VHL FAMILY FORUM

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

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Endolymphatic Sac Tumors in von Hippel-Lindau

Reporting three recent articles(1) by Russell R. Lonser, M.D., H. Jeffrey Kim, M.D., John A. Butman, M.D., Ph.D., Alexander O. Vortmeyer, M.D., Daniel I. Choo, M.D., and Edward H. Oldfield, M.D., Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health.

In 1994 members of the VHL Family Alliance began reporting to us quite a number of issues with hearing. At the time nothing was known about an aspect of VHL that might involve hearing. While many people with VHL had hearing issues, patients were usually told these hearing changes were not associated with VHL, or were the result of brain surgery or medication reactions.

Spurred by insistence of the Alliance that we felt there was more to it, the U.S. National Institutes of Health began a survey of their patients in 1994, which culminated in an important paper in 1997 clearly connecting endolymphatic sac tumors (ELST) with VHL. Despite descriptions of petrous-bone lesions by Brandt(2) and Lindau(3) in the 1920s and periodic reports of ELST in patients with VHL disease, ELSTs were not formally recognized as part of von Hippel-Lindau disease until publication of the Manski paper in 1997.(4) [2483-4]

Since that time the distinguished team of physicians who have authored these three new papers has compiled a significant amount of information and experience working with people with VHL who have been seen at the Clinical Center of the U.S. National Institutes of Health. They have analyzed reported hearing changes, worked out screening guidelines for people to detect changes early, and developed surgical techniques to remove tumors and preserve hearing.

ELSTs are very rare in the general population. In people with VHL, however, they are not rare. In fact, they can be seen on MRI or CT in 11-16% of people with VHL. [p. 2484] When the tumor can be seen, patients usually have symptoms:

- 95% have hearing loss
- 92% have tinnitus (ringing in the ears)
- 62% have vertigo (dizziness) or disequilibrium (balance problems)
- 29% have a fullness in the ears
- 8% have weakness or slackness of the nerve that runs through the cheek of your face.

Hearing loss may occur gradually over a period of 3-6 months or longer, or in some cases it may occur suddenly. Once hearing is lost it is very difficult to regain. Here again, it is very important to watch for early symptoms and address the problem carefully in order to preserve hearing.

In almost 60% of people with VHL who have subtle hearing changes, there is no evidence on imaging of an ELST. The cause of these symptoms is not known, but the authors believe that the symptoms may be due to a microscopic tumor. In this tiny area, even a microscopic tumor can cause some disturbance.

Microscopic analysis of the lesions has shown clearly that they are caused by the same mechanism that causes other VHL tumors. Everyone has two copies of the VHL gene. In people who have the condition called VHL, one of those two copies has an alteration that causes it not to work correctly. As long as the second copy is working correctly, all is well. When something happens to cause a change or deletion in that second copy of the VHL gene, a process begins in that one cell that may result in a tumor.

In the case of an ELST, the tumor forms either in the endolymphatic sac itself, or in the petrous bone. The endolymphatic duct runs from the inner ear to the back surface of the petrous bone and ends

Inside this issue!

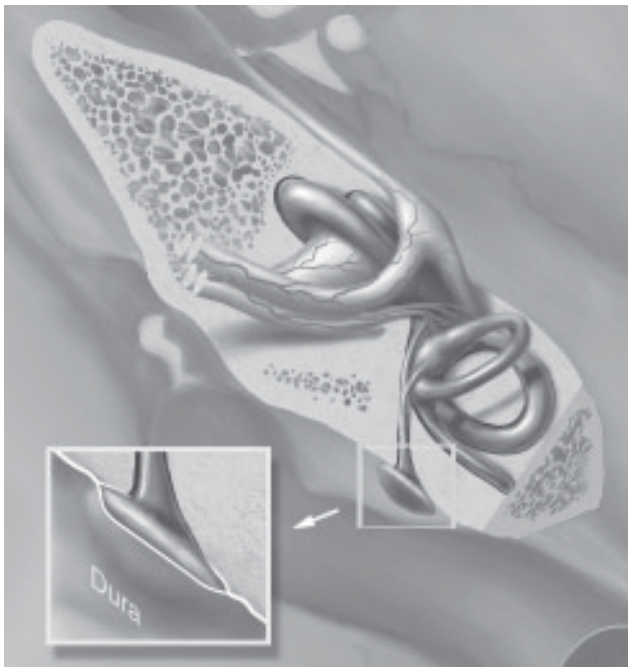

Figure 1. *The inner ear, showing the endolymphatic sac (ELS). In the inset, you can see that the ELS is right up against the dura, the fibrous membrane that covers the brain. The bony structure is the petrous bone. Illustration courtesy of Dr. Lonser.*

beneath the dura at the boundary of the brain as a flattened expansion, the endolymphatic sac. (See Figure 1.) This tiny structure is filled with fluid (called endolymph) and has a delicate system of pressure regulation that is responsible for one's sense of balance and equilibrium. Menière's disease is another condition that is caused by a disturbance in this area, and ELST's are often misdiagnosed as Menière's disease.

It was previously thought that hearing loss from ELST resulted from invasion by the tumor of inner-ear structures. Based on their analysis, however, the authors believe that hearing loss and vestibular symptoms are more likely caused by hemorrhaging of the tumor inside the ear, and resulting damage from the bleeding and subsequent inflammation.

Fluid accumulation (called hydrops) may explain the Menière's-like symptoms (hearing loss, tinnitus, and vertigo) in patients with ELST. Hydrops may result from blockage of the reabsorption of endolymph in the endolymphatic sac, inflammation in response to hemorrhage, or excessive production of fluid by the tumor. Fluid production is typical also of other VHL tumors.

Complete surgical resection of the ELST can make all the symptoms go away and can be performed with the preservation of hearing. Untreated, an ELST can lead to sudden profound hearing loss, which is not reversible. Early surgical intervention is important to prevent permanent damage to hearing and balance. Therefore early diagnosis on the basis of regular screenings is very important. Once there are symptoms that indicate an ELST may be present, high-resolution imaging can be used to detect small tumors or hemorrhage in the inner ear. Further advances in imaging techniques may also improve our ability to detect these tumors early.

Patients who have a visible tumor but who can still hear require surgery to prevent a worsening of their condition. Deaf patients with evidence on imaging of a tumor should undergo surgery if other neurological symptoms are present, to prevent worsening of their balance problems. Further study is needed to determine whether patients with clinical symptoms of ELST, but without evidence of a tumor or hemorrhage on imaging, should undergo surgery to prevent hearing loss or to alleviate symptoms.

References:

1. Russell R. Lonser, M.D., H. Jeffrey Kim, M.D., John A. Butman, M.D., Ph.D., Alexander O. Vortmeyer, M.D., Daniel I. Choo, M.D., and Edward H. Oldfield, M.D., "Tumors of the Endolymphatic Sac in von Hippel-Lindau Disease." *N. E. J. Med.* 2004 350:2481-2486. Dr. Kim is with the National Institute on Deafness, Dr. Butman is with the Radiology Department in the Magnuson Clinical Center at NIH, and Dr. Choo is with the Department of Otolaryngology, Children's Hospital Medical Center, University of Cincinnati.

CA Megerian, DI Choo, et al, "Hearing Preservation Surgery for small Endolymphatic Sac Tumors in patients with von Hippel-Lindau syndrome." *Otol Neurotol* 2002; 23:378-387.

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2. R. Brandt, "Auf der Frage der angiomatosis retinae." *Von Graefes Arch Opthalmol* 1921; 106:127-136.

3. Arvid Lindau, "Studien über Kleinhirncysten: Bau, Pathogenese und Beziehungen zur Angiomatosis Retinae." *Acta Path Microbiol Scand* Suppl 1926; 1:1-128.

4. T.J. Manski, Gladys M. Glenn, Edward H. Oldfield, et al., "Endolymphatic sac tumors: a source of morbid hearing loss in von Hippel-Lindau disease." *JAMA* 1997; 227:1461-1466.

Annual VHL meeting - Copenhagen

--Vibeke Harbud, Chairman, Denmark

We had our annual meeting again this summer, and it is turning into quite an event -- meeting, team-building and of course dinner.

The team-building sessions are very good. They really make the members talk to each other about their experiences, problems, and others issues.

Photo: Vibeke running the Copenhagen marathon

New Renal SPORE in Boston

Dr. Michael Atkins, Director

Kidney cancer researchers at Beth Israel Deaconess Medical Center (BIDMC), and the Dana Farber/Harvard Cancer Center (DF/HCC), have been awarded a prestigious SPORE grant from the National Cancer Institute (NCI). The $13 million, five-year federal grant is the first SPORE awarded for the study of kidney cancer.

An acronym for "Specialized Program of Research Excellence," SPORE grants are presented to groups of investigators from various disciplines that are dedicated to working collaboratively on a particular cancer type. "SPORE grants help to fund and facilitate translational research," explains the grant's principal investigator Michael Atkins, MD, director of biologic therapy and cutaneous oncology at BIDMC and leader of the DF/HCC Renal Cancer Program. "The goal is to bring laboratory discoveries into clinical practice within the relatively short life of the grant." Vikas Sukhatme, MD, PhD, BIDMC division of nephrology, and William Kaelin, MD, Dana-Farber Cancer Institute (DFCI), are co-principal investigators.

The grant focuses on:

- early detection
- minimally invasive treatment
- the growth of new blood vessels (angiogenesis)
- affecting the cell signaling system (signal transduction inhibition)
- enhancing the immune system
- "biomarkers" or chemicals in the blood or urine that might tell us whether the kidney cancer tumor is becoming more or less active, like the PSA for prostate cancer
- ways of predicting a patient's potential response to a particular drug or treatment
- ways of choosing the right treatment for the patient, so as not to lose valuable time trying a drug that doesn't work for this patient.

This grant encompasses a broad effort directed at translating biomedical research into more effective treatments, and advancing the understanding and treatment of kidney cancer.

"Integrating this critical mass of investigators and research projects and disease-directed core activities through the SPORE grant will likely enhance the therapeutic options for our patients with kidney cancer and facilitate more sophisticated and productive research studies," says Atkins. "Our goal is not only to conduct great science but to bring new treatments to renal cancer patients in a timely manner."

The DF/HCC coordinates the cancer research efforts of seven Harvard-affiliated institutions: Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Children's Hospital Boston, Dana-Farber Cancer Institute, Harvard Medical School, the Harvard School of Public Health and Massachusetts General Hospital.

For information on the Renal Cancer SPORE contact : +1 (617) 667-1930, option 1.

Information on the array of clinical trials now available for patients with renal cancer can be found on the DF/HCC Renal SPORE website at www.dfhcc.harvard.edu/spore/ and click on "Renal" at the bottom of the page.

For additional information on the SPORE program offered by NCI, you may wish to visit the NCI website: http://spores.nci.nih.gov/.

United Way?
CFC?
Please print out one or more posters from our website to hang in your office for this year's workplace charity campaigns.
CFC # 0242
United Way - write us in!

Looking for a special gift? Something unique and inspirational?

See page 15 of this issue for some very special CD's and books, from artists with VHL in the family. Proceeds of these purchases go to VHL research.

Mark and Ashlee P., with the proud parents of the bride, Frank and Beverly V.

Wedding Celebration

by Ashlee P., Saskatchewan, Canada

My parents and I really enjoyed the First Canadian VHL Conference in Whistler, British Columbia, in June. As always we learnt new valuable information and met a lot of nice people.

I had mentioned to everyone that I was getting married on July 10, 2004, and was glad I could attend the conference with all the plans going on. We had a wonderful day, the weather was great, 26° C. (79° F.) and everything went well.

As we were talking about fundraisers during the conference, I decided that I could pass a boot [basket[around during the wedding to raise money for VHL. At the wedding, I explained a little about VHL and passed the basket around. I had also placed a few pamphlets on the tables so people could read more about VHL. At the end of the night we had raised $679.03. A few days later I received a letter from my friend Anneliese and she had donated $20 toward my VHL fund. That brought our total up to $699.03. Mark and I have decided to donate an additional $300.97 to bring us to a grand total of $1000.00. We would like this money to go towards research.

Thanks to everyone who donated to our fund and I hope everyone is healthy and happy.

Watch This Spot!

Melissa T. of Texas is preparing for the USA Lake Placid Ironman Triathlon, 2005

She is running to raise money for VHLFA, in honor of her father. "His determination and positive outlook on life is amazing despite what he has been through with his health. He is my inspiration behind the Ironman."

Track her progress at

www.vhl.org/ironwoman

New Clinical Care Center in Nashville

By Selvi Palaniappan, MS, CGC, Vanderbilt University, Nashville, TN

A new VHL Clinical Center has recently opened at Vanderbilt University and the Vanderbilt-Ingram Cancer Center in Nashville. This comprehensive clinical center will become one of three VHL clinical care centers in the Southeast and will provide coordinated care for all aspects of a patient's clinical care.

Initial contact with the medical center and care coordination of care is provided through the Family Cancer Risk Service, directed by Susan Caro. Selvi Palaniappan (say "pal-NIP-pan"), a cancer genetic counselor, speaks with each patient on the phone to answer questions and determine the patient's individual needs. In addition to coordinating the annual care of VHL patients, counseling and genetic testing is also available to confirm a diagnosis of VHL or to test family members who do not have symptoms.

The most advanced imaging methods are available along with a full team of ophthalmologists, urologists, general surgeons, neurosurgeons, and endocrinologists to manage screening and management of all VHL issues. Adult patients will be followed annually by Jeff Sosman, M.D.[1], professor of Medicine, a kidney cancer specialist, and children will be followed by James Whitlock, M.D., Craig-Weaver Associate Professor of Pediatrics and director of Pediatric Oncology.

Endocrinologist Lewis Blevins, M.D.[2], who has a special interest in VHL, will follow patients annually to monitor for pheochromocytoma. Together with the team of physicians and counselors at Vanderbilt Medical Center, the goal is to provide annual screening and management in a caring environment. The VHL Clinical Center at Vanderbilt Medical Center can be reached by e-mail at selvi.palaniappan@vanderbilt.edu or susan.caro@vanderbilt.edu or by phone at +1-877-688-7555.

1. Sosman JA, Targeting of the VHL-hypoxia-inducible factor-hypoxia-induced gene pathway for renal cell carcinoma therapy. *J Am Soc Nephrol.* 2003 Nov; 14(11):2695-702.
2. Beatie J and Blevins LS, Jr., Pheochromocytoma May Herald a Diagnosis of von Hippel-Lindau Disease. *The Endocrinologist* 1997; 7: 344-353.

Has the VHL Family Alliance made a difference in your life? Please help to keep our services strong, and fund research. *Thank you!*

Research on Fatigue

May be due more to depression and poor physical performance than physiological side effects

Fatigue – a common problem in patients who are recovering from various cancers and related surgeries and therapies – is associated with depression and reduced physical performance and not, as previously suggested, with anaemia, a flagging immune system or other physiological conditions.

That is the conclusion of a German research team, reported July 2004, in *Annals of Oncology*.

Cancer related fatigue – defined as an unusual and persistent sense of tiredness that can occur during or after treatment, may affect physical and mental ability and is not relieved by rest – is the most common and distressing problem for cancer patients after treatment. For many patients it is so severe that it limits normal daily activity.

Lead researcher Dr. Fernando Dimeo said that no one fully understood the origins of this extreme fatigue: among the factors proposed as possible causes were anaemia, impaired nutritional status, sleep disturbances, changes in the concentrations of cytokines (small proteins released by cells that affect the behaviour of other cells) due to the interaction between the tumour and the immune system, impaired thyroid, liver or kidney function, mental and social status and a reduced level of activity.

Dr. Dimeo and colleagues from the Charité University Medical Center in Berlin, studied over 70 patients in remission who had been free of treatment for at least three months. They all underwent physical examinations, answered questionnaires and had a range of blood tests after undertaking a series of physical activities.

"We evaluated possible biological and immunological mechanisms of fatigue. We could find no correlation between fatigue, diagnosis, time since surgery or chemotherapy, renal, hepatic or thyroid function, severity of anaemia, serum albumin concentration, cytokine activity or other inflammatory or immune system markers," he said.

"However, the scores for depression and physical performance in those patients with highest and lowest fatigue scores were significantly different even though there was no difference in the values of laboratory tests for the two groups. The mean depression score of those who scored highly for fatigue was 10 times higher than those with low fatigue scores. The mean performance score of those scoring highly for fatigue was five times lower than those with low fatigue scores."

Dr. Dimeo said that there were some limitations to the study. For example, the information from questionnaires may be biased because of patients' subjective feelings and expectations about physical limitations and may not reflect their actual experience. Also, levels of fatigue can fluctuate in patients with cancer, so longer-term studies may provide better understanding of the causes. However, any patients with side effects or signs of infection that might have been responsible for fatigue were excluded from the study.

"We feel, therefore, that our results reflect a genuine lack of association between fatigue and thyroid, immune, haematological, renal and hepatic function, although these conditions may be a factor in certain patients," he said.

"Impaired physical performance and depression seem to be critical components in cancer-related fatigue although we have not yet clarified the association between the two factors. Impaired performance can result in increased dependence, lower self-esteem, reduced social activities, restricted family life and a pessimistic mood. The patient can also interpret poor performance as a sign of poor health and this increases psychological distress. On the other hand, depressed and anxious patients are more likely to limit outdoor activities and resort to a passive lifestyle, which can result in loss of muscle condition and physical performance."

So, the question now facing the researchers is – is the depression the cause of the poor physical performance or is it the other way round? Or could it be that both these problems are related to a third, as yet unknown factor?

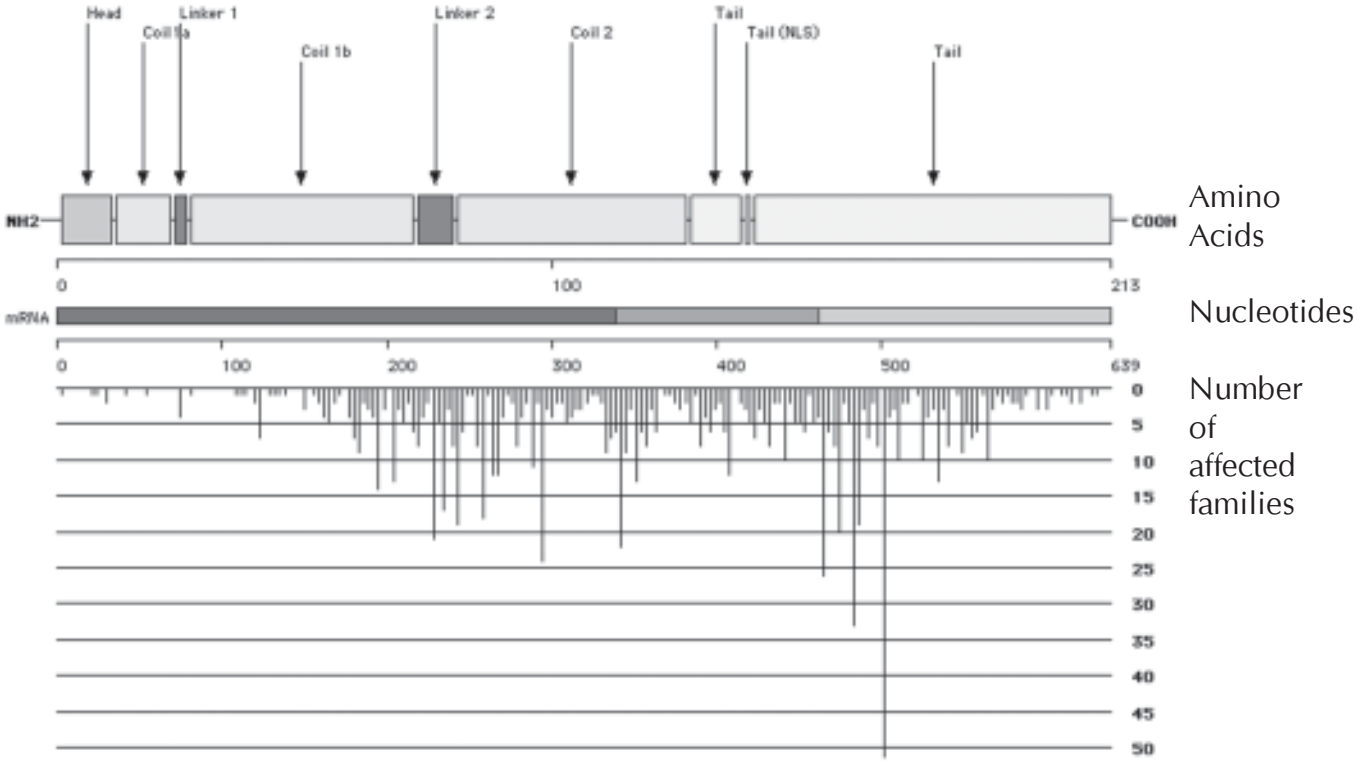
They now plan a larger study. "Although patients who have had major surgery ... may have fatigue that can be related more to nutritional deficits or poor lung function, we feel that our findings may apply to most cancer patients, so we will be examining the correlates of fatigue in further groups of patients," said Dr. Dimeo.

Meanwhile, he added, their existing findings already have implications in the clinic. The diagnostic work-up of patients should include evaluating their workload, psychological status and physical performance.

"There are also treatment implications. In the recent past several publications have underlined the role of anaemia as a major cause of fatigue in patients undergoing chemotherapy. Erythropoetin (EPO) is sometimes given to stimulate the production of red blood cells. But, our findings and those of other studies, show that chronic fatigue in patients who are free of relapse may not be related to haemoglobin concentrations. While all patients with severe anaemia feel tired, a low percentage of patients with chronic fatigue are anaemic."

Source: "Physical performance, depression, immune status and fatigue in patients with hematological malignancies after treatment." *Annals of Oncology*. 15: 1237-1242.2004.
Annals of Oncology is the monthly journal of the European Society for Medical Oncology. www.annonc.oupjournals.org

More than 500 Mutations found in the VHL Gene



compiled by Dr. Christophe Béroud, INSERM, Hòpital Necker, Paris, France.

There are now 501 different mutations registered in the Worldwide VHL Mutations Database, maintained at the Necker Hospital in France by Prof. Christophe Béroud. Each one represents a unique family strain. If two or more families have exactly the same mutation type, they would be seen only once in this database. Thus all the member families in the Black Forest Family in Germany and Pennsylvania count as one.

The accompanying illustration shows the distribution of these mutations along the gene. In blue (the lower scale, marked "mRNA") are the three exons of the gene, with the scale marked in nucleotides. In yellow and green (the wider band marked "NH2"), depicts the different regions of the protein with the scale marked in amino acids.

At the bottom are the number of mutations in each position. Here there is a count of families with mutations in this position.

Dr. Christophe Béroud and his research group at the Necker Hospital in Paris, France, established the Universal Mutation Database on the internet, including the Universal VHL-Mutation Database, at http://www.vhl.org/research

The VHL database includes all published mutations on the VHL gene either in sporadic RCC or in VHL families. This database may be accessed by any researcher, and includes a software utility to query the database online. It also provides a graphical display.

The initial nucleotide numbering scheme (with 505 and 712 mutations) was based on the initial cloning of the VHL gene which did not precisely describe the start and stop markers of the gene. A new numbering system was introduced in the late '90's, where the first amino acid of VHL is number 1. If you know the older number, subtract 213 to arrive at the new nucleotide number, or subtract 71 to arrive at the new amino acid number. It takes three nucleotides to make one amino acid, so there are three times as many nucleotides as amino acids.

For example, the Black Forest mutation (505 in the old nomenclature) is now nucleotide 292 corresponding to AA 98 (292 divided by 3). 712 (old nomenclature) is now nucleotide 499 or AA 167 (499 divided by 3).

This database was developed at INSERM U383 by Dr Béroud and his research group, to assist researchers in identifying the functional parts of the gene, and helping to understand the function of the gene and its protein.

Researchers who use the database are asked to acknowledge in their publications the Universal Mutation Database references listed on the website. Submission of new mutations to the database can be made by E-mail to Christophe.Beroud@igh.cnrs.fr

New Leadership for VHL France

A new set of officers has taken the reins of VHL France. Gilles Bohlinger of Paris is now President. Hélène Sultan and Gil Brunet are members of the Board.

Guy Allegre continues as liaison with the office of Dr. Stéphane Richard, head of the French Study Group on von Hippel-Lindau disease. This is a worldwide group of doctors who speak French, pooling their patients and knowledge to study VHL. It includes doctors from Turkey and Tunisia, and had produced an impressive number of articles both in French and in English. The French group of patients is the second largest in the world, second only to the U.S. National Institutes of Health, and is a more representative cross-section of the VHL patient population than the U.S. group, since it includes all diagnosed patients with VHL in all of France in a single database.

Mireille and Michel Proux were honored this year for their 10 years of service to VHL France. The founded the group in 1993-94, and did the work of incorporating as a registered charity in France. Throughout the 90's the group grew into a network with volunteers providing local support in each region of France. The Proux allied the group with the Nez Rouge, a collaborative fundraising effort for many genetic diseases in France, selling red rubber noses outside grocery stores and at fairs in order to raise money for research, with VHL's portion going to Dr. Richard's group.

Dr. Richard chaired the VHL Symposium in Paris in 1998, with the participation and assistance of the Proux and other local volunteers.

In the last few years, as life has changed for so many of the original volunteers, activities have slowed down and there has not been a patient meeting in France for some years. The new leadership is hoping to change that, and create more visible services again for patients and families in France.

Meanwhile, a vigorous online support group has grown up on the internet, moderated by Gil Brunet, which includes French-speaking people from all over the world, from Canada to the Indian Ocean.

We welcome Gilles, Hélène, and Gil, and wish them great success in the revitalization of VHL France!

Clockwise from top left: Gilles Bohlinger, Gil Brunet, Hélène Sultan. and Erika Trutmann.

New Country Affiliate

by Gerhard Alsmeier, Germany

Beginning September 18 we will have a newly formed group in Switzerland. Up to this point the Swiss have been served through Germany, with Erika Trutmann of Switzerland serving on the Board of Directors in Germany. Chairman of the Swiss group will be Erika's partner, Uwe Graf, and the Vice President will be Regula Eggenschwiler.

We in Germany have strongly supported the idea of setting up a Swiss group, to provide better local services in Switzerland's three official languages. The bonds between the German and Swiss groups will remain strong. We are providing start-up funding for their brochures and handbooks, and our Newsletter will be used in Switzerland, with some Swiss issues. Erika will remain a member of both Boards of Directors. To contact her, write to info-ch@vhl-europa.org

We welcome our neighbor, VHL Switzerland! For more information on this and other countries of Europe, see www.vhl-europa.org, a routing site maintained in Germany for all of Europe.

Un Mot...

Chaque jour qui commence est une page vierge.
Une étendue de temps qui n'a pas encore été vécue.
On peut y écrire ce que l'on veut.
Il n'appartient qu'à soi de décider de réussir cette journée, malgré ses contraintes et ses obligations.
(auteur inconnu au moins par moi...)
Bonnes futures journées... -- *G' île*

Word of the Day...

Each day when it dawns is a blank page
A space in time that has not yet been lived.
You can write on that page whatever you want.
It is up to you to decided to have a good day,
In spite of its constraits and obligations.
Have great days!
-- *Gil B., from the Island of La Réunion, France*

Pre-implantation Genetic Diagnosis (PGD) for VHL

by Wendy K. Chung, M.D., Ph.D.

Preimplantation genetic diagnosis (PGD) offers an alternative to more traditional methods of prenatal genetic testing (chorionic villus sampling or amniocentesis) for couples at risk of having a child with VHL. It allows genetic testing to be performed on early embryos prior to implantation and pregnancy. This provides couples with the opportunity to know that any pregnancy they achieve should be unaffected with VHL and avoids the problem of deciding whether to terminate a pregnancy if more traditional prenatal tests such as amniocentesis identify a VHL mutation in the fetus.

Technical advances in molecular genetics now enable us to diagnose VHL from a single cell of an early embryo without harming the embryo. The information gained by PGD is then used to select genetically healthy embryos for placement in the uterus. Other embryos carrying the VHL mutation are discarded or frozen according to the couple's wishes.

Couples must undergo standard in vitro fertilization (IVF) to use PGD. Healthy, normally developing embryos are biopsied to remove a single cell when the embryo is at the 8 cell stage. The removal of this cell is not felt to affect the health or viability of the embryo or fetus. Genetic testing by molecular genetic techniques using polymerase chain reaction (PCR) are used to genetically diagnose the embryos. The genetic material from the embryos is not altered during a PGD. Unaffected embryos are then implanted in the uterus or cryopreserved (frozen) for future use.

The underlying exact genetic basis (DNA mutation) for your VHL must be known prior to consideration of PGD. Additionally, a laboratory assay must be developed specifically to your mutation and can often take several months to perfect and must be perfected prior to beginning IVF. Few fertility centers in the world have this capability.

I would strongly suggest consultation with a clinical geneticist prior to undertaking this procedure. Genetic counseling is not always routinely included in the IVF process, but it will be important for couples with VHL. I recommend that patients avoid intracytoplasmic sperm injection (ICSI) as part of the IVF since this procedure may be associated with a slightly higher risk of genetic conditions other than VHL and should not be necessary as part of the IVF if the couple has no fertility problems.

The IVF and PGD are not generally covered by health insurance and may cost up to $15,000-$20,000 per cycle depending on your location. It may require multiple rounds of IVF to successfully become pregnant. There may also be risks to a woman with VHL to getting pregnant, so all routine VHL screening should be performed prior to conception and a high risk obstetrician should be consulted to ensure that it is safe to get pregnant.

If you have further questions, please e-mail me at wkc15@columbia.edu.

Wendy K. Chung, M.D., Ph.D.
Herbert Irving Assistant Professor of Pediatrics and Medicine
Director of Clinical Genetics
VHL Clinical Care Center Director at Columbia University

Can any IVF service assist me?

A listing of IVF labs that perform PGD is available at the following website: www.ihr.com. As Dr. Chung describes, however, the actual DNA testing will need to be performed at a special DNA testing facility. Ask whether they are prepared to do single-gene assays, and what their success rate has been. See for example the website of Baylor College of Medicine, www.bcmivf.org/BaylorArt/PreimpGenetic.htm

Is PGD Possible for my Mutation Type?

PGD is currently possible only in cases for which a polymerase chain reaction (PCR) test can be designed. PCR tests can most easily be designed for single base changes or deletions or insertions of one or a small number of bases. Partial or complete deletions of the gene do not lend themselves to PCR based assays.

One family was interested in PGD but the familial mutation was a partial deletion which could not be detected prior to implantation because there was insufficient information on which to base a PCR assay for the deletion.

In cases like this it is sometimes possible to create an assay using an indirect test. It should be noted that this is less accurate than direct testing. There is always some risk that the analysis may be wrong, and in the case of deletions that risk is higher.

Some labs (our own included) are interested in developing a real time-PCR assay to detect deletions in the VHL gene. If we are successful, PGD for families with deletions may be possible in the future.

-- Catherine A. Stolle, Ph.D., Pathology, Children's Hospital of Philadelphia, Pennsylvania. Dr. Stolle is the world's leading expert on DNA testing for VHL.

Tissue for Research

Embryonic and fetal tissue is important for research. Please call our Tissue Bank at please call the VHL Tissue Bank at 1-800-847-1539 to arrange transport. See research project described on page 9

Update on Clinical Trials

Kidney Pre-Surgery Clinical Trial

The Urologic Oncology Division of the U.S. National Institutes of Health (NIH) under Dr. W. Marston Linehan has now opened clinical trial, designed as a pre-surgical therapy for kidney cancer. This initial study will be limited to a small number of people with VHL who need kidney surgery.

Patients will receive a drug, 17AAG from InvivoGen, an analog of geldanamycin, once a week for three months intravenously in Bethesda, Maryland. Then the patient will have a month off before surgery. Once the kidney tumor has been removed, the tumor will be studied under the microscope to help us learn whether the drug is achieving the right response within the tumor.

If this phase is successful, the study will be opened more widely.

To inquire, contact Dr. Marston Linehan, +1-301-496-6353.

The time commitment is significant, but NIH will pay travel costs for U.S. residents accepted into the trial. People from other countries may apply, but would be responsible for their own travel expenses. For more information, see www.vhl.org/trials

Eye Lesions

Dr. Emily Chew at the National Eye Institute of NIH is opening a trial of Lucentis for VHL in September. Lucentis (previously named rhuFab) from Genentech, is a drug recently approved for use with Age-related Macular Degeneration (AMD). It is an angiogenesis inhibitor, injected directly into the eye, hoping to stabilize or shrink tumors of the retina, especially those on or near the optic nerve for which treatment options are limited. The study is limited to testing the effectiveness of the drug on eye tumors. Because of the way it is administered, it will likely have little or no effect on other tumors. To inquire, contact Dr. Emily Chew or her coordinator, Katherine Shimel at +1-301-402-2863 For more information, see www.vhl.org/trials

Research Project needs Fetal Tissue

If anyone loses a child through miscarriage or decides not to use embryonic material left over from IVF, there is a research project that would appreciate donations of VHL-positive embryonic or fetal tissue for autopsy. The goal of the project is to determine whether the seeds of tumors in the brain and spinal cord are in fact laid down during embryonic development and only "turned on" at a later time. Understanding this process may help us control tumor growth. If you have tissue to donate, please call the VHL Tissue Bank at 1-800-847-1539 to arrange transport.

Medical Alert

Caution before taking herbal remedies

-- Dr. Andrew Weil, 19 August 2004 www.drweil.com

Be aware of herb/drug interactions. Herbs and drugs that have similar purposes (such as sedatives, blood thinners, or stimulants) should not be taken together, nor should herbs and drugs with opposite actions (a sedative herb taken with a stimulant drug, for instance). Ask your local pharmacist about any known adverse reactions, or check out the book "Herb Contraindications and Drug Interactions," third edition, by Francis Brinker, ND.

Communicate with your physician. It is important to tell your doctor of any herbs you are taking, especially before surgery. Blood-thinning, sedative, and stimulant herbs may have adverse effects on surgery and subsequent recovery. Some herbs may interfere with prescribed medications, as well. Be sure to disclose any herbs or supplements you are currently taking if a new medication is prescribed.

Avoid taking herbs while pregnant or breastfeeding. There are some exceptions, such as ginger in capsule or candied form and chamomile tea. Always consult your obstetrician for more information to avoid possible complications.

Woman hopes to educate doctors about rare disease

By Scott Rockefeller, Press & Sun-Bulletin, Binghamton, New York, Wednesday, May 26, 2004

Imagine going to your doctor's office with a cold and having to explain to your doctor what a cold is and why you think you have it. Imagine your doctor, and most of the subsequent doctors you see, telling you that you don't have a cold because it is just too rare to have.

You have just, to some degree, put yourself in the shoes of Binghamton resident Cathy Clifford. Clifford, 40, has been living for close to a decade with "von Hippel-Lindau," or VHL, a rare genetic disorder, which causes tumors to form in places in her body that have a high blood flow. Clifford said it took about 10 years, and a long line of doctor's visits, for a puzzled doctor to think she might have the rare condition.

Clifford had surgery for kidney cancer in 1994, as well as a 1996 surgery to remove a cancerous brain tumor. All told, Clifford has had 22 tumors.

Clifford doesn't want anyone in the Southern Tier of New York State to experience what she did on the road to discovering that she had VHL. Clifford, who runs the Western New York Chapter of the Massachusetts-based VHL Family Alliance, has sent a letter to local health providers outlining her history and the facts about VHL.

The VHL Family Alliance has declared May VHL Awareness Month.

"Early diagnosis helps us live a full life," the relentlessly upbeat Clifford said. "Without diagnosis there is no chance of survival."

According to the Alliance, VHL affects one in 32,000 people worldwide. While the vast majority of people with VHL inherited the condition from a parent, about 20 percent of those affected have a new mutation, meaning no one in the person's family has had VHL.

The Alliance also said the child of a person with VHL has a 50 percent chance of having the condition.

For Clifford, the road to discovery began when she was 17. She began going through debilitating spells of dizziness and seemingly out of nowhere, lost the hearing in her left ear. Clifford also had vision and digestive problems.

"I was told there wasn't a disease that affects the ears and eyes like that," she said.

Local doctors told Clifford many of her problems were linked to stress and could be treated with therapy. When her father died of congestive heart failure, and it was later discovered that kidney cancer had spread through his body, she knew something was definitely wrong and she was determined to find out what it was. Clifford, to this day, said she is 90 percent positive her father had VHL, and that many new cases of VHL aren't discovered until an autopsy.

Ten years later, Clifford is preparing to join 600 other VHL patients at the National Institute of Health in Washington, D.C., where she goes about every six months to check on existing growths and find out if there are any new ones. Clifford is confident a cure for the condition will be found, at the genetic level, one day.

"They're so close," she said optimistically. "All I know is if I hadn't been aggressive I wouldn't be here today."

Clifford isn't sure how her open letter to the local medical field will be received. But if it helps doctors discover that even one other person in the area has the same condition, it will be worth it, she said.

For the meantime, Clifford urges anyone who goes to a doctor's office to be thorough in finding answers, as well as paying attention to their own medical condition and history.

"When you go to a doctor you have to tell them everything, not just why you're there that day," she said.

Songs of Love for Children

The Songs of Love Foundation, a group of over 350 talented artists nationwide, creates customized songs for children with chronic illness. Collaborating with over 300 hospitals, private health-care institutions, and with various individual families, they have produced intimate musical portraits (which are never duplicated) for thousands of children and teens.

Their mission is to keep giving encouragement and love to those who need it most through the medicine of music. If you are a parent or health care provider, you can request a personalized song for children battling serious illness, free of charge. Each song is delivered on CD and the song's lyrics contain the child's name and favorite things and people. Visit the website at www.songsoflove.org and fill out a confidential Profile Sheet to request a song.. It takes 4-8 weeks to fulfill a request. For additional information call 800-960-SONG (7664)

Report from VHL Symposium

Kochi, Japan, May 20-23, 2004

Report by Joyce Graff

The conference in Kochi was wonderful. The city of Kochi is very beautiful, and our hosts treated us to the best of Japanese hospitality.

Thursday was devoted to basic science, and the researchers shared some remarkable advances in understanding what happens in the cell. VHL is at the cross-roads of all the angiogenic processes in all cancers, and is now implicated also in colon cancer in the general population. People with VHL are not at higher risk for colon cancer, but when a colon cancer starts in anyone, the tumor shows that there has been damage to the VHL gene that unleashes the growth of the tumor. It's good for us in that lots of pharmaceutical companies are focused on VHL research, trying to learn how to control the levels of VHL, or to normalize the consequences of too little VHL protein in the cell.

Friday we heard reports on new learning from genotype/phenotype alignment and much about the amazing new computer-assisted imaging and surgical techniques. Much of the technology comes from Japan, and there were wonderful demonstrations of laparoscopic techniques and microsurgery facilities to improve the outcomes of brain and spinal surgery.

Dr. Lonser from NIH presented the work his team has done on endolymphatic sac tumors, understanding better how they grow and at what point one should move to surgery, to prevent hearing loss. See page 1 of this issue.

There is also mounting evidence from many parts of the world that it is very important to monitor the central nervous system before symptoms occur, and make sure to operate on a tumor before it becomes too advanced. Dr. Lonser said that most of the tumors he operates on these days are under 3 cm.

Saturday was focused on the families, most of whom were not able to get off work until then. We had translation services from the university, and were able to have very good interaction with them. The families here have not had the benefit of the kinds of meetings we have run in the U.S., so they do not yet understand how best to manage their health. Dr. Shuin is encouraging the Japanese VHL Family Alliance, headed by M. Shinkai, President of the Japanese VHLFA. So far they have a website and online discussion in Japanese.

Dr. Taro Shuin, Urology Department, Kochi Medical School, President of the Congress

We had at least two dozen Japanese doctors in the room through the family question and answer session. There was a panel of eight physicians from all over the world responding to questions, and others listening carefully, learning what the Japanese families are thinking and worrying about. Due to a technical problem, the university translator could only hear a few of the panel members and not the families. One of the family members, Bungo K., did an outstanding job of on-the-spot translation to and from Japanese to facilitate the conversation.

After the meeting some families had to go quickly to meet their buses or trains, but 16 of us stayed together and had dinner at a Japanese restaurant, sitting on cushions on tatami mats at a low table, served by women in kimonos, with delicious food on large platters along the table. Three of the people there were able to help with the language, and we had a lively and delightful conversation.

People are people, all over the world. The concerns they expressed are the same concerns I have heard all over the world. We were two from Germany, one from Australia, one from U.S., and 12 Japanese. There are some cultural differences, due to the different health care system and medical culture, and to the societal pressures in this country, but with those flavor variations it was a conversation that might have occurred in any other country.

We felt that we made some strong bonds with the local families, and will continue to share ideas with them. They learned the benefits of being together. People are always shy in the beginning to attend meetings, not knowing what the experience will be like. This was a great experience for all. We all have the same goal: to live well with VHL and manage our health. We look forward to learning from them and with them as their local organization grows.

VHL in China

-- a report by Joyce Graff

After the Kochi meeting, I went on a vacation trip into China, to visit my friend Dr. Si Yun Shu, Director of the Institute of Neuroscience at the First Military Medical University of China, in Guangzhou, and Chairman of the Department of Neurobiology. I had met her years ago when she was doing a post-doctoral fellowship with my father, Dr. Harry Wilcox, who was a professor of Anatomy at the University of Tennessee.

One afternoon she hosted a conference on VHL for faculty and medical students of the university, and physicians from the hospital. Dr. Kai-Tai Yao, a professor in the cancer center and a member of the Chinese Academy of Sciences, gave an overview of VHL in Chinese.

Then I gave my talk in English about VHL, the VHL Family Alliance, and the Kochi meeting. I talked about the various aspects of VHL and how doctors have been able to increase the rate of diagnosis in other parts of the world. If there is one case of VHL in 32,000 people, then there must be 30,000 people with VHL in China. The keys in other countries have been to raise consciousness among physicians of the various aspects of VHL, to suggest when to screen and do differential diagnosis for VHL, and then in addition to make information available to patients and physicians about how to manage one's health.

They were very engaged and asked very good questions. One doctor asked if there were a VHL Family Alliance chapter in China. I said not yet, but we are of course glad to work with a Chinese affiliate group. For example, a Chinese discussion group on the internet might be the first place to start. With such a large country, high internet connectivity, and such a low rate of diagnosis at the moment, it will be hard to link people together across such distances.

My vacation trip took me on to Beijing, where I met with Dr. Kan Gong, a Urologist, from the First Hospital of Peking University. I had met Dr. Gong at the Kochi meeting.

The members of the Urology Department presented their research to me, each in turn. They are all studying some aspect of VHL, mostly changes in the VHL gene in sporadic tumors rather than focusing on the VHL syndrome. Dr. Liu in particular has a collection of 89 kidney cancer tumors, and has found changes in the VHL gene in 55% of his samples. He has also collected non-tumor tissue from these same patients for comparison, and only one has VHL syndrome.

They are doing some very interesting work on HIF-1-alpha and VEGF. They have published papers

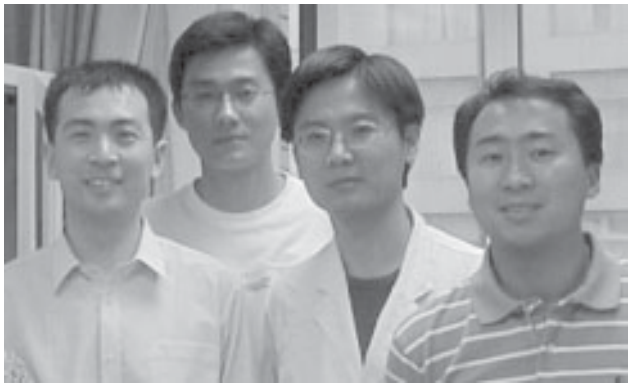
Dr. Si Yun Shu and Joyce Graff in Guangzhou

in Chinese. Through the Kochi meeting they will be connecting with other researchers doing similar work in other parts of the world. Dr. Gong was very enthusiastic about the contacts he made in Kochi.

I gave the presentation I had prepared for Guangzhou and we talked about VHL in China. We talked about strategies that have been used in other countries to raise the rate of diagnosis over the past ten years. This team has currently asked doctors throughout China to refer to them all cases diagnosed with VHL. I said that in other countries it has been helpful to broaden the request -- ask to see all patients with RCC tumors who are under the age of 40, or who have tumors on both kidneys. In this way they are likely to find not only VHL but also other hereditary cases of kidney cancer.

Dr. Gong was very impressed with the family interaction in Japan, and hopes to help create a similar family alliance in China. I said that we would be happy to share information and interact with the group, and explained how we work with other international affiliate groups. It takes a certain amount of energy from the families as well, so we will all look for a few good family members who can help to bridge the language gap and link China with the resources available in English and other languages.

In the two months since these meetings we have come into contact with two new VHL families in China, and Dr. Shu has been helpful in finding a capable neurosurgeon for one patient. We are looking forward to strengthening these new ties with Asia.



Left to right: Dr. Ning Liu, Dr. Zheng Zhao, Dr. Ning Zhang, and Dr. Kan Gong, Department of Urology, Peking University Hospital, Beijing

Cathy Sherman of Birt-Hogg-Dubé symdrome and Florian Hofmann of VHLFA Germany, enjoying a Japanese box lunch at the Symposium in Kochi. BHD is another hereditary kidney cancer syndrome discussed at the Symposium.

Many Thanks for your Contributions!

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cont'd from page 13

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Evabeth Thomas, by Ray & Patricia Larson, Raymond & Maxine Moore
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Birthday Fundraiser in Canada


Wren

-- Trish B., Alberta, Canada

In August 2000, our eldest son (then 21) was diagnosed with 2 hemangioblastomas of the cerebellum. After three neurosurgeries, they were able to successfully remove both tumors. We soon discovered, however, that removing the tumors did not mean that our son was no longer in danger.

It was his neurosurgeon who first explained to us that our son had developed these tumors due to having a disorder we had never heard of before, Von Hippel-Lindau. Over the next several months and after numerous appointments with a variety of specialists, we discovered that it was suspected that our younger son, who was legally blind in his left eye from the removal of a tumor he had developed when he was 17, also had the disorder.

Since then our family has gone through a whirlwind of testing. Unfortunately, genetic testing has been unable to help us define who exactly has the disease in our family and who may not, since our sons' mutations have proven to be hard to find.

We have two other daughters who now go through the regular screening process to ensure they remain healthy. Our youngest daughter turned 10 on January 10th, 2004. This year for her birthday party, in lieu of presents that she really does not need as she has so many toys and clothing items, she opted to ask for donations to either our local food bank, or to the Canadian VHL Family Alliance for research into finding a cure for this disorder.

I helped her to draft up an invitation that would explain what she was requesting and why, and she invited 13 of her friends to her party. The day of her party I was a little concerned that she might regret not having any presents to open, but when I asked how she was feeling about her decision to request donations, she reminded me that she really wants her brothers to be around for a long time so they can see her graduate, get married and raise kids of her own. She also said that she might have this disorder too -- and so could I or her sister -- and so she felt what she was doing was really right.

As she opened each envelope from the kids who came to her party, I was so impressed with both her and them. As the dollars they were donating on her behalf added up, you could see their eyes light up. I believe they were all feeling as though they were a part of a bigger whole, and that with everyone pitching in they had done something really amazing and worthwhile. When I counted up the final amount of $175.00 their eyes widened in amazement and they all clapped and exclaimed, "Wow!"

I promised that I would ensure that you knew exactly who contributed to this donation and why. Thirteen incredible children and their families, along with our daughter who we are really proud of, wanted to make a difference in someone's life. The following is the list of each of the children's names: Ben, Catherine, Michelle, Riley, Cole, Elise, Meaghan, Mikaela, Carmen, Samantha, Juliana, and finally our daughter Wren.

Please accept this $175.00 gift in honour of Wren's 10th birthday, and of her two older brothers, Derrick and Justin V.

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