condition and it came across in his kind words and empathy.

For most of us, Dr. Hoff will be the greatest man that we will ever know. His life, although too brief, was well lived. His legacy can be seen in the love of his family, patients and colleagues. He will be greatly missed.

VHL Research Questionnaire

This information will enhance our Tissue Bank, and help us inspire more researchers to study VHL. Please place all surgically removed tissue in our Bank, and submit this questionnaire before the end of 2007. Return this form to VHLFA, 2001 Beacon St, Boston, MA 02135

PART 1- Personal Information

Part 1 will be kept separately from the rest of the information; it will not be added to the database.

Personal Information

Today's date (dd/mon/yy): _____/_____/_____ Date of Birth (dd/mon/yy): _____/_____/____

First Name:_____ Last Name:_____

Last Name at birth (if different from above):_____

Address:_____
Street

_____
City State/ County Zip/ Post code

Home Phone: (____)_____ Email Address: _____@_____

I want to be informed about research results: Yes_____ No_____

Data from parts 2-7 will be added to the research database

PART 2- General Questions

Year of Birth (dd/mon/yy): _____/_____/_____ Sex:_____

Ethnicity: _____
(e.g. White, Hispanic, Black or African-American, American Indian, Asian, Native Hawaiian/Pacific Islander. If other or mixed, please specify.

Height: _____ Weight:_____

PART 3- Family History

1. Is your family affected by VHL? Yes____ No ____ I don't know ____
2. Has the mutation in the VHL gene been found in your family? Yes____ No____

   If yes, year of analysis? _____ Which laboratory? _____

VHL Research Database, funded in part by a grant from Alex's Lemonade Stand Foundation

3. Please fill in the table on your family history:

Family member	Who has VHL? (tested, confirmed)	Who does NOT have VHL (tested, confirmed)	Who might have VHL?	Unknown	Total number
Mother					
Father					
Brother(s)					
Sister(s)					
Son(s)					
Daughter(s)					
Grandfather					
Grandmother					
Uncle(s)					
Aunt(s)					
Cousin(s)					
Nephew(s)					
Niece(s)					

PART 4- Medical History

1. Age of your first symptoms:_____ 2. Age when first diagnosed:_____

2A. What was the first feature identified? _____

3. Which clinical care center/ hospital/ nursing care facility is currently taking care of you?

_____

_____

What are the regular intervals of your screenings?

Twice a year: _____ Yearly:_____ every 2 years _____ others: _____

When were your last screenings? Year:_____

The current status of your vision:

	Good Vision	Partial Vision	Blind	Enucleated (removed)
Left Eye				
Right Eye				

The current state of your hearing:

	Good hearing	Partial hearing	Disturbance	No hearing
Left Ear				
Right Ear				

VHL Research Database, funded in part by a grant from Alex's Lemonade Stand Foundation

von Hippel-Lindau disease can have a variety of lesions. Please check as accurately as possible the lesions and/or cysts which apply to you. N/E stands for "not evaluated", meaning you have not had screening for that body part. The word lesion is used to describe angiomas, hemangioblastomas, and tumors.

	Yes (Include number of tumors/ lesions/ cysts and year when diagnosed)	**No**	*N/E*	**Surgery** (year)	**Do you still have tumors/ lesions/ cysts?** (If yes include number)	**Other** (please specify)
Eyes: Retinal lesions Left Right						
Retinal detachment						
Brain: Cerebellar lesions						
Brain stem lesions						
Other e.g. pituitary, supratentorial						
Spinal Cord: Lesions inside the cord						
Lesions outside the cord						
Syrinx						
Other						
Kidneys: Cysts left Cysts right						
Renal Cell Carcinoma Left Right						
Pancreas: Cysts						
Lesions						

N/E = not evaluated

	Yes (Include number of tumors/ lesions/ cysts and year when diagnosed)	**No**	*N/E*	**Surgery** (year)	**Do you still have tumors/ lesions/ cysts?** (If yes include number)	**Other** (please specify)
Adrenal Glands: Lesions left Lesions right						
High blood pressure						
Extra-adrenal pheo(s) or paragangliomas						
Hearing changes: Endolymphatic sac tumor						
Tinnitus (ringing in the ears)						
Men only Epididymis: Cystadenoma left Cystadenoma right						
Women only- In VHL there are benign tumors that can occur in the reproductive organs, which are very difficult to diagnose. Have you ever been told that you had a lesion, tumor, or mass in or near any of the following? If so, what action was taken if any?						
Broad ligament: Fallopian tubes						
Ovaries						
Uterus						

5. **Other Issues**:

OTHER medical problems you think may be related to VHL, please explain below.

Return this form to VHLFA, 2001 Beacon Street, Suite 208, Boston, MA 02135 - Thank you!

Nephrogenic Systemic Fibrosis (NSF):

An Uncommon side effect of MRI Contrast Agents in Patients with Renal Impairment

by Peter L. Choyke, M.D., National Cancer Institute, pchoyke@nih.gov

Until last year, few side effects had been reported with Gadolinium-based contrast agents for MRI. In consequence, they were considered among the safest agents used in humans. However, in August of 2006 that changed. Then, a disease called Nephrogenic Systemic Fibrosis (NSF), which was first recognized in 1997, was reported to have developed in patients with impaired renal function who had received one of the MR contrast agents in common use, Gadodiamide. Thus, it was only in 2006 that a connection between NSF and gadolinium contrast agents was established. This is an observation of interest and importance to patients with VHL given the frequent use of contrast enchanced MRI in their management. Although all the answers are not yet here we will present some of the questions surrounding NSF and the risks associated with it in patients receiving MRI contrast agents.

What is NSF?

NSF is a disease process that produces progressive fibrosis. Most commonly it involves the skin in which it produces sites of skin thickening that can be painful or itchy. If it occurs around the joints it can cause joint stiffening which can be disabling. In some cases, the fibrosis can involve the internal organs. In about 5% of cases this can lead to death due to progressive organ failure. Thus, when it occurs, NSF can be a serious condition.

Who is at risk for NSF ?

Most VHL patients who receive Gadolinium contrast agents are NOT at risk for NSF. This is because most patients with VHL have normal or nearly normal renal function and because NSF seems to occur almost exclusively in patients with very impaired renal function or who are on dialysis. In about 3-5% of patients with severely impaired renal function, NSF appears to develop within a few weeks to months after the administration of a Gadolinium contrast agent.

The gadolinium agent most frequently (90% of cases so far) associated with NSF has been gadodiamide or Omniscan made by GE Healthcare (formerly Amersham). However, reports are emerging of NSF occurring with other agents (Magnevist, Berlex Labs, Optimark, Mallinckrodt Labs) although as of this writing no cases have been associated with ProHance or MultiHance (Bracco); however, according to what is known now- it is important that a patient having an MRI scan be aware of the potential risk for NSF with any brand of gadolinium-based contrast agent.

How was the link between NSF and Gadolinium contrast agents discovered?

Reports began to emerge in 2006 about a link between gadodiamide and NSF. NSF was noted first in patients who were on dialysis and who received double or triple doses of gadodiamide for MR angiography studies, however, as attention was drawn to NSF, physicians started reporting NSF in patients who had received only a single dose of one of several gadolinium contrast agents.

What causes NSF ?

At this point, the cause of NSF following injection of Gadolinium contrast agents is unknown. One theory is that the Gadolinium ion may become separated from the rest of the contrast agent molecule to which it is bound and that the resulting "free", unbound Gadolinium induces fibrosis. Indeed, some investigators have found "free" Gadolinium in the tissues of patients with NSF but this is only indirect evidence of the cause of NSF. Impaired renal function increases risk according to this theory since the kidney is the primary means by which gadolinium contrast agents are eliminated. Patients with impaired renal function take longer to clear Gadolinium contrast agents from their body once they are injected; the prolonged residence time of the agent in the body increases the chances of creation of "free" Gadolinium. This theory is plausible but there is little hard evidence to support it.

What levels of renal impairment predispose to NSF?

Patients on dialysis due to renal failure are at highest risk for NSF. Patients with impaired renal function not requiring dialysis may be at risk as well. The worse the renal function the higher the risk. The serum Creatinine value is a common measure of renal function and is common use, however most kidney specialists rely on the Glomerular Filtration Rate or GFR to define the level of renal function. This involves the collection of timed blood and urine samples. An estimate of GFR can be calculated from the serum Creatinine value by including patient age and weight. The official National Kidney Foundation system classifies "moderate" chronic kidney disease as a GFR between 30 and 59 ml/min/1.73 m^2, "severe" chronic renal disease as a GFR between 15 and 29 ml/min/1.73 m^2 and "end stage" chronic renal disease as a GFR < 15 ml/min/1.73 m^2 or on dialysis.

The FDA has stated that caution should be

exercised in administering Gadolinium contrast agents to patients with *moderately* impaired to end stage renal function. Many feel this guideline is too conservative based on what is known today. Until more is known, however, it is the only official guideline. Several journal articles have been published or will be published stating that severely impaired or end stage renal function would qualify for a caution. Under the FDA guidelines in excess of one out of four Americans over age 70 could be excluded from receiving Gadolinium contrast agents because of a glomerular filtration rate (GFR, a measure of kidney function) of less than 60cc/min, and roughly 7.7 million Americans have a GFR between 30 and 60 (National Kidney Foundation). All VHL patients with GFRs **indicating** "moderately" and "severely" impaired renal function should this issue with their doctor to determine whether it is appropriate to receive gadolinium contrast agents. Until more is known, you and your physician must balance the benefits of the study against the risk of NSF.

Should VHL patients at risk for NSF have MRI with Gadolinium?

For the patient with VHL the question of the use of Gadolinium with MRI is one of weighing the risk of developing NSF versus the benefit of the diagnostic information that the contrast-enhanced MR images provide. Approximately 3-5% of patients with renal dysfunction who receive gadolinium develop NSF according to what is known today (March 2007). Clearly, in some cases the benefit of the MRI (e.g. from detection and accurate depiction of a brain or kidney tumor) outweighs the small risk of NSF. However, since the benefit of contrast-enhanced MRI varies among patients, each patient at risk for NSF should discuss the risks, benefits, and alternatives with her or his physician before proceeding with the MRI.

Can the patient get a CT scan instead of a MRI?

Unfortunately, CT contrast agents have their own problems when it comes to renal function. In patients with impaired renal function, iodinated contrast agents can lead to further damage to the kidneys. Therefore, for most patients with impaired renal function, contrast enhanced CT is not an alternative to contrast enhanced MRI.

Another question to be addressed is whether the MRI exam can be performed without Gadolinium-based contrast media. This is not a viable option for many patients since much of the diagnostic information provided by the MRI is obtained only by virtue of use of the contrast agent. However, it is always worth exploring this possibility.

If an MRI with Gadolinium is performed in a patient at risk for NSF, what can be done to reduce that risk?

Currently two basic approaches are available: i.e., reduce the patient's exposure to the contrast agent and avoid agents with known higher risk. Whatever agent is used, the least dose necessary to complete the study should be used (e.g. half dose) and double and triple dosing should always be avoided. If a contrast enhanced MRI is performed in a patient with severely impaired renal function, it is recommended that hemodialysis (not peritoneal dialysis) be performed immediately after the MRI scan. The use of Omniscan should be avoided (Omniscan has been banned for use in patients on dialysis patients in Europe). At this time (March 2007) there have been no reports of NSF with the gadolinium agent ProHance (Bracco); hence, until evidence to the contrary emerges, its use may be something to consider in the patient at risk for NSF (But it is a safe assumption that eventually all of the available agents will be implicated with some degree of risk for NSF.

The "NSF Story" is constantly evolving and patients are well advised to check the literature on the web about developments. Until firmer guidelines are established this will be a difficult time for patients with VHL and renal impairment who need contrast enhanced MRI scans.

What resources are available for patients and their doctors to consult?

There is a growing list of on-line publications concerning NSF. They are written by experts in the field and may be useful in helping you sort through this problem with your doctor.

FDA guidance on the use of Gadolinium contrast agents in patients with impaired renal function: http://www.fda.gov/cder/drug/advisory/gadolinium_agents_20061222.htm

The International Center for Nephrogenic Fibrosing Dermopathy Research (ICNFDR), a clearinghouse of information on the subject, http://www.pathmax.com/dermweb/

2007 Radiology article on NSF entitled "Nephrogenic Systemic Fibrosis: Risk Factors and Incidence Estimation"" http://radiology.rsnajnls.org/cgi/content/full/2431062144v1

2007 AJR article on NSF entitled Gadiodiamide-Associated Nephrogenic Systemic Fibrosis: Why radiologists should be concerned" http://www.ajronline.org/cgi/reprint/188/2/586

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E-mail: info@vhl.org; Tel: 1-617-277-5667; Fax: 1-858-712-8712 **Internet website http://www.vhl.org**
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Dr. Richard Cohan, University of Michigan, on oral contrast for CT scans

Dr. Nahum Goldberg, Beth Israel Deaconness Hospital and the Kidney SPORE, on radio frequency ablation

Amy Lynn Budd, Artist in Residence at the Perishable Theater Arts Program, Providence, talking about her own recovery and giving a participatory demonstration on dancing your way to recovery (wear comfortable clothes)

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