



VHL Family Forum



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Report from the Paris Symposium

by Berton Zbar, William Kaelin, Eamonn Maher, and Stéphane Richard

Five years after the identification of the VHL gene, physicians, scientists and concerned VHL family members met to review the current state of knowledge on the diagnosis and treatment of VHL and to summarize the latest information on the biochemistry of the VHL protein (pVHL).

Genetic diagnosis of VHL

Groups from the U.S. National Institutes of Health (NIH) and the University of Pennsylvania reported that they were able to detect VHL mutations in 100% of 93 VHL families studied (Stolle et al, 1998). Previous success rates were rarely better than 92%. The improvement in detection rate was attributed to the use of new techniques (quantitative Southern blotting, and fluorescence in situ hybridization), allowing them to detect deletions of the entire VHL gene (Stolle et al, 1998; Pack et al). These deletions of one copy of the VHL gene were not detected by procedures ordinarily used for VHL mutation detection, and can not yet be done by every testing lab. This improved ability to detect inherited (germline) VHL mutations should enable clinicians to distinguish disorders that look like VHL from VHL itself, clarifying difficult diagnoses, and making testing available in families whose mutation could not previously be found.

The use of long range PCR, a non-radioactive method to detect germline deletions in the VHL gene, was reported by C. Cybulski (Szczecin, Poland). The Polish group is sequencing the gene to find breakpoints, to determine whether there are hot spots for germline deletions, places where deletion of several amino acids are more likely to occur.

Detection of VHL mutations in patients with no family history of VHL

Procedures for the diagnosis of VHL in an individual with a family history of VHL are well established. Several studies determined the frequency of VHL germline mutations in individuals with a single manifestation of VHL and no family history of VHL.

These studies provide valuable information for physicians seeing patients with these disorders.

H. Neumann (Freiburg, Germany) reported that 1.6% of 189 German patients with sporadic renal carcinoma had a germline VHL mutation. F.J. Hes (Utrecht, the Netherlands) found that 5% (1/22) of patients with isolated central nervous system hemangioblastoma had a germline VHL mutation. S.A. McKee (Birmingham, England) reported 1 of 42 patients with an isolated central nervous system hemangioblastoma studied to date had a germline VHL mutation. From a national study of retinal angiomas in the United Kingdom (Webster and Maher), it was estimated that individuals with an isolated retinal angioma had a 30% probability of having VHL.

Hes studied 17 patients with isolated pheochromocytoma, (7 with solitary, 4 with multiple or recurrent, 3 with familial and 3 with bilateral tumors). No germline VHL mutations were detected in this group of patients with isolated pheo. S. Giraud (Lyon, France) studied 6 kindreds with familial pheo, and 16 patients with isolated pheo. Germline VHL mutations were detected in 2 of 6 kindreds with familial pheo, and 4 of 5 patients with isolated bilateral pheo.

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Formation of national study groups

National groups to improve the diagnosis and treatment of individuals with von Hippel-Lindau disease have been established in Great Britain, Denmark, France, Holland, Italy, Japan, Poland, and the United States. T. Shuin (Kochi, Japan) reported that 28 Japanese VHL families were identified recently, bringing the total number of Japanese VHL families to 62. Dr. Shuin surveyed different university hospitals in Japan to identify the treatment approaches to VHL renal cancer in these hospitals. Dr. Shuin prepared a VHL web site in Japanese. (<http://www.vhl.org>, choose Japanese language support). C.J.M. Lips (Utrecht, the Netherlands) reported that 24 VHL families have been identified in the Netherlands (approximately 50% of the estimated number of Dutch VHL families). A national network has been set up to promote early detection and improve clinical management.

G. Opocher (Padua, Italy) has organized a coordinated working group for the diagnosis and treatment of VHL patients. This service sees patients from Northern Italy. Facilitated access to different clinical specialists is provided along with a coordinated follow-up. So far, 10 Italian VHL families have been identified. K. Krzystolik (Szczecin) has established a Polish VHL Registry. Seventeen unrelated Polish VHL families have been identified. S. Richard (Paris) described the French cooperative VHL working group which was organized in 1990. Data is available on 650 VHL affected individuals in 165 distinct VHL families. A reference program for managing VHL families is being developed in Denmark (E. Kjeldsen).

Genotype phenotype correlations

No specific type of germline VHL mutation was associated with endolymphatic sac tumors, or retinal angiomas. Neumann identified several new missense mutations. C. Bérout (Paris) described the VHL mutation database which is available on the internet at <http://www.umd.necker.fr>.

Pancreatic tumors in VHL

P. Choyke (Bethesda) found solid pancreatic tumors in 12% of the National Cancer Institute (NCI) VHL patients. Metastases from VHL pancreatic tumors was observed in only 2% of NCI VHL patients with pancreatic tumors. Computerized axial tomography (CT) with contrast enhancement was the best method to screen for pancreatic tumors in VHL patients. In a large series of VHL patients studied with abdominal CT-scan, P. Hammel (Paris) showed that 70% of these patients had some pancreatic manifestations.

Evidence for Modifier Genes

Variation in disease severity among VHL family members (with the identical germline mutation) has been frequently observed. E. Maher, A. Webster, and co-workers (Birmingham and Cambridge, U.K.)

looked for evidence of gene(s) modifying the effects of germline VHL mutations. No clear evidence has yet been found that would lead to a particular modifier gene.

VHL animal models

James Gnarr (New Orleans) described his attempts to produce an animal model for von Hippel-Lindau disease. Previous attempts to produce a "knock-out mouse" (a mouse with no VHL gene at all) have been unsuccessful. Gnarr replaced one copy of the VHL gene with a mutant allele lacking exons 2 and 3, and part of exon 1. Mice that had only this mutant allele died during embryonic life. The cause of death appeared to be defective placenta formation. The placentas in mice with no working VHL gene (VHL $-/-$) had too few blood vessels to be viable. Mice with one copy of the VHL gene (VHL $+/-$) after two years of observation have shown no increase in tumor formation. A number of possible explanations were raised for the failure of renal tumors to form in VHL $+/-$ mice including: (a) insufficient number of precursor cells, and (b) the possible role of other tumor suppressor genes or oncogenes in renal carcinoma in mice. The phenotype or characteristics of the VHL $-/-$ mice was similar to the phenotype of vascular endothelial growth factor $-/-$ mice. Gnarr also presented evidence for interaction of the VHL and the MET proto-oncogenes.

Functions of the VHL protein

A number of chemical functions of the VHL protein have been identified. We do not yet understand all the implications of these function, but we are beginning to understand the particular processes that are influenced or regulated by the presence or absence of the VHL protein (pVHL).

W. Kaelin (Boston) and A. Pause (Martinsreid, Germany) presented studies on the function of pVHL. The VHL protein appears to have several distinct functions. The function that has been studied most intensively is the regulation by VHL of reactions similar to those induced by too little oxygen (hypoxia) including the vascular endothelial growth factor (VEGF) mRNA [building block]. The VHL protein down-regulates VEGF. An understanding of how pVHL regulates VEGF has come from studies of proteins that bind to pVHL. pVHL has been found to form a complex of four substances (a tetramer) with elongins B and C, and Cul2. (See Figure 1.) This tetramer bears structural similarities to tetramers in yeast that participate in the



Figure 1: The complex or *tetramer* formed by pVHL, elongins B and C, and CUL2 is conceptually like a set of gears or mechanical components working together to do a bigger or more complex job than any one of them could do alone.

breakdown of cellular proteins. VHL may participate in the breakdown of proteins that regulate the expression of VHL target genes.

Cells with mutant VHL proteins failed to make a fibronectin extracellular matrix. This defect could be corrected by introducing some normal VHL protein. VHL binds, at least indirectly, with fibronectin associated with endoplasmic reticulum.

Zbar (Frederick, Maryland) reported studies by Ivanov and Lerman that identified carbonic anhydrases 9 and 12 as target proteins of the VHL gene. VHL down-regulates carbonic anhydrases 9 and 12.

Mutant VHL proteins that lacked the elongin binding domain have no ability to down-regulate CA9 and CA12. Mutant VHL proteins with intact elongin binding domain retained some ability to down-regulate CA9 and CA12. Of particular interest, other workers independently described the presence of a unique antigen on the surfaces of clear cell renal carcinoma cells. This antigen (MN), the target of antibody G2250, is identical to CA9. In other words, a cell surface antigen characteristic of clear cell renal carcinoma cells, is regulated by the gene whose mutation leads to clear cell renal carcinoma.

Experimental treatment of VHL

D. Gross (Jerusalem) treated irradiated nude mice grafted with tumor tissue from a VHL patient. Gross showed inhibition of tumor growth by treatment with linomide (quinoline-3-carboxamide) an anti-angiogenic drug. In both the prevention and intervention experiments, tumor size was decreased in the drug-treated mice. Histologic examinations of grafted tumors showed a decrease in blood vessels in the tumors of treated mice. This particular drug has fairly high toxicity in humans, but anti-angiogenic drugs are expected to be helpful in managing VHL. William Kaelin (Boston) reported plans for clinical trials of another drug that inhibits binding of vascular endothelial growth factor with a receptor. (See page 4 for details.)

Treatment of VHL renal carcinoma

The "3-centimeter rule" was described by B. Zbar (Frederick) speaking for the Urologic Oncology Branch, NCI. The policy followed in the management of VHL patients with renal tumors is to delay surgery until one of the renal tumors is equal to or greater than 3 cm. in diameter as measured by computerized axial tomography (CT). No metastases were detected in 54 patients followed at the NCI with renal tumors 3 cm. in diameter or smaller (Walther). Kidney-sparing surgery was the preferred approach when surgery was required. The average observation period was five years. Y. Chrétien (Paris) reported on the surgical treatment of 41 patients with VHL renal cell carcinoma.

No metastases were found where the largest tumor was less than 4 cm. Patients were treated by nephron-sparing surgery. Patients treated using *ex vivo* (bench) surgery had complications so frequently that bench surgery is no longer recommended. In Neumann's series of VHL patients, no metastases were observed with renal carcinomas in patients with tumors less than 7 cm. Three of four patients were treated by nephron sparing surgery. The five and ten

year survivals were 100% and 81%. Huson (Oxford) reported a VHL patient with a renal tumor measuring just 3.2-3.5 cm on CT with metastases to the spinal

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cord. There was broad agreement among the physicians present that 3 centimeters is the best guideline for when to operate on kidney tumors.

Treatment of CNS hemangioblastomas

S. Richard reported that CNS hemangioblastoma remains the most frequent cause of death in the French series of 215 VHL patients (*J. Int. Med.*). M. Niemala (Helsinki) evaluated stereotactic radiosurgery as an alternative to microsurgery for the treatment of hemangioblastomas. Solitary small or medium sized hemangioblastomas usually shrunk or stopped growing after radiosurgery, recommended margin does is 110-15 Gy. The adjoining cysts did not respond to radiosurgery but required drainage, sometimes repeatedly.

Comparative sequence analysis of the VHL tumor suppressor gene

E. R. Woodward (Cambridge and Birmingham) sequenced the VHL gene in a range of primates, Old World monkeys, and New World monkeys. Conservation of genetic structure of the Elongin and Sp1 binding domains was found at the amino acid level in all species analyzed, but changes in nucleotide sequence were detected. This preservation of structure indicates that pVHL performs an important basic function.

Broad Ligament Cyst and APMO

J. Graff (Boston) described the characteristics of cysts in the area of the broad ligament. The tumor is an adnexal papillary cystadenoma of probable mesonephric origin (APMO). The tumors occur in tissues associated with the mesonephric tubules near the ovaries and uterine tubes and in remnants of the mesonephric duct close to the side walls of the uterus and vagina. The name APMO was suggested to replace "broad ligament cysts" since they are not cysts and they often occur below the broad ligament. The VHL Family Alliance is hoping to raise consciousness about this benign tumor in order to reduce possible cases of unnecessary surgery where they may be misunderstood to be more alarming kinds of ovarian or uterine tumors.

Pioneers Needed for the New Frontier

by Joyce Graff, Massachusetts

A medical team under Dr. William Kaelin of the Dana Farber Cancer Research Institute is proposing to conduct a Clinical Trial of a new drug which may have promise in constraining the growth of tumors in people with VHL. The trial is going through the final approvals, and is now expected to begin about January 1999.

Progress is never made without pioneers, people who are willing to venture out onto the frontier and open new territory for everyone. The VHL Family Alliance needs people with VHL to apply to participate in this and the other studies that will be starting up over the coming years. It is important that we show the pharmaceuticals that we will do our part to support innovation in management of VHL.

Clinical trials are not for everyone, and we urge you to make an informed decision based on your own personal risks. Younger people who are basically in good health will probably not want to participate in early trials of any description, as we still do not know what long-term risks there may be. But at the same time, we do need pioneers. If no one is willing to sign on for a voyage that risks sailing off the edge of the earth, we will never find the New World. For those among us whose treatment choices are already limited, we urge you to consider becoming a pioneer. No one can promise you that any experimental drug will be the one that will reverse tumor growth, but the chances now are better than ever before. We can promise that as a community we will learn from these studies, and that it will significantly advance progress toward medical management for all of us.

There is a survey form posted on the internet, or people can contact Dr. Kaelin's team directly at 617-632-4747. Remember that taking this first step is not a final commitment that you will participate, it is an expression of interest. You will be evaluated to determine that you are physically eligible, provided with more detailed information about the risks and potential benefits to you, and then given the opportunity to join the study or not.

This drug is in pill form. It has been specially designed to inhibit vascular endothelial growth factor (VEGF). Dr. Kaelin's team has been one of the key teams in learning about the function of the VHL protein – what it does normally, and what happens when the normal VHL protein is absent. What we know so far is that when there is too little normal VHL protein in a cell, there are higher levels of VEGF, and VEGF has been found in high concentrations around brain and kidney tumors, both in VHL and in other conditions. We are hopeful that this drug will be effective in limiting the growth of tumors

in VHL, and also that it will be helpful against related brain and kidney tumors in the general population. This trial will help to determine whether that is true.

What's the objective of the study?

Volunteers are needed to help determine correct dosage levels for this drug, and then to determine if it is effective in stopping tumors. The study will be divided into two parts. The objective of the first portion is to determine what is a therapeutic dose. Participants will be carefully monitored to see if there is an effect on tumor size, or if any side-effects appear. This portion of the study will be limited, and the criteria will exclude many people with VHL. However qualified participants with VHL will be very important in this phase.

The second portion of the trial is meant to determine the effectiveness of this drug, specifically on the tumors of VHL. Two groups of subjects will be included, measuring the effect upon brain tumors and upon kidney tumors. Participants will be monitored to determine whether brain and kidney tumors can be reduced in volume, and new tumors kept from forming. This portion of the trial will begin once sufficient information has been gathered from the initial portion to determine the dose of the drug that is safe and well tolerated. This will possibly occur as early as summer 1999. This second portion of the trial will enroll only VHL patients.

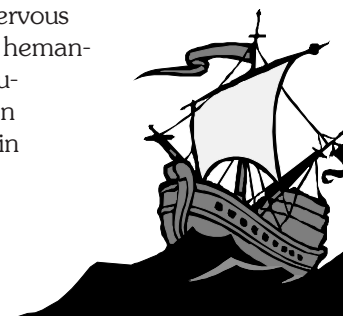
What is the time commitment?

People who participate in the second portion of the trial will need to come to Boston for 1-2 days of testing at the beginning of the trial, and then again once a month for 1-2 days. After the fourth month the intervals may be spaced out somewhat longer, but people should plan on monthly visits.

People who are accepted into the study will be required to have DNA testing. It is a requirement that participants have a confirmed diagnosis of VHL, and that they know their mutation. DNA testing is now available through any geneticist in your own area. It is recommended that samples be sent to the University of Pennsylvania testing lab, 1-800-669-2172

Who is eligible?

The first portion of the trial is restricted to VHL patients with inoperable kidney cancer and no central nervous system lesions (no brain heman-gioblastoma, no spinal tumors). This is a common restriction in early trials in general. People with CNS involvement will be considered for the second portion of the trial.



Participants in the second portion of the trial must have

- One or more cerebellar hemangioblastoma(s) with a measurable solid component
- Or one or more Renal cell carcinoma tumors of less than 3 cm. in size, with or without cerebellar hemangioblastoma
- Or people with inoperable kidney cancer, with or without cerebellar hemangioblastoma

All participants must be 18 years or older, in reasonable health (not bed-ridden, not seriously anemic or suffering from other unresolved medical problems). See details in box.

For further information on this study, please contact Dr. Kaelin's office directly at 617-632-4747, Fax 617-632-4381, or write to Dr. William G. Kaelin, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115.

What Questions Should I Ask?

The NCI brochure *Taking Part in Clinical Trials: What Cancer Patients Need to Know* is available free by calling 1-800-4-CANCER, or on the internet at <http://cancertrials.nci.nih.gov/>

How Can I Get to Boston?

If you are not in the immediate Boston area, there are resources that may be able to assist you.

The National Patient Air Transport Helpline (N-PATH) maintains current data on all known charitable, charitably-assisted, and special discount commercial long-distance air medical transport options. Call the hotline at 1-800-296-1217 (or see <http://www.npath.org>) to request assistance. We have already contacted them about this study. The operator will take your information and work to assist you.

The Corporate Angel Network (CAN) provides free air transportation for cancer patients traveling to and from recognized treatment centers in the United States without regard to their financial resources. CAN arranges for patients to use empty seats on corporate aircraft operating on business flights. Call 1-914-328-1313 or see <http://www.corpangelnetwork.org>

Who is eligible?

The first portion of the trial is restricted to VHL patients with inoperable kidney cancer and no central nervous system lesions (no brain hemangioblastoma, no spinal tumors). People with VHL lesions of the brain or spinal cord may be eligible to join the second portion of the study.

Participants in the second portion of the trial must have

- One or more cerebellar hemangioblastoma(s) with a measurable solid component
- Or one or more Renal cell carcinoma tumors of less than 3 cm. in size (such that they are comfortable that the tumors can be watched and do not require conventional treatment), with or without cerebellar hemangioblastoma
- Or people with inoperable kidney cancer, with or without cerebellar hemangioblastoma

All participants must:

- Be 18 years or older
- Have a Karnofsky performance status of greater than 70. This is a measure of overall well-being, and serves to exclude people who are very feeble (bed-ridden)
- Have an essentially normal white blood cell count
- Have a hemoglobin greater than 9 g/dl (are not seriously anemic)
- Have a platelet count greater than $100 \times 10^9/L$
- Have liver function tests within 2.5-fold of upper normal limits
- Have a serum creatinine less than or equal to 2.0 mg/dL (normal is 1.5)
- Or creatinine clearance of an acceptable level (greater than 30 ml/min). This drug is metabolized by the liver and does not rely too heavily on renal excretion, so this is less restrictive than studies for many other drugs.
- Have a life expectancy greater than 3 months
- Sign a written informed consent

Who will be excluded from the study?

For the second portion of the trial, participants with any of the following conditions will not be eligible:

- Prior bone marrow or stem cell transplant
- Pregnant, or at risk of becoming pregnant. All participants (male and female) will be required to practice reliable birth control throughout the period of the study.
- Other severe or uncontrolled medical issues (uncontrolled diabetes, heart failure, infection etc.)
- Acute or chronic liver disease
- HIV positive
- Disease which might interfere with the absorption of the drug (e.g. gastrointestinal disease that interferes with the absorption of the drug, such as diarrhea from pancreatic insufficiency)
- Taking coumadin
- Have received any investigational drugs within 4 weeks prior to the start of the study, or have not recovered from the toxic effects of such therapy.
- Have had chemotherapy, biological therapy, or immunological therapy within 4 weeks prior to the start of the study, or have not recovered from any side effects of these therapies prior to the beginning of the study
- Have had radiation therapy or surgery less than 2 weeks prior to the beginning of the study, or have not recovered from that surgery or radiation
- Have active non-VHL malignancies, other than non-melanoma skin cancers
- Other VHL-related tumors (other than brain or kidney) that require treatment at the time of study entry.

For further information on this study, please contact Dr. Kaelin's office directly at 617-632-4747, Fax 617-632-4381, or write to Dr. William G. Kaelin, Dana-Farber Cancer Institute, 44 Binney Street, Boston, MA 02115.

Managed Care

by Altheada Johnson, New York

I attended a telephone conference sponsored by Cancer Care called "Managed Care: What you need to know" in June, 1998. The speaker was Kim Calder, Associate Executive Director of the National Alliance of Breast Cancer Organizations (NABCO).

Fee-for-Service vs. managed care means there are three parties rather than two. The choice of providers is limited to those in the Health Maintenance Organization (HMO), and you and the provider have less control over medical decisions.

There is lots of managed care jargon. It is very important to understand all the alphabet soup. Ask lots of questions when things are not clear. Understand the type of plan you have and the role of health professionals in your plan. With HMOs, providers are divided into generalists (family doctors) and specialists. Family doctors are the gate-keepers. They decide how much service you need from a specialist.

Understand how your plan works. Plans are controlled by law, type and group size. Know and read your Membership Handbook or Guide. Understand your rights and responsibilities. It is not your doctor's responsibility to know how your plan works. The doctor may participate in several different plans.

The advantages of managed care plans include lower out-of-pocket cost, no claim forms, and lower premiums. Checkups and preventive care are covered. HMOs are good at keeping people healthy, but not very good at helping people with chronic illnesses like VHL and cancer. The disadvantages include the fact that only the services of the 'network' provider are covered. You must obtain authorization to see a specialist, medical decision-making is subject to review and approval of the plan, and problems arise when patients have complex health problems.

When a request for service is denied, you should file an appeal or grievance. It is very important to follow the guidelines given for appeals in your membership handbook. Secure support from your family physician, specialist or their office personnel and focus on the decision being appealed. Appeals are usually worth the time and effort, and doctors are usually good at justifying their request for treatment. If legal action is necessary, make sure there is good evidence of the need. A letter from a lawyer is often helpful -- even if it's your brother-in-law. However, if further legal advice or action is needed, make sure you have someone with expertise in insurance claims.

Helpful numbers:

- Your local Bar Association for a lawyer with expertise in insurance issues
- Your state's Department of Insurance (in the blue pages of U.S. telephone books)
- Patient Advocate Foundation 1-800-532-5247

Ask the Experts

DNA Testing...Again?

Question: My family was tested for VHL in the past. We were told that they did not find the mutation, but that they did not feel the test was reliable for our family. Are the tests better now? Is it worthwhile to send blood samples again? -- Jennifer O., Michigan

Answer: Yes, it might very well be worthwhile to send your blood samples again. Early tests were only reliable for families where the mutation was known; for families with other alterations in the gene, the reliability was very low. With advances in our knowledge about the VHL gene and advances in gene sequencing technology, we can now find more than 98% of all VHL gene mutations. This is not true of all labs. Your doctor can check the "hit rate" statistics on Helix to determine a lab's accuracy rate. The labs at the University of Pennsylvania and that at the University of Kansas have the highest hit rates in the U.S. -- Roberta Pagon, M.D., Genetics, Children's Hospital Medical Center, Seattle, Washington

How Long Should it Take?

Question: I went in for DNA testing over a year ago, and have still not received my results. How long should I expect testing to take? -- Helen S., Calif.

Answer: People who pay to submit blood samples to a clinical lab should expect to obtain results within two to four weeks. While previously it could take many months to sequence the gene, today's technology has sped up the sequencing time. Each lab has slightly different equipment, but they should be able to tell you when you submit your sample when to expect results. The most efficient VHL testing labs are in Pennsylvania and Kansas.

People whose blood samples are submitted through a research protocol may experience delays due to staffing issues or conflicting priorities in the lab. If you are not a paying customer you do not have much control over the length of time that may pass. They may not be obligated to advise you of the results at all.

Check with the geneticist through whom you have submitted the samples. Two weeks will usually be the minimum; two months may be understandable if your mutation has not previously been found; more than that is excessive. If these avenues don't work, you can escalate your concern.¹ If necessary you could ask your personal physician to obtain the results directly from the lab (with a release form signed by the patient). -- Joyce Graff, Co-Chair, VHLFA

1. Escalate your concern to the administration of the hospital, or to the Internal Review Board that governs research projects for that hospital; to the VHL Family Alliance 1-800-767-4845 or info@vhl.org; or to the American Board of Medical Genetics (Tel: +1 (301) 571-1825; Fax: +1 (301) 571-1895; <http://www.faseb.org/genetics/abmg/abmgmenu.htm>, which confers diplomate status on geneticists throughout the world.



Maria and the Baby Seals

-- Maria S., Pennsylvania

I know that my story is not unique, and that many of you have had the same experience or worse. I had a hemangioblastoma removed from my brain about five years ago. My doctor told me everything was fine and sent me home. Nothing to worry about. But I still had symptoms.

My family doctor felt that my medical conditions were beyond his knowledge. I requested copies of all my medical records and began searching for an internist. Reading through my medical records, I saw a report from the hospital stating that I should be checked for von Hippel-Lindau disease. I called up my doctor and asked what it was. He wasn't sure, but it had something to do with tumors. "Just have a CT scan of your brain done every year, and you'll be fine." Being the type of person who has to know, I went to the library and looked it up. There was one paragraph in a medical dictionary, giving very little information -- information I now know to be wrong. The librarian suggested she do some research -- I received two pages on VHL with a referral to the National Organization for Rare Disorders (NORD). They in turn referred me to the VHL Family Alliance.

The first time I called, I spoke to Barbara Redding. After I got my info packet, I called again. Peggy Marshall helped me so much, not only with the information I needed about VHL, but also emotionally. I had been through doctor after doctor and was told that it was nothing. I had been given wrong information. Nowhere was I given the level of complete information that I have received from the VHL Family Alliance.

I finally found a doctor in Pennsylvania who knew about VHL. While I was waiting in his office, I saw on his wall a picture of a baby white harp seal with the words under it: "Save Us". I felt just like that seal, alone and frightened, scared that I was going to be beaten down by this disease. I wanted all the doctors to "Save Us" with proper screening and testing. I'll never forget that picture. I kept thinking about it and how people with VHL feel. I have that picture hanging up in my living room now and every time I look at it I am reminded of all of the people with VHL that are saying the same thing.

It was right after this visit to the doctor that Peggy asked me if I was interested in starting a chapter in Pennsylvania, I jumped at the chance. I feel Pennsylvania needs to be more informed about this disease that is not so rare, just under-diagnosed. I wouldn't want anyone else to go through what I did to find information about VHL. I need to let the medical professionals in Pennsylvania know what VHL is and how to screen for it. I feel I can do that much here in Pennsylvania.

Needless to say, I now collect pictures and figurines of baby white seals.

Atlanta Meeting

June 4-6, 1999

"This educational conference brings together consumers and health care providers as well as educators and the latest research information. Such a consortium is a paradigm for sharing information," says Dr. Louis J. Elsas II, Professor of Pediatrics and Biochemistry at Emory University School of Medicine. "The Division of Medical Genetics, Emory University, is proud to co-sponsor with the VHL Family Alliance the Sixth International Patient/Provider Conference on von Hippel-Lindau." Dr. Elsas will co-chair the meeting with Eva Logan, chair of the Georgia Chapter of the VHLFA. Eva welcomes y'all to Atlanta and invites you to join us at the Sheraton Colony Square Hotel, 188 14th Street, N.E., Atlanta, Georgia 30361.

Families gain a once-in-a-lifetime experience of meeting others with this condition, and the leading physicians and researchers with expertise on this disease. Physicians gain insight into living with a rare disorder, and the diagnostic techniques and treatment options that can make a world of difference in a patient's quality of life.

Emory University will award up to **14.5 hours of continuing medical education (CME) credits** for doctors who attend this meeting. Final registration is not yet set, but will be approximately \$125 for most attendees, and \$180 for those obtaining CME credits. Credits for nurses, dietitians and genetic counselors can also be arranged. Please inquire.

We need you to make the experience complete! Start shopping now for inexpensive airfares, or saving up those frequent flyer miles! Nearby businesses may also be willing to donate frequent flyer miles to help with your transportation. Sessions are planned from noon on Friday the 4th through noon on Sunday the 5th. The hotel is about 30 minutes from the airport, and shuttle service for \$10 per person one-way is easily available. Advance reservations are recommended for wheelchair service. Call 404-524-3400.

Reservations must be made directly with the hotel before May 5 to qualify for the VHLFA conference rate of \$99 for up to four adults in one room. Call Sheraton at +1-404-892-6000, or 1-800-422-7895 (U.S. outside Georgia), or fax to 404-733-6997.

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the Emory University School of Medicine and the VHL Family Alliance.

The Emory University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians. Emory University School of Medicine designates this continuing medical education activity for up to 14.5 hours in Category 1 credit toward the PRA of the AMA. Each physician should claim only those hours of credit that s/he actually spent in the educational activity.



Volunteers Making a Difference

Help in a Crisis -- Robin K., Texas

On January 8 of this year my husband Joe was diagnosed with VHL.

We had never heard of VHL and were very confused and scared. He had brain surgery on January 9th. The next week CT scans showed multiple cysts and tumors on both kidneys. We were told by three urologists, a nephrologist and an oncologist that total removal of both kidneys was the only way to save Joe's life.

Three days prior to his total nephrectomy I called the VHL Family Alliance 800 number to see where we could have his kidneys sent for research. Peggy Marshall answered the call. She listened to my story, my fears and anxieties. Then she shared with me information that would change the course our life was taking. She told me about the research and more conservative surgeries the doctors at NIH are performing.

Within hours, two other ladies had called and shared their stories with me concerning VHL kidney cancer. We called NIH the next day, and Joe had his first surgery about two and a half weeks later. On March 9th, the surgeons removed 17 tumors from his left kidney, but saved about 80% of his functioning kidney. On June 11th, he had 12 tumors removed from his right kidney, and 90% of the functioning kidney was saved.

Tests performed in June all proved his left kidney was functioning great after the March surgery.

Words cannot express how thankful we are. Not being faced with dialysis or a transplant at age thirty is a blessing for Joe. He is doing wonderfully and has an incredible attitude. The surgeons at NIH are quick to remind us that this is not a "cure," but a setting back of the clock ten or twenty years. We understand that, but are thankful for any time to let research continue and technology advance.

Joe and I are Christians and give our Lord praise for strength, answered prayers and guidance these past six months. We believe He directed our path, which led us to the VHL Family Alliance. Peggy Marshall gave me hope and inspired me when I was in my darkest hour. We had no idea there were people living active lives with VHL. The Alliance is so important to newly diagnosed families like ours. We would have never received such valuable information from our local doctors. Our deepest appreciation to the Alliance for all you do is sent from myself, Joe, and our two young sons.

...**Thank you** to everyone who helped in this crisis, and a special Thank-You to **every one of you** for the miracles you create through your gifts and efforts.

A Letter of Thanks -- Fran M., Michigan

Please accept my sincere appreciation for the honor you have bestowed on me by selecting me as the 1998 Chapter Chairperson of the Year. VHL is a fight ... a war, if you will ... for some people. To win a war, you have to know your enemy. I believe knowledge is power and the information provided by the VHLFA conferences helps me to understand my enemy. When there is a calm in the storm and my personal battle with VHL is not raging, I realize that VHL is simply, albeit unfortunately, a part of my life. I want to understand myself, including this part of me.

For making all of this help and information possible -- the conferences, the *VHL Family Forum* newsletters, the web page, the 800 line support -- I want to express my heartfelt thanks to the VHL Family Alliance.

I will proudly display the lovely plaque that was sent to me. As much as I feel privileged to receive this award, I feel even more gratified to have been able to be of service to the VHL community and the physicians in my state. My greatest reward comes not from the VHLFA, but from other VHL patients and their families. Being a chapter chairperson in Michigan has been the most fulfilling experience of my life.

Years ago, I felt desperate, helpless and alone with VHL as I searched for information to help my daughter, who was confronted with a kidney tumor at a young age. Joyce Graff and others showed me I was not alone, and compassionately directed me to and guided me through a maze of conflicting information.

When I help someone else, as Joyce helped me, I receive the best reward of all. When someone thanks me for my help, sends a note or card, or calls just to let me know how they made out, I know the time I spend doing chapter work is well worth it. When an excited patient calls to tell me their good scan results, I feel their joy as though it were my own.

I want to also lovingly thank my husband, Mike, and my children, Molly and John, for their understanding and patience with me. They have willingly shared me with many other people they have never met and whose names they will never know. They have helped me lug displays and tables to other cities in every weather condition. They have stayed by my side through a lot, and respected my desires and goals.

A special thanks to the skilled and compassionate VHLFA Clinical Care Program Physicians in Michigan, the VHLFA Board of Directors and Medical Advisory Board, and the wonderful volunteers and members who generously donate their time, talents, and emotional and financial support to help us in the search for a cure.

Keeping Up with Jay

Jay Platt: This hike is a great test of personal endurance and perseverance.

The weather has been bad, and I have days when I just don't want to hike. I have headaches, I just don't want to get up, and it's awful hard to get out there. But I push through it. I'm committed to completing the hike, my wife Paz and my many friends in the VHL Family Alliance are committed to supporting me in doing it, and I'll get through it.

I have to really dig down into myself and go on when I don't feel good. I realize I'm lucky compared to a lot of other people. We all could do more than we do. We have to get out of our "comfort zones," way beyond what we know we can do well. I'm not stupid -- I won't put my health at risk -- I know how to push myself without danger. A lot of the depression I feel is just fatigue. It's easier to quit, of course. Your mind argues with itself all day: half tells you it's enough, why push yourself, just stop; the other half tells you to keep going, you can do it. Attitude counts, much more than the physical strength. It's 90% mental, 10% physical.

Jim C, New Jersey: I met up with Jay in Mass. Sunday October 11th and hiked for a day with him. I had a great time. He kept telling me that I didn't hold him up -- Yeah, right! My practice 15-mile hikes on flat trails here in Jersey in no way compared to the barely 9 miles I walked in Jay's dust.

With a 50+ pound pack, Jay hikes faster than I walk normally. I would have had to slow-jog to keep up with him. (Jay is 6', I'm 5'6", so his stride is longer than mine). Besides the height and conditioning gap, Jay uses two adjustable walking sticks that Paz gave

him. The man rivals a mountain goat. The only time I kind of caught up was when Jay was going down some steep, rock slopes. No more than 3 minutes later, Jay would disappear into the trail ahead, (usually straight up) and I'd occasionally hear his sticks clicking through the woods.

Overall, things went about like I thought they would. I had fun experiencing my limitations, and hearing Jay talk about his situation will help me with my own upcoming medical experiences with VHL. I really don't think anyone can really comprehend what Jay is doing. I don't have the words to express it. It's just phenomenal.

Maria S., Pennsylvania: Jay was nothing like I expected. I expected someone older, heavier and

serious. He was tall and lanky, having lost 25 pounds already on this hike. He was friendly, humorous and down to earth. He had a friendly smile, and kind twinkle in his eye.

I showed him the fruit I had brought for him, and he was like a kid at Christmas time. He said he loves kiwi and eats the skin and all! He was also glad to see strawberries! He couldn't thank us enough! He ate and drank like there was no tomorrow. It was such a pleasure to see him eat like that. I really felt like I was doing something for him for a change, since I felt like he was doing this hike for me. Me and thousands of others with VHL, both diagnosed and those not yet diagnosed.

He seemed so hungry and thirsty! We talked about him and how he was doing as we ate. We relayed stories back and forth. I asked him if he was in any pain, and how his head was doing, since I know he has a brain tumor and I know what that feels like. He told me he had headaches a few times, and they were getting bad enough that he had to take extra strength aspirin. He also had dizzy spells. He was explaining to my girls what it felt like. He said it was like covering one eye, and spinning around and around until you get dizzy.

I felt a jolt in my stomach as he told me this. I guess until then, I really didn't realize what this man was actually going through. It made me even prouder to know him and sad to think he wanted to do this to raise money so others wouldn't suffer and to maybe come up with a cure so none of us would have to deal with this for the rest of our lives life.

Let's keep up with Jay! If every one of us could raise just \$100 we could more than meet our goal. So let's do a little bit extra, let's stretch beyond our "comfort zones" and push beyond. What can you do to help? Send your donation now.

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“

Jay, I want to congratulate you on your worthwhile enterprise. It has touched me very much. My prayers and my thoughts will be with you during your arduous trek. My contribution is a small token of my appreciation. Best of luck!

-- Micheline L., Mexico

”



Hi! The enclosed are checks from my co-workers in support of Jay. What a guy!!" -- Michelle S., BMS Management, Texas

VHL Family Forum

Our Thanks to those who are Keeping Up with Jay! Donations sent in honor of Jay's efforts:

Lynn Andrews, Tennessee
Rob Athans, Ohio
Robert R. & Helen Aylmer, Virginia
Don & Lori Bazinet, California
Betty Beebe, Tennessee
David J. Behnke, Connecticut
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Susan Burgoon, by Barbara Smith
Alice Coday, by Stephanie Armacost
Our son John Stewart Duval, by Stewart & Mary Frances Duval
All our good friends, by Joyce Graff
Damon Graff, for his patience and persistence, by Joyce Graff
Lawrence Harper, by Barbara Smith
Altheada Johnson, by Gregory & Cynthia Martin
Janie Kelting, by Andres & Luran Jack
Becky & Jean Lima, but Tony & Darva Berkompas, Carolyn & Howard Rubin
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Jean Lima, by Becky & Peter Lima
Robert Lydon, by Clare O'Brien, Indiana
Fran Mott, Molly and John, by Pauline & Donald Kwiatkowski, Henrietta Nash, Carol Werner
Jodi Scheitler, by Mike & Martha Gengler

Vol 6, No. 3, September, 1998

Eugene Tokar, by Lucy Znak
Lisa Wolyniec, by Rebecca & Nathan Wolyniec

Read article about S/Sgt J. Platt in *Navy Times*. Glad to help an all-volunteer organization.
-- Stu C, Washington

In Memory Of...

Blanche Binall, bu Sharon Lutazzi
Howard Caldwell, by Harry & June Wilcox
Don Chew, by Mr. & Mrs. Morris Cole; J.D. & Janice Duff; Joseph & Theresa Fischer; Mary & William Lax; Peggy & Don Marshall; Albert L. Meena, M.D.; Mr. & Mrs. Mike Osborn; Rapid Delivery Service, Inc.; Marge Render; Leroy & Jean Stram
Joe & Marie, by Lois P. Erickson
John Duquette, by Bernadine Gertz
Roy Fangman, by Vicky & Stanley Palmer
John C. Graham, by Sally & Robert Bayer, Lisa & Randy, Rebecca & Nathan Wolyniec
Frank Warren Graff, by Joyce Graff
Charles Hall, by Tondra Bolinger
Madge Hall, by Jerry Nicks, Arlene Southard, L. Zuidweg
Peter & Viola Hunsberger, by Grace Moyer
Patricia Kelly, by Kathleen & Shaun Kelly, Jane Shaner, Marielle Zuidweg
C. Michael Kruse, by Sharon Lutazzi
Josephine Pasternack Miller, by Bernadine Pasternack, Stephen Pasternack, Lillian Piechota, L. Zuidweg
Meg Moody, by Tom & Nancy Lusk
Frank "Todd" Osborn, by Frank & Georgia Osborn, Kathi Osborn, Julie, Robert & Mario Sanchez, and and Becky Osborn
Sharon Pastway, by Tania Durand, Sharon Lutazzi
Barry Regal, by Sharon Lutazzi
Mark Remenar, by Frank Remenar
Denise Garfield Rouleau, by James Lunny
Vernon Schlesselman, by Helen Dankenbring
Larry Stockman, by Helen Dankenbring
And Special Thanks for Special Efforts:
Our champion team at the Irish Women's Mini-Marathon, Dublin, for \$8,250
Lou Antosh, LA Communications, Inc., Cinnaminson, New Jersey
Maria Shipton and Larry Sutton, Pennsylvania
Kivex Corporation, Bethesda, Maryland, for hosting our website
Donations received through United Ways throughout the country
Patti & Ken Kohlen and their charity dinner that raised \$1,900 for VHL Research
Eva Logan and the Silent Auction Committee in Atlanta for \$6,025
BTD Manufacturing, Detroit Lakes, Minnesota, for a grant of \$10,000
BMS Management for their collective office
Rockfish Gap Outfitters, Waynesboro, Virginia
Pharmaceutical Strategic Initiatives, Cary, North Carolina
REI Outfitters, Cary, North Carolina

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Iowa: University of Iowa Medical Center, Iowa City. Ann Muilenburg, Coord. Tel: 319-356-2674; Fax: 319-356-3347.

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* **Minnesota:** Mayo Clinic, Rochester. Mary Kelly, Clinic Coordinator, or Vicki Couch, genetic counselor. Tel: 507-284-8198; Fax: 507-284-0161; E-mail: couch.vicki@mayo.edu

New York: Mount Sinai Hospital, New York City. Jane Halperin, M.S., Neurology, Tel: 212-722-1784; Fax: 212-860-6629.

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Washington: University of Washington, Seattle. Robin L. Bennett, M.S., Division of Medical Genetics, Tel: 206-548-4030; Fax: 206-543-3050.

Please let us know about your experiences with any Clinical Care Center. Thank you!
Clinical Care Committee, 1-800-767-4VHL, vhccc@vhl.org

Editor's Mailbag

"I am a third generation VHL survivor, I was diagnosed with VHL at age 15 and am now 33. I have lost the sight in one eye, and have had kidney and spinal tumors.

I have a question about the "two-hit theory" introduced in Jay's article in the September issue of VHLFF. For those of us with this disease, it takes a great deal of concentration and energy to deal with VHL. Does this "two-hit theory" now imply that we also need to worry about what we may have exposed ourselves to in the environment that caused the tumors to grow? I'm glad that Jay got his retirement, but was this just a means to an end? The last thing that a VHL survivor needs is to spend their energy figuring out who or what to blame for their disease."

-- *LoriAnn, Minnesota*

The "two-hit model" is a well respected theory of how familial cancers work, and was not invented for Jay's case. It was devised over 20 years ago by Dr. Alfred Knudson of the Fox Chase Cancer Research Center in Philadelphia, and twenty years of research have endorsed this theory.

You are quite right that the last thing we need is to lay blame. In Jay's case, he successfully demonstrated to the Marines that while they were not to "blame" for VHL, they could also not be held "blameless." We now know that environmental factors do play a role, and the Marines put him in

contact with some pretty strong chemicals in the high-risk category. Jay is certainly not to "blame" for his illness either! The insurance system in this country is in serious need of reform because the traditional ways we have spoken about "pre-existing conditions" just don't work any more now that we are learning about genetic predisposition factors. The bottom line is that everyone needs health care to keep them well, happy, productive, and paying taxes, and as you describe, exercises in laying blame are a waste of time and energy.

Should you worry about what factors in the environment may have started your tumors in motion? Don't let it become a focus of your attention -- you have much more important things to worry about -- but if you have a theory, please send it along. Your theories are as good as those of the experts, and might assist us in identifying them. For example, they have found that some juvenile diabetes is kicked off by a mild allergy to cow's milk. Does that mean that a parent of a child with juvenile diabetes should be "blamed" for giving the child cow's milk? No. We didn't know, and it's a normal thing to do. One of these days we will identify what kinds of environmental factors can cause those second hits. It could be something as ordinary and innocent as a mild allergy to cow's milk. It will be useful information that will permit us to reduce our risks, but it should never be about "blame". You'll see more in future issues on this topic. -- *Joyce Graff, Editor*

Therapy for the Brain

Editor's introduction: Brain tumor patients and their families have long noted a variety of temporary difficulties in thinking, changes in emotions or emotional response following brain surgery. It has always been difficult to talk about. The doctor says "you're cured," but you feel that something is different. It makes sense that brain tissue, like muscle tissue, is injured by the surgery itself. Just as with muscle tissue, the brain requires time to heal.

Two recent publications have addressed this issue in constructive ways, identifying the issues and suggesting ways to get your brain back into shape.

Dr. Christina Meyers of the Department of Neuro-Oncology at M. D. Anderson Cancer Center has done extensive work with brain tumor patients, identifying the cognitive (or thinking) and emotional changes people sometimes experience, and developing strategies for rehabilitating the brain, similar in concept with physical therapy for the muscles. Her study¹ of rehabilitation of the brain following surgery for malignant brain tumors, was conducted at the Challenge Program at the Texas Institute for Rehabilitation and Research (TIRR). Most patients required treatment for one to four months. (See article that begins on page 13.)

In addition to her strategies for rehabilitation, the observations in this study are the strongest arguments seen to date for pre-symptomatic screening for brain tumors. Since slow-growing tumors tend to cause few deficits, and fast-growing tumors with intra-cranial pressure or the "mass effect" cause the greatest deficits, it will be important to deal early with cystic lesions, before they grow to critical dimensions. Imagine taking a lemon and putting it inside your skull. No matter where you put it, it creates intense pressure on every part of the brain.

Dr. Mark Sherer, a neuropsychologist who is Director of the Challenge Program and co-investiga-

The observations in this study are the strongest arguments seen to date for pre-symptomatic screening for brain tumors.

tor for the study, concurs with Dr. Meyers' opinion that some brain tumor survivors can benefit from focused rehabilitation treatments.

"The brain tumor patients in our program," says Dr. Sherer, "often have a more dramatic turnaround than the others we treat who may have had a stroke or suffered a traumatic brain injury. Some of their improvement is due to our teaching them a specific strategy, such as how to get around a memory problem or to improve communication skills."

"But, he continues, "another big part of the effectiveness of rehabilitation is due to a shift in thinking on the part of the brain tumor survivor. They shift from being a patient who's having things done to them to being a person who feels as if they are more in charge of their lives. They begin to see some hope and to see that there are possibilities out there for them."²

Diane Roberts Stoler, a health and sports psychologist, who herself has sustained brain injury, created a reference guide for people who through automobile accidents, sports injuries, work-related accidents, physical assault, head trauma -- or brain surgery -- may experience mild traumatic brain injury (MTBI). Having gone through the experience of MTBI herself, Stoler set out to provide help and information for other MTBI survivors, their families, and their friends.

Both craniotomy (surgery inside the skull) and even stereotactic radiosurgery (without opening the skull) can produce mild injury to brain tissue, or swelling and pressure changes inside the skull, which will result in MTBI. The book offers practical suggestions for coping with the problem. Also covered are financial, insurance, and family issues; the rehabilitation process; and eventual outcomes. (See article beginning page 15.)

1. A more complete article on this subject is C. Myers et al, "Efficacy of Post Acute Brain Injury Rehabilitation for Patients with Primary Malignant Brain Tumors," *J. Clinical Oncology*, 1997.

2. As quoted in M. C. Blakeman, "New Study Proves Benefits of Rehabilitation for Brain Tumor Patients," *Search*, newsletter of the National Brain Tumor Foundation, Fall 1996.

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 Clinical Care Committee: +1-708-687-7080 or vhlccc@vhl.org
 VHLFA Internet Web site: <http://www.vhl.org>
 NORD Web site: <http://www.rarediseases.org>

See you in Atlanta!
See page 7 for details.

Gifts that Support Research

"Pierre Jacomet's rendition of the Goldberg Variations by J.S. Bach is a stupendous performance! It is absolutely fascinating because of the outstanding high virtuosity and unequalled inspiration. Hetty and I would like to buy 30 CD's to give as gifts this season."
 -- Dr. Hartmut P.H. Neumann, Germany

"I just finished watching the VHL video -- WOW!!!!!! I was so impressed I can't wait to order my own copy! It was great to put faces to the names I've been hearing and reading about, as well as those I e-mail. It really helped on a day I needed it. Thanks again"

-- Sue A., North Dakota [see page 19 to order](#)

Rehabilitation Strategies

By Christina A. Meyers, Ph.D., ABPP, Neuro-Oncology, M.D. Anderson Cancer Ctr, Houston, TX.

The World Health Organization classifies the impact of neurological changes in three areas: impairment, disability, and handicap. Each is a separate question:

An **impairment** or deficit is a physical change, a disruption of a neurological connection in the brain that involves neurological, cognitive, and emotional changes.

A **disability** is a reduction in the ability to perform activities because of the neurological impairment. For example, a change in vision or perception caused by a right hemisphere brain tumor, which causes difficulties in visually scanning or inattention in the left visual field, may impair an individual's ability to read, which is a disability.

A **handicap** is described as a disruption of the social role of the individual and the ability to function within the family system, at work and in society. Handicap is generally what is referred to when discussing quality of life.

The severity of the handicap depends upon the unique circumstances of each patient, his values, temperament, occupation, amount of family support, access to services, and so on. A person can be handicapped by a relatively small disability, or a rather severe impairment may cause little handicap. For example, disability in reading may not be particularly handicapping to the occasional reader, but might cause a secretary to lose a job. Thus all three levels of function (deficit, disability, handicap) need to be assessed for appropriate treatment of the brain tumor patient.

Neuropsychological testing is the method of assessing cognitive or thinking impairments caused by brain tumors and other neurologic illnesses. This testing is fairly comprehensive, since patients with lesions in different locations will have different types of impairments and there are different patterns of cognitive deficits association with radiation and chemotherapy effects. The functions generally assessed in the neuropsychological examination include attention, memory, reasoning, speech and language, visual-perception, executive functions (frontal lobe), motor coordination, and mood.

The tests should also address the specific concerns of the patient and family. Our survey of spouses and caregivers of primary brain tumor patients reported most concern with problems such as forgetfulness, inability to work, doing less housework, problems with reasoning and problem-solving, and lack of motiva-

tion. In contrast, the concerns least cited include difficulties with balance, walking, continence, dressing and speaking.

Cognitive effects of brain tumors

Because brain tumors such as the hemangioblastomas of VHL arise slowly, they usually cause milder and more variable cognitive impairments than do strokes in the same location. *The rate of tumor growth is also important.* Tumors that are extremely slow growing over years may give rise to virtually no cognitive deficits, while tumors with more "momentum", or a fast-growing cyst, may cause severe impairments. In general, cognitive impairments in brain tumor patients are related to the site of the lesion. Patients with left hemisphere tumors usually have lower scores on tests of language function, verbal learning and memory, verbal reasoning and right-sided motor dexterity, while patients with right hemisphere tumors have difficulties with visual-perceptual skills, building objects and left-sided motor dexterity.

Impairments of frontal lobe executive function (manifested by impairments of cognitive flexibility, abstraction, motivation, planning and organizational skills, ability to benefit from experience, personality changes, etc.) are frequently seen in brain tumor patients. One reason is that the frontal lobes make up one-third of the brain, so a large proportion of brain tumor patients in general have frontal lobe tumors. People with VHL very rarely have frontal lobe tumors, but they may also have executive deficits. This is due in part to the fact that the frontal lobes are connected

to all other parts of the brain, and in part to the "mass effect" caused by increased pressure. Tumors in the cerebellum can cause disruption of the connections between the brain regions in addition to

problems with eye-hand coordination. The effects of treatment (radiation and chemotherapy) generally cause problems with information-processing speed, executive functions, memory, concentration, and motor coordination. Table 1 describes the cognitive deficits attributable to the tumor versus treatment effects.

Quality of life (QOL)

Many brain tumor patients experience increased emotional reactivity, lowered frustration tolerance, and reduced family functioning. One study found that 29% of patients were anxious and 21% were depressed. Mood and personality change tend to be separate from cognitive problems. The location of the tumor

Source/Site	Common Deficits
<i>Brain tumor</i> Left Hemisphere Right Hemisphere Anterior (but can occur in any location) Cerebellar	Language, verbal reasoning, right-sided strength and dexterity Visual-perception, visual construction, left hemispatial inattention, left-sided strength and dexterity Executive functions Eye-hand coordination, concentration, memory (especially for learning skills), executive functions
<i>Treatment</i> Subcortical white matter	Neurobehavioral speed, memory, bilateral motor dexterity, executive functions

Table 1: Cognitive Impairments in Brain Tumor Patients

may also have an impact on the type of mood and personality changes that are seen.

QOL functioning of brain tumor patients cannot be separated from their family and social environment. The disease can cause changes in life-style and roles for family members as well as for patients. Uncertainty regarding the disease history and outcome is a source of stress for the family.

Intervention strategies

Unfortunately, some brain tumor patients are unable to resume all of their normal activities following diagnosis and treatment. However, there is a great deal that can be done to maximize most patients' ability to function at the highest level possible. Given the right support, most VHL brain tumor patients can improve their ability to function at home and in work and leisure pursuits, and enjoy an improved level of independence and quality of life (see Table 2). Relaxation and focus can be enhanced by biofeedback of Galvanic skin response or electromyographic feedback, or simply by relaxation therapy, meditation, self-hypnosis, and the like.

Pharmacologic strategies

Neurobehavioral slowing is very common in brain tumor patients. Stimulant treatment, such as Ritalin, can be useful in the treatment of concentration difficulties, slowed motor and cognitive function, and fatigue, and can help to elevate mood as well. Unfortunately there is not yet long-term experience with this agent to determine what doses are most effective and for how long.

Rehabilitation strategies

Physical, occupational, and speech therapy.

Rehabilitation strategies for neuro-oncology patients should be directed toward their specific disabilities and realistic future goals. These include physical, occupational and speech therapy to help regain function. For instance, approximately 15% of brain tumor patients have difficulties swallowing although many will not report specific complaints and may be at risk for aspiration and choking. Over one-third of patients have some speech difficulties at diagnosis, which may include word-finding problems, difficulties understanding speech, problems with reading or writing, or a combination of communication problems. This suggests a large role for speech therapy in the care of the brain tumor patient. Patients who have developed weakness or incoordination may benefit from physical and occupational therapy to help improve their ability to walk and perform activities of daily living.

Cognitive and vocational rehabilitation. A preliminary study showed that when brain tumor patients were given cognitive and vocational therapy, these patients required shorter stays, had less treatment costs, and better overall outcome in terms of independence and productivity compared to patients with traumatic brain injuries. Cognitive rehabilitation is designed to improve independence level. Vocational rehabilitation is designed to improve productivity, which may include volunteer work, performing household activities, going back to school, working at

Table 2: Intervention Strategies

<i>Pharmacologic</i> Stimulant therapy	Attention, psychomotor retardation, fatigue
<i>Rehabilitation</i> Physical therapy Occupational therapy Speech therapy Cognitive Vocational	Physical mobility, locomotion Upper extremity function, activities of daily living Communication skills, swallowing Independence, specific neuropsychological deficits (e.g. memory, problem-solving, social behavior); relaxation, focus (through biofeedback, relaxation therapy, meditation) Productivity in vocational, educational, home, and leisure pursuits
<i>Education, Counseling</i>	Coping skills of patient and family

a modified job, or maintaining competitive employment.

Education, counseling, and support groups.

Patient and family education is also extremely important. Even subtle cognitive and personality changes may have an adverse effect on social and vocational functioning. Patients who experience these symptoms may wonder if they are going crazy or inaccurately attribute their symptoms to other causes. Patients and families may feel isolated and alone or "unusual" in experiencing neurobehavioral symptoms. The more

knowledge a patient and family have about the disease, treatment, and expected problems, the more effectively they can deal with the care of the patient. Even simple coping strategies, such as taking intermittent naps, writing notes, and taking special care to plan and organize activities, may be all that is necessary to effectively cope with symptoms. Support groups and counseling can also be very helpful in assuring patients and families that their experiences are not unusual, and help them deal with the grief, anger, frustration, and other problems that are frequently manifested over the course of the disease.

Coping Strategies

From *Coping with Mild Traumatic Brain Injury* (Avery Publishing Group, 1998) by Diane Roberts Stoler, Ed.D., and Barbara Albers Hill.

Lynn, a 26-year-old dental hygienist, was driving to work one morning when her car was rear-ended at a red light. The fifteen-mile-per-hour impact caused no damage to either vehicle, and the seat belt kept Lynn's body in place. Only her head moved, quickly snapping forward and back. Lynn felt momentarily disoriented, but the feeling passed, and she went on her way without giving the matter much thought.

By lunchtime, Lynn had a severe headache. She discounted it as stress related. By evening, she also felt nauseated and extremely tired. At first, Lynn suspected a virus. But as the days passed, her headaches escalated and her fatigue increased. She also began to have problems sleeping, concentrating, expressing herself, and making decisions. To her patients, coworkers, and family, Lynn seemed uncharacteristically short-tempered and forgetful. Their continuing remarks to this effect led the puzzled young woman to see her physician. The eventual diagnosis? A mild traumatic brain injury (MTBI), a result of the months-ago incident at the traffic light.

Lynn's story is not at all unusual. In fact, each year more than 2 million Americans suffer mild head trauma from falls, blows, collisions, sports injuries, and violent head movement such as whiplash. In addition, people who undergo brain surgery, or whose heads are treated with radiation, are similarly affected. Like Lynn, a significant number suffer debilitating aftereffects for months or years afterward – despite a perfectly normal outward appearance. Part One of the book *Coping with Mild Traumatic Brain Injury* will help you better understand this phenomenon by providing a detailed look at the causes, significance, and evaluation of mild traumatic brain injury (MTBI).

Part Two of the book covers specific physical symptoms and consequences of MTBI. We present information about the nature of each problem, why it occurs, and how it can be identified and treated. This will help you and your family to understand what you are experiencing, and to make informed choices about treatment.

Effects such as fatigue, headaches, dizziness, sexual issues, vision problems, hearing problems, sensory and metabolic disturbances, muscular and motor problems, and seizures are described, reasons explained, and strategies offered for alleviating the problem. We present here some excerpts from the chapters on Fatigue and Relationships.

Fatigue

"Prior to my MTBI, I maintained a very busy day. I would rise at 7:00 a.m., get my children off to school, go to the gym for two hours, have lunch, see five or six patients a day, and do supervision. After dinner, I would spend time with my family and end the night by writing progress notes on my patients until 11:00 p.m. Even at that hour, I had enough energy left to play my guitar and talk on the phone with my friends.

"After my MTBI, I spent the first two months sleeping nineteen hours a day. When I was up, I felt very fatigued all the time. Currently, my energy is limited to the hours between 8:00 a.m. and noon. By 1:00 p.m., the fog starts rolling in, making me feel inefficient or, at worst, spacy. By 3:00 p.m., my day is virtually over.

"I've learned to cope with my fatigue by doing my writing or other thinking activities in the morning, when I have more energy. On my worst days, I cook dinner at noontime for my family or have my sons Brad and Alan do the cooking. One afternoon a week, I update a grocery list that I store in my computer, and shop with my youngest son, Alan. He helps keep me on track at a low-energy time of day."
– D.R.S.

MTBI fatigue has several different aspects. Each of them deserves attention during the treatment process. Sleep disruption may be the underlying cause of your exhaustion. Lost energy reserves may be the problem. Perhaps it is mental fatigue that troubles you the most. Or you may find yourself struggling with two of three of these problems. The following are a number of tried-and-true tactics to help combat each facet of fatigue. You may wish to experiment with a few of

these suggestions to see which ones best help you maintain control over this bothersome symptom:

- To fight sleeping problems, go to bed at a set time every night, regardless of how you are feeling. Allot at least six but not more than ten hours for sleeping each night, and make it a point to rise at the same time every day, whether you have slept well or not.
- Limit your intake of fluids after 8:00 p.m. to avoid having your sleep disturbed by a full bladder.
- Avoid taking naps if possible. Brief snatches of sleep can play havoc with your body's ability to get a full night's rest.
- Take pain medication as prescribed to minimize the possibility of interrupted sleep.
- To cope with physical fatigue, organize your daily activities according to a priority list. This way, by the time you become fatigued, your most important responsibilities will have been taken care of.
- Avoid getting overtired. This can set you back for days. Pace yourself, take frequent rest breaks, and solicit the help of others.
- Vary your activities to avoid monotony, but do not try to tackle more than one task or activity at a time.
- To combat intellectual and emotional fatigue, avoid excessive stimuli such as sound and light.
- Acknowledge your limited thinking capacity, and use it wisely. Schedule activities that require concentration for times when you are freshest.
- Ration your mental energy carefully during a week that contains a big event.
- Use shortcuts. For instance, prepare a general grocery checklist on which you need only add or delete items. Ask a family member to draw simple maps of the places you need to go. Combat memory problems with a pocket-sized tape recorder, math problems with a calculator.
- Take periodic rest breaks. If you feel a wave of fatigue coming on, sit or lie down and relax.

MTBI fatigue strikes different people in different ways. That physically leaden feeling, that frustrating loss of focus, and the inability to get a decent night's sleep are all common aftereffects of brain trauma. These problems can occur individually or in any combination.

Recovery from MTBI fatigue, which typically takes six months to a year, usually begins with a slow, sporadic return of surplus energy. As with many symptoms, you will start to have good days – but you will have occasional relapses that are difficult to predict. Often, the reappearance of a mental second wind in the early evening will be the first sign that your fatigue is beginning to abate.

There is no simple cure for fatigue, but using appropriate medication, modifying your surroundings and activities, and rationing your stores of energy can bring relief and a welcome sense that you are regaining control of your life.

Living with Someone with an MTBI

An MTBI affects everyone whose life is touched by the injured person, particularly family and friends. How these important people are affected, and the way in which they respond, can affect an individual's recovery process and eventual outcome.

"My mother, who has had several strokes, is very understanding, because she has gone through many of the same experiences as I have. However, my extended family has offered limited support because they've done little to educate themselves about my problems. Sometimes I feel like I'm the caregiver and must enlighten everyone, and this is a burden I do not want. I want to feel free to just get better and get on with my life. My saving grace has been psychotherapy, my cyberspace confidantes, and my steadfast friends, who have accepted me and my unpredictability without judgment.

My husband and I have gone to marital counseling to help us cope with my MTBI. I've learned to accept my limitations, lack of reliability, and unpredictability. I've also

discovered that it's okay to have someone look out for me. My husband is discovering that my responses aren't always reliable, and that it's not productive to get angry when I do things that he feels are unwise or unsafe." – D.R.S.

Living with an individual who undergoes the personal changes associated with traumatic brain injury is not easy. It is important to remember that feeling anger or frustration at times is normal, and that despite these feelings, you deserve a great deal of credit for the support and assistance you offer daily. The following are a number of tactics that can help make it easier to deal with a loved one who has had an MTBI:

- Ask your loved one's neurologist about the medical reasons behind the MTBI person's behavioral and other problems. Simply understanding what is really going on may help reduce your frustration.
- Educate yourself about the nature of your friend's or family member's deficits.
- Realize that a person with MTBI passes through several very difficult phases during recovery. Learn about each stage and try to devise fresh approaches to dealing with it.
- Ask the brain-injured person about how he or she feels, and accept these feelings as real.
- Help the injured person set realistic goals and formulate strategies for achieving them. Track your loved one's progress with a success log, and give him or her full credit for everything he or she accomplishes.
- Get to know the new person, and appreciate him or her not in comparison to the old person, but as a valid and worthwhile individual.
- Accept your frustration as normal, but express angry feelings to someone other than the injured person.

“ Life breaks everyone, but some people become stronger in the broken places.
– Ernest Hemingway ”

Did You Know . . .

that you can write in VHL Family Alliance as your preferred charity in a United Way campaign?

Find other people in similar situations through support groups and on-line computer services.

- Avoid letting your physical or emotional reserves become drained. Discover what activities refresh and rejuvenate you, and schedule time every week to pursue them.
- Focus on the strengths and talents that your loved one still possesses.
- Help your friend or family member learn to live in the outside world again by taking walks together around the yard, neighborhood, and town.
- Find out about services that provide assistance to people with MTBI in the home, workplace, and community. Your local rehabilitation center can advise you as to the types of help that are available.
- Consider personal, couple, or family counseling if coping with your loved one's MTBI is causing emotional or marital problems.

Finally, it is important to realize that you need not be solely in charge of your loved one's recovery. Many types of assistance and support are available to you and the person with MTBI. If you are not sure what type of help you need or where to begin looking, call your state brain-injury association or the national office of the Brain Injury Association for advice and referrals.

Caring for a friend or family member after an MTBI is a huge undertaking, but you need never shoulder the job alone. The ordeal can be lessened by the realization that many postconcussive symptoms lessen with time. Dealing with a person with MTBI takes patience ... patience ... patience.

On with Living Again

There will be days when your judgment is off, when your memory is unreliable, or when you cannot seem to get past your pain. So too will there be times when you are able to function very well. Don't forget that before your MTBI, you had good days and bad days, too. Remember that conditions as varied as the barometric pressure, hormonal changes, foods, medication, and the stress of daily living can affect you. Be kind to yourself and use your energy wisely – but don't be afraid to live life. Mourn the loss of the "old you" and enjoy learning all the good things about the "new you". Take a few risks, find humor in everyday things, and reconnect with friends and family at your own pace and on your own level.

The words of the Serenity Prayer provide excellent advice to help you forge through adversity to a new quality of life: Accept the things you cannot change, change the things you can, and try to recognize the difference. Here's wishing you life, and living again!

3. Excerpted and adapted from *Coping with Mild Traumatic Brain Injury* (ISBN 0-89529-791-4) by Diane Roberts Stoler and Barbara Albers Hill, ©1998, pages 5, 49, and chapters 4 and 24. Published by Avery Publishing Group, Inc., Garden City Park, New York, 800-548-5757. Used by permission.

A Word to Grandparents

– Mary Pinkata, M.S., Arizona, excerpted from "A Handful of Hope," a booklet for grandparents of children with serious medical issues.

When your grandchild has been diagnosed with a serious medical issue, it opens a new and very different chapter in your relationship with your grandchild and with your own child.

New beginnings are never easy, especially when traveling in uncharted territory. Your adult son or daughter will be on an emotional and physical roller coaster trying to juggle their time, energy, and resources in order to cope. Give them the gifts of patience and understanding, and your love, care, and concern.

Some things are beyond our control including a diagnosis of a hereditary disease. However, we do have control of the attitude we choose to develop. A positive **attitude** will make a world of difference to yourself, your child, and most importantly, to the well-being of your grandchild.

Talk to your son or daughter. Let them know you are there to support them. Ask them to tell you specific ways you can help.

Take good care of yourself, so that you can cope with the stress and have the energy to help out if you are asked. Consciously strive to get enough rest. Exercise. Eat good meals. Keep nutritious snacks available, instead of junk food.

Recognize your feelings and allow them to be expressed, either by keeping a journal or talking things over with a trusted friend. A few meetings with a member of the clergy or another professional counselor can also be a big help.

Get in touch with other grandparents who have faced a similar situation. This provides a wonderful way to share feelings and ideas and to keep a positive attitude. [Call the VHLFA hotline, and ask to be put in touch with another grandparent.]

Your grandchild is a **child first**. The disease is only a part of him or her. Recognize his or her talents and abilities. Avoid rewarding any negative behaviors.

Balance your time and your attention among **all** of your grandchildren. Don't favor or ignore the one who is sick.

Please note: For families with von Hippel-Lindau disease, a diagnosis of VHL may also bring a request for you to participate in genetic testing. This is important to determine whether others in the family may be at risk for VHL. VHL may occur for the first time in a grandchild, as a random occurrence in nature, or it may have lain relatively dormant in a family for one or more generations. Your participation may be key to saving the life and health of others in your family.

A Handful of Hope is available from Pilot Parent Partnerships, Inc., 4750 Black Canyon Hwy, #101, Phoenix, AZ 85017.

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1999 Calendar Features Member Art

The 1999 VHLFA Calendar will be sent to all members as our gift to you, to thank you for your support now and throughout the year.

This year's calendar, created and edited by Lisa & Pierre Bonneau and the Arizona chapter, features the winners of this year's art contest! Many thanks to everyone who submitted art work for consideration. The five winners are:

Heidi Walter, Ohio
Donna Jones, Louisiana
Lisa Bonneau, Arizona
Altheada Johnson, New York
Joyce Graff, Massachusetts

Get your entries ready for the Year 2000 Calendar!

They're going fast! Order soon to get copies for your friends and relations.

"We love the little VHL calendars. It's a great design, and this year's calendar has art work from several members -- what a nice momento from "the Family"! When I see it on my doctor's desk, I know that there's a little space for VHL at the top of his large stack of things to do." -- *Sherri D., Tennessee*

"Karen Koenig's beautiful book of poignant poetry, and Patricia Foote's book of practical suggestions for managing your own medical journey are powerful views into the lives and hearts of others with VHL."

-- *Joyce G., Massachusetts*

See below for ordering information.

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*On the Trail for VHL*

Let's Keep Up with Jay!

October 30, 1998

Dear Jay:

Welcome to Harrisburg! As you reach the half-way point of your remarkable journey on the Appalachian Trail, I wish to commend you for your courage and commitment to helping those afflicted by von Hippel-Lindau Syndrome. You are truly a hero in every sense of the word.

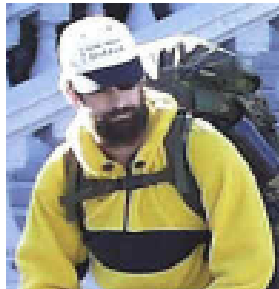
While your efforts to raise money for further VHL research are exceptional, the great value of your mission lies in the hope that your perseverance is providing to others. In heightening public awareness of this disease, you have shown that no obstacle, medical or environmental, can defeat the human spirit.

Your footsteps on the Appalachian Trail may be solitary, but you are not alone in your pursuit. Today I join those who have gathered here to greet you, and the thousands of Americans afflicted by this disease, in support of your mission. Best wishes as you continue your journey.

Sincerely,

Arlen Specter

Arlen Specter, United States Senator
(Republican from Pennsylvania)



Jay has now gone more than half the distance, and has raised \$37,000 as of December 1 -- how about you?

How much can you contribute to match Jay's effort?

A penny a mile for \$21.60?

Ten cents a mile for \$216?

A dollar a mile for \$2,160?

Jay's part in accomplishing his goal is walking the entire 2,160 miles of the Appalachian Trail -- a phenomenal effort of courage and persistence.

However, without your contribution, he still will not reach his ultimate aim of raising \$100,000 to support research and education to conquer VHL.

Please give what you can . . . and help us reach other potential donors.

Together we can change the world!

Your contributions are working! See this year's Research Report for exciting progress, and pages 4 and 18 of this issue.

VHL Family Forum

Newsletter of the VHL Family Alliance
171 Clinton Road
Brookline, MA 02445-5815

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