VHL Family Forum

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Endolymphatic Sac: Hearing Loss in VHL

-- reporting a paper by Thomas J. Manski, MD; Dennis K. Heffner, MD; Gladys M. Glenn, MD, PhD; Nicholas J. Patronas, MD; Anita T. Pikus, MA; David Katz, MD; Robert Lebovics, MD; Kathryn Sledjeski, MS; Peter L. Choyke, MD; Berton Zbar, MD; W. Marston Linehan, MD; and Edward H. Oldfield, MD[1]

Endolymphatic sac tumors (ELSTs) are extremely rare in the general population. While some of the aspects of von Hippel-Lindau disease (VHL) were reported as early as 1884, ELSTs were not described until a century later. While there had been a few isolated cases reported of people with VHL having invasive tumors of the temporal bone[2], until now there was no definite linkage between VHL and ELST (see Figure 1).

A new study[1] from the National Institutes of Health reports that hearing loss and ELST are frequently associated with VHL and should be considered when screening individuals at risk for VHL and when monitoring patients with an established diagnosis of VHL. Many patients with VHL have hearing loss even when an ELST is not visible on an MRI. It could be that there is an ELST which is too small to be seen on the MRI, or there may be other causes of hearing loss, we just don't know yet. Audiologic[3] evaluation and MRI should allow early detection and help to limit or avoid hearing loss in people with VHL.

In 1993, Lois Erickson and other volunteers on the VHL Family Alliance hotline noticed that a number of people with VHL were reporting hearing issues ranging from ringing in the ears and Menière's disease[4] to severe hearing loss. About the same time, researchers at the National Institutes of Health had noticed that several of their patients with VHL had invasive tumors of the temporal bone and endolymphatic sac.

To determine if hearing issues and ELSTs are a component of VHL, a research team at the U.S. National Institutes of Health (NIH) under Dr. Thomas Manski undertook to look back at the records of 374 people whose brain MRIs were on file at NIH, 121 of whom have VHL. Thus in this MRI grouping were 253 MRIs of people screened but *not* diagnosed with VHL.

Medical records were reviewed and telephone interviews conducted to detect history of hearing loss, tinnitus, or vertigo. The results of that study showed that there was a relationship between VHL and some degree of hearing disturbance. 33 people with evidence of ELST on their MRI (10 of these 33 people), or with persistent or recurring symptoms of hearing loss (32 of them), tinnitus (23), or vertigo (11) were asked to return for further radiologic and audiologic evaluation. The 30 people who accepted underwent MRI and CT focused on the petrous[5] bones. In addition, the team reviewed the findings from four VHL patients with ELSTs referred to the Armed Forces Institute of Pathology (AFIP) and analyzed the 13 prior case reports of tumors in the petrous bone of patients with VHL. This grouping, which has some overlap with the MRI group, consisted of 37 people specifically selected for ELST or hearing issues.

For the hearing issues group, MRI was performed on the internal auditory canal and the petrous bones. These people also underwent complete audiologic (hearing) and otolaryngologic (ear, nose and throat) evaluations. Audiologic assessment included psychoacoustic[6] measurements of pure tone and speech stimuli, studies of middle ear integrity, and electrophysiologic studies of cochlear and auditory

Inside this issue!

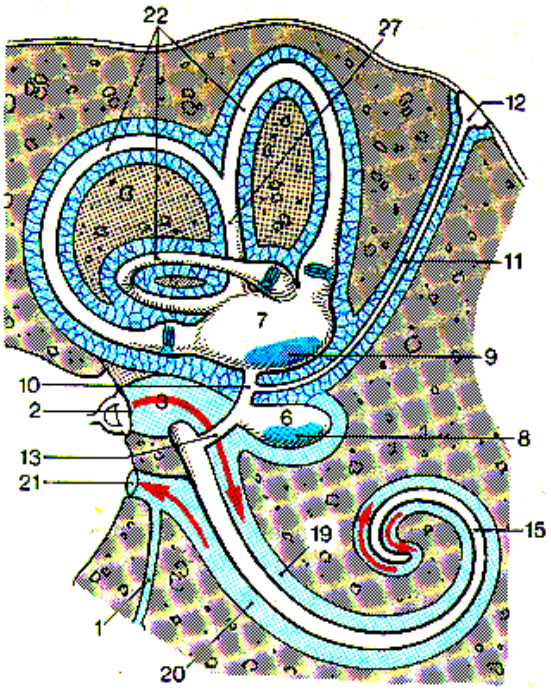

Figure 1: Endolymphatic sac. The endolymphatic duct (11) runs from the inner ear to the posterior surface of the petrous bone and ends beneath the dura at the boundary of the brain as a flattened expansion, the endolymphatic sac (12). Illustration by Gerhard Spitzer, as published in Color Atlas and Textbook of Human Anatomy, *3:319, by W. Kahle, H. Leonhardt, and W. Platzer (Georg Thieme Publishers, Stuttgart, 1978).*

brainstem function. VHL gene analysis was also performed for some of these patients.

The next 66 patients seen at the VHL clinic were also evaluated in this same way, with complete audiologic and radiologic examination for hearing issues and ELST. This group was a relatively random selection of people with VHL, with perhaps some greater percentage of people with hearing issues, since the VHL Family Alliance was actively referring to NIH people with hearing issues.

In the MRI grouping, 13 of the 374 patients had petrous bone lesions consistent with ELSTs visible on MRIs. Two people had bilateral lesions. Thus MRI revealed 15 ELSTs in 13 (11%) of the 121 patients with VHL, but no ELSTs in the 253 patients without VHL. These 13 patients experienced hearing loss (13), tinnitus (12), and a variety of symptoms of dysequilibrium (8). Only one person had some loss of muscle power in the facial muscles. Of those with some hearing loss, the loss occurred between the ages of 12 and 50 years (average = 22) and had been there for 3 to 31 years (average=15.3 years). In 8 (62%) of these people, hearing loss was their first symptom of VHL. Five people (38%) reported a sudden complete loss of hearing on the side with the tumor. The four patients with complete hearing loss on one side and invasive temporal bone tumors larger than 2 cm.

	With VHL	Without VHL
Number of people	121	253
Number of ELSTs	15	0

Figure 2. Of 374 MRIs reviewed at the National Institutes of Health, 15 ELSTs were found in 13 people. While 11% of the 121 patients with VHL had ELSTs, no ELST were found in the patients who did not have VHL.

underwent removal of these tumors. Each was definitely identified as an ELST.

Audiologic testing revealed that hearing for pure tones was abnormal in all ears with ELSTs identified on MRI. Ten affected ears demonstrated absent or profoundly decreased pure tone hearing, 2 had mild to moderately handicapping pure tone deficits, and 3 showed pure tone sensitivity changes that were not yet handicapping. Acoustic reflex studies were abnormal in 11 of the 15 ears.

VHL genotype information was available for 10 of the ELST patients from 9 different families. Affected patients belonged to VHL type 1 and type 2 families. In 7 of the 10 patients, there were 4 large deletions and 2 mutations ending at a stop codon. Thus in this small sample, distribution of types of VHL was broad, with a large proportion of mutations predicted to truncate the VHL protein. At this time, genetic screening will not permit identification of VHL patients who are particularly susceptible to development of an ELST.

In the clinic group, forty-three (65%) of the 66 patients from the VHL clinic, without additional screening criteria, had abnormalities in pure tone testing,[7] including 11 patients (17%) with handicapping or profound hearing loss; 23 (54%) of the 43 patients had some degree of hearing loss in both ears. Among the 49 patients from the clinic with proven VHL, 32 (65%) had pure tone abnormalities and 3 (6%) had ELSTs evident on MRI (2 of whom had bilateral MRI-visible ELSTs).

Their results indicate that hearing loss, often bilateral, is frequently associated with VHL and that many patients with VHL and hearing loss have ELSTs. The results suggest that, left untreated, most ELSTs will eventually cause hearing loss which can progress to total deafness. People with ELSTs most commonly complain of hearing loss, frequently accompanied by tinnitus and a variety of vestibular symptoms (nystagmus, vertigo, or a tendency to fall). When progressive growth occurs, these tumors may impinge on adjacent neural structures, may cause the facial nerves to lose tension or sensation, and may even (very rarely) cause paralysis of the vocal cords.

The findings of this team indicate that the prevalence of hearing loss (65%) and ELSTs (at least 6%,

higher if hearing loss is the result of hidden ELST in patients with normal MRI) is at least as high as the occurrence of other more commonly understood manifestations of VHL. We cannot say that hearing issues are always caused by ELST (only 3 of 49 patients with VHL had MRI evidence of ELST), but current evidence suggests that fewer than 10% of adults in the general population in this age range have detectable hearing loss. Moreover, in 62% (8 of 13) of patients in the study, hearing loss was the first symptomatic manifestation of VHL. Since ELSTs are rare in the general population, and as their association with VHL implies a common genetic origin, patients with an ELST should receive a screening evaluation for VHL.

The very long interval between the onset of symptoms and the diagnosis of ELST is probably due to the fact that good imaging technology is quite recent, and ELSTs are small. They have commonly been mistaken for hemangioblastomas, metastatic renal cell carcinomas, cholesteatomas, or ectopic choroid plexus papillomas. Even with modern MRI techniques, most patients are diagnosed only after significant or total hearing loss leads to modern audiologic evaluation.

In 8 of the people studied, the symptoms came on slowly and progressed slowly over a number of years, potentially permitting early diagnosis and treatment to preserve functional hearing in the affected ear.

The ideal treatment of ELSTs should eliminate the tumor while preserving hearing. It appears as if curative therapy for ELSTs requires complete surgical excision, as partial resection, with or without postoperative radiation therapy, is associated with a high incidence of tumor recurrence. Early identification of small ELSTs, before complete hearing loss has occurred, should improve the likelihood of preserving hearing after the removal of the tumor. Only 5 ELSTs (3 patients) associated with some preservation of hearing in the affected ear have received surgery. In all 5 ears the preoperative level of hearing was preserved after surgery. Although results in these patients indicate that it should be possible, too few ELSTs have been removed before severe hearing loss has occurred to establish whether hearing preservation can be achieved regularly with total tumor resection. Treatment plans must also consider that these tumors usually grow slowly. To justify early surgery, probability of cure must heavily outweigh risk of hearing loss associated with the surgery itself. This is especially true in people with bilateral ELST who are deaf in one ear and are found to have a small ELST involving the hearing ear.

Hearing loss and ELST should be considered part of the VHL syndrome. When screening individuals at risk for VHL and monitoring known VHL patients, a detailed audiologic examination should be included.

Recommendations for audiologic examination of people at risk for or known to have VHL

Studies of pure tone and speech threshholds, biomechanical evaluation of the middle ear (tympanometry and acoustic reflex studies), auditory brainstem responses, and otoacoustic emissions accomplished in the context of a detailed audiologic individual and family history

For people with symptoms, neuro-imaging techniques may be added, especially MRI of the petrous bones (with special attention to the region of the external aperture of the vestibular aqueduct).

Although results of audiologic evaluation were consistently abnormal in patients with radiographic evidence of ELST, the abnormal hearing test results were nonspecific, and no pattern or combination of findings was clearly diagnostic of an ELST. Audiologic examination and MRI should be repeated on a regular basis if symptoms of hearing loss, tinnitus, vertigo, or imbalance appear. Since we are still learning about the natural course of these tumors, the interval for repeating these studies remains to be established. Enhanced awareness of the association between VHL and hearing loss and ELSTs by patients and physicians and use of the diagnostic evaluations described here should allow early detection of ELSTs and hearing loss and may enhance management and prevention of hearing loss in VHL.

1. "Endolymphatic Sac Tumors," by Manski et al, *Journal of the American Medical Association*, 277:18, May 14, 1997.
2. The *temporal* bone is near the temple. The hard bone you can feel behind your ear is the temporal bone.
3. *Audiologic* evaluation: testing and measurement of the hearing.
4. *Menière's* disease: a disorder causing extreme dizziness and vertigo. While its exact causes are unknown, it is thought to be a symptom of subtle changes in the pressure in the endolymphatic sac.
5. The *petrous* bone is the hard (stone-like) portion of the temporal bone which projects inside the skull and houses the inner ear.
6. *Psychoacoustic* testing is where the person whose hearing is being studied is listening and responding, as opposed to other audiologic studies which measure electro- or neuro-physiological functions of certain parts of the auditory system without the subject responding in any way.
7. These people have pure tone threshholds poorer than 20 dB, which was less than criteria for normal.

The National Institutes of Health has defined a research protocol to investigate the natural history of ELST hearing loss with VHL, and surgical treatment of ELST to conserve hearing. This study will be directed by Dr. Edward H. Oldfield and Dr. Daniel Choo.

If you would like to apply for admission into the protocol, please contact Dr. Oldfield's office at 301-496-5728.

Survey Results

Attitudes Toward Genetic Testing

-- by Lisa C. Carcieri

As many of you already know, I began a research study a few months ago to investigate VHLFA members' attitudes towards genetic testing. The research study was a requirement for my graduation from a master's degree program in genetic counseling. Individuals who were 18 years of age or older and who had a parent and/or sibling with VHL were asked to complete and return a survey. Five hundred members received the survey in February 1997, and I received over *two hundred* responses. **Many thanks** to all who participated!! As promised in the cover letter to the survey, this article is a summary of the results and significant findings of the study.

VHL Family History. Seventy-one percent of those who responded had a diagnosis of VHL. 23% said they didn't know if they had VHL, and 6% replied that they did not have VHL. Of those with VHL, 17% reported that they were mildly affected, 45% said they were moderately affected, and 36% said they were severely affected. Of the sixty-eight percent of respondents who had children, 43% had at least one child with VHL, and an additional 45% said they didn't know if any of their children were/would be affected. Many (44%) had known that VHL was in their family for more than 20 years, and 17% had known for fewer than five years.

Screening. Ninety-four percent of individuals who have VHL reported that they undergo periodic screening (MRIs, CT scans, eye exams, etc.) for signs of VHL. Only 38% of at-risk people who don't know if they have the altered VHL gene are screened regularly. Some respondents commented that their doctors did not know what to look for, that they could not afford screening, and that the screening was not covered by their insurance.

Genetic Testing. Forty-five percent said that they had undergone genetic testing for VHL. Of these, 14% were still waiting for results at the time that they completed the survey. About 80% of people who had been tested said that they received information prior to testing and that they were satisfied with the amount of information received. This level of satisfaction was the same regardless of whether the information was provided by a doctor, a genetic counselor, or another source (such as the VHLFA). The fifty-five percent of respondents who had not been tested were asked whether they planned on being tested. 26% said "yes," 32% said "no," and 14% said "I don't know." For many individuals, genetic testing was not necessary, as they already knew they had VHL.

Attitudes toward Genetic Testing. This section comprised the bulk of the survey. Participants were asked whether they agreed, disagreed, or were neutral regarding nine reasons *to* have genetic testing for VHL and ten reasons *not to* have genetic testing.

Reasons to Have Genetic Testing. The most agreed-with reasons to have genetic testing were: "I want to increase the frequency or extent of screening if I have the altered gene" (80% agreeing), "I want to end the uncertainty of not knowing if I have the altered gene" (71%), and "The test result would help me to plan for the future" (73%). Many respondents also agreed with "I want to stop screening if I don't have the altered gene" (64%), "I might find out that I don't have the altered gene" (63%), "I would take better care of myself if I knew I had the altered gene" (64%), and "I want to learn about the risk to my child(ren)" (68%) as reasons to be tested. Thirty-six percent of never-married individuals indicated that the test result would influence their decision to get married. Fifty-nine percent of individuals without children said that the test result would influence their decision to have children.

"Only 38% of at-risk people who don't know if they have the altered VHL gene are screened regularly. Some respondents commented that their doctors did not know what to look for, that they could not afford screening, and that the screening was not covered by their insurance."

Reasons Not to Have Genetic Testing. The most agreed-with reasons not to have genetic testing were: "I am concerned about losing my insurance if I have the altered gene" (57%), "There is no cure or prevention for VHL, only treatment and management" (52%), and "I am concerned about the reaction of my family or spouse to the test result" (52%). Fewer people were concerned about their own reaction to the test result. Twenty-nine percent of respondents agreed that they were concerned about their reaction to a positive result (i.e. hearing the news that they do have the altered gene), and only 18% agreed that they were concerned with their reaction to a negative result (i.e., hearing that they do not have the altered gene). Reactions were split over the accuracy of the test, with 33% agreeing that they were concerned about the accuracy of the testing and 31% disagreeing. Forty percent of participants agreed that the testing was too

The secret of achievement is to hold a picture of a successful outcome in mind.
-- *Henry David Thoreau*

expensive. 51% disagreed with the statement "now is not a good time in my life to be tested," and only 6% agreed.

Participants' Comments. The last part of the survey consisted of two "open-ended" questions. The first invited respondents to comment on any of the survey's previous questions. The second question was "What would you like health care professionals to know about living in a family with VHL?" Many of you took advantage of the blank spaces underneath these questions! Some told personal and moving stories of their families' experiences with VHL. Some sharply critiqued and others complimented their medical caregivers. Many of you expressed your appreciation of researchers studying VHL. Although there was a wide range of responses, a few themes emerged. Overwhelmingly, the most popular comment was that doctors need to become educated about VHL. Many people commented that their physicians do not have even a basic understanding of VHL. Others expressed their frustration over doctors' unwillingness to work as a team, lack of attention by their doctors to their reports of symptoms, and the need to repeatedly "teach the experts" about their condition.

If you are interested in genetic testing... Several respondents wrote that they would like to have genetic testing but were uncertain how to go about it. One way to start the process is to contact a genetic counselor in your area. A genetic counselor is a health care professional who is specially trained to talk with individuals and families about genetic conditions and testing. He or she can also coordinate the acquisition and shipping of samples. To find the genetic counselor nearest you, contact:
The National Society of Genetic Counselors
233 Canterbury Drive
Wallingford, Pennsylvania 19086-6617
Phone: +1 (610) 872-7608
Fax: +1 (610) 872-1192
E-mail: NSGC@aol.com

For More Information and/or a complete copy of the results . . . please contact the VHLFA hotline at (800) 767-4VHL or info@vhl.org.

Acknowledgments. I would like to express a special thank-you to the three participants whom I interviewed by phone. Your experiences taught me so much and were an extremely valuable addition to my thesis. Thanks also to Joyce Graff for her assistance with this study, and for agreeing to publish the results in the *VHL Family Forum*. ❑

Ask the Experts

Question: What do the terms "grade" and "stage" mean when applied to VHL kidney tumors? What's the difference between the two? What does it mean when they say it was a "grade two" tumor?

Answer: Grade and stage, when applied to kidney tumors, are separate but related terms.

Grade refers to the "aggressiveness" of the tumor when the tumor is looked at by the pathologist under the microscope. Kidney tumors can be graded on a 1 to 4 scale, with Grade 1 being the least "malignant appearing" and Grade 4 being the most aggressive appearing. In practice, grade is infrequently used in referring to kidney tumors and is less useful in characterizing a kidney tumor than is stage. A Grade II tumor would be one that is moderately well-differentiated, that is moderately aggressive appearing under the microscope.

Stage of the tumor refers to how advanced the kidney tumor is in the patient. The stage of the kidney tumor is generally determined by radiographic studies such as CT Scan, Magnetic Resonance Imaging and/or ultrasound. A Stage I kidney tumor is a very small kidney tumor that is totally confined within the kidney. A Stage II tumor is one that has grown out through the lining (capsule) of the kidney. A Stage III tumor is one which has invaded outside the kidney into either the local nodes draining the kidney (the hilar nodes) or into the vena cava (the large vein that goes up to the chest or the renal vein (the vein from the kidney to the vena cava).
-- *W. Marston Linehan, M.D., Head, Urologic Oncology Section, National Cancer Institute, Bethesda, Maryland.*

Over 40% of Americans will develop cancer; over 20% of Americans will die from cancer. Within five years cancer will be the leading cause of death in the United States, responsible for over 6 million years of life prematurely lost each year and an annual cost to the economy of over $100 billion. . . . [The budget of the National Cancer Institute] represents an investment in research, but more importantly an investment to improve the Nation's health. It is an investment in hope -- the hope that springs from the discovery of the tools and knowledge that we must have to reduce the awful burden of cancer.
-- *Richard Klausner, M.D., Director, United States National Cancer Institute*
For your copy of the NCI Budget Proposal, an excellent review of NCI achievements and plans, with a section about VHL, call the Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). TTY access 1-800-332-8615.

Insurance and Genetic Disorders

by Paula Sicard, Esq., Chairman, Insurance and Legal Committee, VHLFA

While the following article focuses on a U.S. insurance issue, there are similar concerns in other countries. Even where there is universal health insurance, there are great concerns about access to life insurance and employment opportunity. Be sure to communicate with your local government representatives and get involved in legal discussions toward maintaining privacy of genetic information, and freedom from discrimination based on genetic information. In the U.K., the Committee on Science and Technology of the House of Commons is actively working on this issue.

Insurance Issues and Genetic Disorders were discussed by Joan Weiss and Andy Imparato at the 1997 Patient/Provider Conference. One topic was the Health Insurance Portability and Accountability Act, affectionately known as the Kasselbaum-Kennedy Bill, which was passed by Congress at the last session and *technically* becomes effective as of July 1, 1997. This law was designed to ensure that when a worker left a job where he or she was enrolled in a group health insurance plan, that worker could not be denied enrollment in the new employer's group plan because of genetic information. The new group insurer cannot make eligibility conditional based on genetic information it has about the worker, and cannot use genetic information alone to demonstrate a "preexisting condition" without a specific diagnosis of the condition. The law applies to both insurance companies and employers' self-funded plans which provide group health insurance plans.

The Bill is regarded by many as a good start; however there are important limitations which people contemplating a job change must not overlook. First, although the law has an official effective date, that date is somewhat deceiving. In reality, the law becomes effective on the annual "date of renewal" of the employer's group health insurance policy. Obviously, the renewal date will vary from employer to employer so individuals contemplating a job change should not assume that they are automatically entitled to the Bill's protections as of July 1st. Ideally, the worker should try to ascertain the annual renewal date of the new employer's group policy and should make every effort to delay the job change until that date. Second, although the group insurer is prohibited from raising a single individual's premium, it may not prevent the insurer from increasing the new employer's group rates across the board.

Other general considerations when contemplating a job change include the following. First, if the new employer's group health policy is offered by a large national insurer such as Blue Cross/Blue Shield or Unisys, that insurer processes billions of dollars in claims annually and may be likely to process larger or more unusual claims as a matter of course. The smaller insurers, on the other hand, are apt to more closely scrutinize individual claims. Next, if the new employer's group plan is self-funded, the employer pays all insurance claims itself, rather than paying policy premiums to an insurer, and absorbs the actual medical expenses incurred by its employees. Thus, the employer has a direct incentive to minimize claims to keep its costs down. In many instances, the self-funded employer uses an independent plan administrator to oversee its health insurance claims process, so don't be fooled by a name different from the employer's.

When trying to obtain coverage for a particular procedure or test, it may be helpful to negotiate coverage with your insurer and argue that the up-front cost of what you are seeking is less than the costs likely to arise for therapy, etc., if you cannot have the test. If you are unhappy with the actions of your insurer, you can complain to your state's Insurance Commissioner. There is one in every state and he or she oversees all insurance companies which do business within the state. Also noteworthy is the fact that the Equal Opportunity Employment Commission (EEOC) has now defined "disability" in its compliance manual to include individuals who suffer discriminatory treatment on the "basis of genetic information relating to illness, disease or other disorders." This definition has yet to be challenged in court so its protective effect remains uncertain. Similarly, Andy Imparato pointed out that the Americans with Disabilities Act (ADA) contains a little-known provision prohibiting discrimination on the basis of "association" with someone with a disability (and presumably, by EEOC definition, a genetic predisposition).

A number of proposed bills are circulating in the current Congressional session, and this topic is a hot one. The VHL Family Alliance encourages *everyone* to communicate with your Congressman, by letter or by telephone. Emphasize the need for more insurance protections for people with genetic disorders who already have some type of health insurance. Stress that those without should be able to obtain health insurance, not denied because of their health status or genetic predisposition. Perhaps even share a personal experience which may strike an emotional chord. Your opinions are important, and in most instances, the politician/recipient will send you a response. The more letters and calls received, the higher priority the issue gets, so please take a few minutes to express your desires and concerns to your elected officials.

A sample letter is reprinted below and may be copied or used as a model. The names, addresses and telephone numbers of the Congressmen from your area may be obtained by calling the Federal Informa-

tion Center at 1-800-688-9889 and asking an Information Specialist to send you a current congressional address listing. Your local telephone book should also contain a federal government section which lists telephone numbers for your congressional districts from which to obtain current addresses. The Alliance would appreciate knowing about a call you made and/or receiving a copy of any letter you sent.

For those of you with personal questions, the Alliance of Genetic Support Groups (AGSG) has an Insurance Discrimination Specialist who will speak with individuals on Mondays and Wednesdays from 10 AM to 5:30 PM and Fridays from 9:30 AM to 1:30 PM Eastern U.S. time at 1-800-336-GENE (336-4363). This area of the law is not only complex, but is changing every day. Please share any helpful information you receive with the AGSG so that others might benefit as well.

Dear (Congressperson):
re: Insurance Crisis

I am writing to express my deep concern about the current insurance crisis we are facing in this country. Most important is the fact that many people are simply unable to obtain health insurance. Of those who do, most are prisoners to individual policies with exorbitant premiums or to the group plans offered by their employers.

Several bills are presently pending before Congress which supplement and expand PL 104-191 (the Kasselbaum-Kennedy Bill) and I encourage you to give them your wholehearted support. Public Law 104-191 was designed to ensure that when a worker left a job where he or she was enrolled in a group health insurance plan, that worker could not be denied enrollment in the new employer's group plan because of genetic information. However, that law does not prevent the insurance companies from raising the premiums for the whole group. It also does not address the more basic need of uninsured individuals to obtain health insurance. Some of those uninsured individuals quality for government assistance through Medicaid or SSI, but many are left without any recourse.

I am also concerned that, in light of recent genetic developments, more and more individuals are being discriminated against on the basis of genetic predisposition. Those people must be entitled to make their own personal genetic inquiries without fear of health, life, and disability insurance repercussions. (You may choose to describe a relevant personal experience at this point).

I am anxious to receive your input in this matter.

Sincerely,
(Your name and address)

Social Issues in Genetics

An Internet-based Newsletter, *The Gene Letter*, discusses the scientific and societal issues in Genetics. Its purpose is to inform consumers and professionals about advances in genetics and to encourage discourse about emerging medical, ethical, legal, and policy dilemmas.

The Gene Letter was established by the Shriver Center under a grant from the U.S. Department of Energy/ELSI Program, by Dr. Philip R. Reilly, M.D., J.D., Dorothy C. Wertz, Ph.D., and Robin J.R. Blatt, R.N., M.P.H.. In its first year, *The Gene Letter* is appearing every other month with news updates as appropriate. Regular columns include one or more on: Health, Science, Ethics, Law, Society, International Developments, Book Reviews, a Student Corner, In the News, Events, Conferences, and a list of Gene Resources. *The Gene Letter* also operates an uncensored chatroom. http://www.geneletter.org

United Way Donor Choice

Does your company solicit donations through United Way? You can give to VHL Family Alliance through your company's **United Way** plan! Payroll deductions are a painless way to give small amounts throughout the year. We're not among the organizations listed on the form, but ***you can write us in!*** It's called Donor Choice. Give them our name and address, and they will do the rest. Because of the administration costs at United Way, they suggest a minimum pledge of $25. You can participate in the company program, your employer usually matches the contributions, United Way deducts their administration charge, and the remainder comes to the VHL Family Alliance to help fund research and education about VHL.

We are affiliated with the **Combined Federal Campaign** in the Atlanta and Wisconsin areas. If you would like to have us register with CFC in your area, please notify the hotline at 1-800-767-4VHL or vhl@pipeline.com.

Or as ever, give directly! Many employers will match direct donations. Please enclose the appropriate matching gifts paperwork from your employer, and we'll do the rest!

Your gifts are appreciated, no matter the channel you take. Thank you for helping to improve diagnosis, treatment, and quality of life for people with VHL.

Bethesda meeting!

One hundred twenty-five family members and thirty-five physicians and health care professionals gathered in Bethesda, Maryland, for the Fourth Annual International Patient/Provider Conference on von Hippel-Lindau Disease, May 2-4, 1997. This was our largest meeting to date, and as ever contained a rich treasure of information about VHL. Audio recordings of the sessions and sets of handouts are available for purchase on page 15.

On Friday preceding the conference, Dr. Edward Oldfield directed a Focus Conference on the use of stereotactic radiosurgery for hemangioblastomas in VHL. Dr. Oldfield's report appears separately.

Saturday morning we were greeted by Dr. Francis Collins, Director of the National Institute for Human Genome Research, the newest of the National Institutes of Health. The human genome research effort has been elevated to its own Institute, demonstrating the importance of this work to the nation's health care in the next decades.

Dr. Marston Linehan outlined the scope and purpose of the VHL research being conducted at the National Cancer Institute. Some 30 people from a number of different disciplines are involved in VHL research in an effort not only to cure VHL, but also to cure kidney cancer in the general population, and to learn tactics to use against other cancers as well. Dr. Berton Zbar shows us some of the work he is doing on two other forms of inherited kidney cancer, and Dr. Othon Iliopoulos from the Dana Farber Cancer Research Institute in Boston outlined the work he and Dr. Kaelin are doing to understand the function of the VHL Protein and its role in regulating cell division and growth. (See Boston meeting report, p. %%).

Dr. Catherine Stolle from the genetics testing service at the University of Pennsylvania described the process of molecular diagnosis of VHL and the steps to take to obtain DNA testing for VHL. Dr. James G. Herman of the Johns Hopkins Oncology Center showed us that the VHL gene can get "knocked out" or inactivated by other methods than mutation, one of which is a process called "methylation", which may be caused by environmental influences. Many kidney cancer tumors in patients with normal VHL genes have been shown to have this kind of inactive VHL gene function.

North Carolina chapter representation: Myra, Audrey, Nancy, Wendi, and John.

Dr. Gladys Glenn, who heads the VHL Clinic at the National Cancer Institute, described the full clinical evaluation which is done at NCI. In working with hundreds of people with VHL over nearly eight years, she has found that a combination of testing, education, and counseling is the best combination for helping people manage their health. She and her colleagues at NCI publish articles and provide backup services for local physicians throughout the United States. Dr. Peter Choyke, chief radiologist for the Clinic, shared some of the imaging studies of people with VHL, showing some of the distinctions which they have found to be important. By studying a series of people over time, they have come to understand the growth patterns of certain tumors, and how they progress. Over the last 10 years there have been significant changes in the genetics, management, and imaging of VHL. The breadth of experience gathered at the NCI clinic and through the efforts of a number of other centers and physicians has clarified the role of the various kinds of imaging techniques for screening and follow-up.

Dr. Fray F. Marshall from Johns Hopkins, Dr. Hartmut Neumann from Freiburg, and Dr. McClellan Walther of NCI presented their work with kidney tumors in VHL. Dr. Walther told us that it is not unusual for people with VHL to develop as many as 30-60 tumors in both kidneys before the age of 30. It is not the number of tumors that matters, but rather their sizes and stages of development. All three

Todd C., Wisconsin; Dr. Sam Tisherman, Pittsburgh, PA; Dr. Gladys Glenn, Maryland; Terry B., Wisconsin.

agreed that tumors can be watched up to a size of at least 3 cm., delaying intervention until there is one tumor greater than 3 cm. Dr. Neumann's policy is to wait even longer, since in his experience with patients in Europe, he has not seen a metastasis unless there was at least one tumor 7 cm. diameter or larger. Others feel that this is too risky. Whenever surgery is performed, the goal is to remove as many of the tumors as possible, "resetting the clock" back 5-10 years in the progression of the disease, while preserving as much functioning kidney as possible. While kidney transplant is an option, there was agreement that the primary objective should be to keep the patient's own kidney functioning. Dr. Walther said that he had removed as many as 100 tumors and still left functioning kidney.

Melissa Minster designed a rich and full schedule.

Dr. Neumann, Dr. Walther, and Dr. Douglas Ball of Johns Hopkins shared their experiences with pheochromocytomas, with discussion of the uses of laparoscopic surgery. This new technique is still being piloted, but seems appropriate for some kinds of larger pheos, especially when the entire adrenal gland is being removed. Dr. Neumann does not operate on asymptomatic pheos unless they are in women who want to become pregnant. He uses organ sparing surgery as much as possible because of the tendency of another tumor to develop on the other side.

Dr. Steven Libutti shared his research on pancreatic tumors of VHL and their management. In his reviews of the pancreatic manifestations shown in the people studied at NCI, he has found that the most common pancreatic tumors follow the general guidelines for kidney tumors. Tumors of the islet cell portion of the pancreas, however, need to be watched carefully as they can grow rapidly and can metastasize. Islet cell tumors should usually be removed soon after diagnosis.

The most popular portion of the weekend's program was the segment on VHL and Children. Kelly Hill of Kids Konnected described the program which Jon Holtz and several other children designed to support kids whose parents have cancer. Julie Rutberg and Don Hadley, genetic counselors, described the work they do with families affected by genetic conditions like VHL, helping parents decide whether or when to test children for VHL, helping parents with strategies for telling their children about VHL, and helping families find counseling and assistance in dealing with the issues that arise in dealing with the physical and mental strains of a chronic illness, or simply the threat of an illness like VHL.

On Sunday there were break-out sessions for the seven children from 8 to 16 who were in attendance; and a separate session for adults. Each group dealt with their own special interests, with a trained facilitator present. Feedback from these groups was very positive -- with requests to do it again!

Our Sunday morning meditation was particular poignant this year since three families had recently lost loved ones -- Craig Warnick, Tom Werner, and Catherine Ann Redding. Death is a part of life, whether VHL is with us or not. Catherine Ann did not have VHL, but died suddenly of a stroke at the age of 28. Susan Warnick, speaking for Craig, shared another of the Craig Warnick theme songs: *Never Surrender* by %%. June Peters shared her study of meditation, and led the group through a guided relaxation exercise which was calming and centered us for the rest of the day.

Dr. Oldfield reported the results of the Focus Conference on Stereotactic Radiosurgery (SR). This technique is attractive because there is no surgery to recover from. But, as Dr. Prasad from the University of Virginia said, it cannot be considered "non-invasive." It is a surgical technique, and it can cause damage, just as open surgery can. We need guidelines for which tumors are and are not approachable because of their size, location, etc. There are areas of the brain, like the optic chiasm, where SR is not the right technique. If a tumor is close to the surface of the brain, is very approachable with open surgery, and the risk of injury to healthy brain tissue is relatively low, then open surgery is still a good option. However, for tumors deep within the brain, which might otherwise be considered "inoperable," SR can be the perfect answer. There was agreement that the optimal tumor for SR is 10-12 mm. or smaller and

The Hotline Team: Peggy Marshall, Mississippi; Barbara Redding, Florida; Eva Logan, Georgia; and Altheada Johnson, New York.

where there is no cyst creating pressure inside the skull. Dr. Adler said it is also best to have a "patient patient," one who is willing to wait as long as two years for the results to be apparent. Dr. Nauta is finding good results from spacing out the treatment, to decrease the swelling effect. He used an analogy with exposure to sunlight -- comparing the effect to the difference between spending two hours on the beach in Miami on the first day of your winter vacation, versus spending 10 minutes in the sun twice a day for the week.

Dr. Hurko and Dr. Nauta shared their thoughts on the optimal methods for long-term follow-up, balancing caution with the financial realities of HMO and insurance coverage. Drs. Oldfield, Choo, and Pikus shared their findings from the ELST study they have recently completed (see cover article).

Dr. Robert Welch presented a history of VHL in the retina, and his own patients with VHL over his career, with a series of fascinating drawings of retinas which he and others had made of their patients before retinal photography was in widespread use. Dr. Emily Chew shared her observations from working with hundreds of people with VHL in the NCI VHL Clinic. Small lesions are easy to treat successfully while large lesions are notoriously difficult to treat. If the tumor is located on the optic nerve, treatment is particularly difficult. Fortunately, tumors on the optic nerve may remain asymptomatic for long periods of time. For people at risk for developing VHL, she recommends a dilated eye examination at least once a year. Good vision can be maintained in many affected people, especially if the lesions are detected and treated early.

Joan Weiss, founding director of the Alliance of Genetic Support Groups (AGSG), shared the research which she and others recently published (*Science*, 274:621, October 1996), studying the perceptions of 332 members of genetic support groups with one or more of 101 different genetic disorders in the family. It was found that as a result of a genetic disorder, 25 percent of the respondents believed they were refused life insurance, 22% believed they were refused health insurance, and 13% believed they were denied or let go from a job. Fear of genetic discrimination resulted in 9% of the respondents refusing to be tested for genetic conditions, 18% not revealing genetic information to insurers, and 17% not revealing information to employers. The level of perceived discrimination points to the need for more information to determine the extent and scope of the problem.

Cia Manolatos, VHL Clinic, NIH.

Andrew Imparato, esq., of the U.S. Equal Employment Opportunity Commission, described the legislation which can be used to help protect people from employment discrimination, but there are loopholes which are regularly used by employers to pass over people with a variety of health conditions, not all of them genetic, in an effort, they believe, to manage their "investment" in their employees. It is critical that people share their stories, as the Congress does not always believe stories told to them by other government officials -- they are very much moved by stories from their own constituents. Even if families need to remain anonymous, sharing their stories with the VHLFA or with the AGSG or the National Organization for Rare Disorders will help to provide real stories from real people which can be used to emphasize the need for protection.

As ever, it was wonderful to be together. We were all very grateful to the National Institutes of Health and to Johns Hopkins University Hospital for their unstinting support of this meeting. We all appreciated the efforts of the speakers, and of the administration and support staffs. Special thanks to Maggie in Dr. Linehan's office and Stephanie in Dr. Hurko's office for their support of us and of the speakers.

Dr. Haring Nauta, Texas, and Joyce Graff, Brookline.

When's the Next Meeting?

Workshop on MEN and VHL, June 25-28, 1997, Leeuwenhorst Congress Center, Noordwijkerhout, **The Netherlands**, near Amsterdam.

VHLFA Patient/Provider Conference, **Seattle**, Washington, spring 1998.

Third International Symposium on VHL, **Paris**, France, September 1998.

VHLFA Patient/Provider Conference, **Atlanta**, Georgia, spring 1999.

Massachusetts Chapter meeting

— Laurel Newson, Massachusetts

There were 13 people in attendance. Joyce gave a welcome and overview of what is going on in the VHL Family Alliance. She told us that we are now in touch with nearly 7,000 peoople with VHL in 27 countries! This is a long way from 1993 when many of us first heard about the VHL Family Alliance.

Dr. William Kaelin gave a wonderful, easy to understand presentation of the work going on in his research lab, to identify the function of the VHL protein. He also introduced us to three researchers on his team who have made some of the breakthroughs in the work.

Dr. Kaelin explained to us that everybody carries two copies of the VHL gene. The VHL gene is a tumor suppressor gene, and only one copy of the VHL gene needs to remain intact for the cells to function normally. One copy of the VHL gene is inherited from each parent. Since the copy inherited from the parent without VHL is healthy and usually functioning, most cells are fine. But if that second copy of the VHL gene gets changed by some environmental impact, then a tumor begins to form.

This same series of events can occur sporadically, in a person who inherited two working copies of the VHL gene. In this case, both copies of the VHL gene in a single cell have to be changed so that they do not work properly.

Kaelin's team has shown in the lab that if VHL tumor cells in a mouse is injected with the normal VHL genetic material, the cell normalized and the tumor shrinks. This shows that there is hope for therapies based on replacing the genetic material, or replacing the VHL protein in tumor cells.

Kaelin also went on to describe what they believe to be the role of the VHL protein in signalling a loss of oxygen in the cell. Erythrocythemia (too many red blood cells) is sometimes seen in people with VHL. Normally, this would be the body's response to too little oxygen — if you were on a high mountaintop or in a cave with limited oxygen, the body would make extra red blood cells to pull as much oxygen out of the air as possible. This was one clue which led them to see that the absence of the VHL protein tells the cell that there is not enough oxygen, so the cell sends out distress signals that it needs more oxygen. In the case of a wound, where additional oxygen is needed for repair, the body's normal response is to build more blood vessels to bring more blood to bring more oxygen. In VHL, however, these additional blood vessels create a hemangioblastoma.

June Peters, Maryland

The process is ongoing to identify the functions of the VHL protein, so that scientists can understand how they might intervene in the chain of events and change the outcome. He explained one method for finding other types of proteins with similar traits. If they can restore the function of the VHL gene, or substitute another drug for the VHL protein, or change the reaction of the chemical that calls for blood vessel construction, then they may be able to stop the development of a tumor.

Research on the kinds of mutations (genotypes) that occur in the VHL gene may lead to a better understanding of the particular manifestations of VHL that people in that genotype may encounter.

Dr. Kaelin's talk was very interesting and informative, and we are all invited to tour Dr. Kaelin's lab in the Dana Farber Cancer Research Institute in Boston.

We also announced that the VHL Family Alliance is forming a Team VHL to take part in the 1997 Boston Marathon Jimmy Fund Walk, Dana Farber's annual fund-raiser. This walk will take place on Sunday, September 28, 1997, and we will have more information at a later date. We need both walkers and sponsors. All money raised goes to Dana Farber Cancer Research Institute, where it will be directed to Dr. Kaelin's team to work on the VHL protein. For more information, contact Laurel at, 617-324-1821.

England and Canada

The new Chairman of VHL Family Alliance in **England** is Gillian Houlders of Gosport in Hampshire. Gillian has VHL, is married and has one daughter. She is eager to reach out to even more people in England. There have been some problems with the existing membership list in Britain, so if you know people in England who may have fallen out of contact with the group, please ask them to contact Gillian at +44 (0)1329 286806, or contact us in the U.S. and we will pass the information through to her.

Paul Bonneau and Tania Durand of Canada are expanding their efforts to grow the Canadian affiliate. Tania joins the team in Ontario, and is planning activities and educational projects in that area. Both Tania and Paul can be reached by calling the hotline at 800-767-4VHL, or writing to info@vhl.org.

Thanks to Retiring Board Members -- Welcome New!

It takes a lot of people-power to make up the VHL Family Alliance. Volunteers give of their time and talents in many ways, mostly at the local level. We welcome your efforts, whatever time you have to give.

We take this opportunity to thank those who have given an extra special amount of their time, in a two or three-year term on the Board of Directors. The Board is the governing group, organizing and producing publications, distributing information by phone, fax, e-mail, and on paper, sustaining communications with the membership and the various chapters and affiliates worldwide, soliciting and evaluating research proposals, and raising and administering the money it takes to do it all. We will be introducing the new Board members to you over the next few issues.

Bill Dickson has done an outstanding job with the Research Committee, building it from the bottom up. He defined procedures for submitting grants, and worked out a cooperative arrangement with Dr. Allan Rubenstein and the National Neurofibromatosis Foundation that we would participate in their research review process, adding two members to their existing Review Board and submitting our proposals for review by the full membership of the Board, a distinguished group of scientists whose interest in NF and genetic disease overlaps about 80% with VHL.

Bill turns over the Research Committee Chairmanship to Myriam Gorospe, a post-doctoral fellow at the Institute on Aging, who has relatives in Spain with VHL. Myriam is our tireless Spanish translator -- she translates our materials into Spanish for her cousins and shares them with us. Thanks to Myriam, our Spanish language site on the Internet is one of the best resources on the net in Spanish for information on genetics and DNA testing, and she gets calls not only for VHL but also for other conditions.

Many of you know Audrey Tobin as the Treasurer who helps register each of the state chapters with their state attorneys general and tax authorities. She and her daughter Kelly Tobin Heselton have build up an excellent set of processes and procedures for managing our money, keeping track of income and expenses and helping the Board forecast our needs. Audrey will continue working with state registrations, but turns the official Treasurer role over to Kelly this year.

Kelly has already been doing a large portion of the Treasurer's job for the past two years, tracking everything on her trusty personal computer. Kelly is an Information Systems Auditor with Norwest Audit Services, Norwest Bank. We were delighted to have Kelly with us in Bethesda, adding greatly to the conversation and balancing the books for the meeting. Kelly has an aunt and cousin with VHL.

Tom Rodenberg has been our family attorney, sharing his expertise in working with insurance companies with others, answering questions about rights and procedures, and advising the Board on legal issues.

Paula Sicard will assume the chairmanship of the Insurance and Legal Committee. Paula is a bankruptcy attorney in Florida, whose brother has VHL. She is planning some new initiatives. See her article in this issue.

Peggy Marshall and Altheada Johnson were re-elected to the Board. Peggy continues as the Chairman of the Chapters Committee and the Hotline Committee. She has been performing these key roles for us for the past three years, and has built both to a high standard of excellence. She and Don originated and maintain a handbook of information that keeps the hotline volunteers armed with the information they need to assist callers, and provides ideas and procedures for the chapter leaders in the U.S. and Canada.

Altheada Johnson continues as Chairman of the Board and as Chairman of the Membership Committee. She has taken on very seriously the expansion of our membership, finding people with VHL who may or may not already have a diagnosis, especially in the underserved areas of the population. In the past two years she has been a speaker at four conferences, and appeared on the radio. Both Peggy and Altheada participate on the Hotline Committee, answering calls for several weeks at a time.

We are delighted to welcome Don Marshall to a position on the Board. Don has been the Chairman of the Publications Committee for the past three years, working to make sure we have supplies on hand, and sending materials out to new members. Nearly every member has received a letter from Don. He and Peggy co-chair the Mid-South Chapter, spanning Mississippi, Tennessee, and Arkansas, and have been known to drive to chapter meetings from Florida to North Carolina.

Renée Rosado, who has been serving on the Fund-Raising Committee for the past year, joins the Board and assumes the chairmanship from Lois Erickson. Renée's late husband had VHL, and she is very close to his family, many of whom have VHL. Her goal is to raise money for research on management and cure of VHL.

Lois has agreed to develop the Professional Education Committee, helping us spread information about VHL throughout the community of medical

professionals, and perhaps also to add more information about VHL into medical school curricula. Ideas and contacts will be much appreciated. While Lois is not a medical professional herself, her mission is to make sure that wherever our young people may move in the course of their careers, they will find good medical care for VHL.

Ellen Lydon, Chairman of the Clinical Care Committee, joins the Board. Ellen is a registered nurse in Illinois whose husband has VHL. Ellen will be working with members to determine how the Clinical Care program can best serve their needs, and with the Centers themselves to determine how the program might be improved.

Your suggestions are very welcome in the shaping of the next years' agenda for each of these committees. The Board are all your representatives. We need to hear from you to help us direct our energies in the ways that will serve you best. Please take the time to share your thoughts and ideas with these people, and perhaps volunteer to help out!

Don Marshall

A husband, father, grandfather, uncle, great-uncle and brother-in-law to a large affected VHL family, Don has dedicated himself to helping others live with and find a treatment to manage VHL. For the past four years he has been the Publications Coordinator for the VHL Family Alliance, sending new patient packets to those seeking information and managing the printing and distribution of most VHL material. He also is the co-chair of the Mid-South chapters, including Mississippi, Tennessee, Louisiana, and Arkansas, along with his wife, Peggy Marshall. He also assists Peggy with the coordination of the 800 line, State Chapters, and creating the Chapter/800/ Internet menual for the VHLFA.

Don is a Vocational Electronics and Computer Instructor at the local Vocational Technical Center and is presently completing his Masters Teaching Program at Mississippi State University. Peggy and Don reside in Corinth, Mississippi, along with their two daughters and four grandchildren.

The future of the VHL Family Alliance depends on dedicated committment from many people, "I am glad I can offer any of my talents to this cause to help my World Wide Family to meet the challenges of Living with VHL."

Peggy Marshall was reelected to the Board of Directors to serve her second term. Peggy is Vice Chair of the VHLFA, Chair of the Chapters Committee and the 800 line Committee. Since she became Chapters Chair, she has added 22 new state chapters. The 800 Line is a committee of five that answers calls requesting information, needing assistance and having someone to listen to when support is needed. Peggy is also Co-Chair of the Mid-South Chapters and is a Day Care provider in Corinth, Mississippi.

Peggy feels, "There is more hope than ever to find a treatment for VHL through the efforts of the VHLFA, and I want to continue to be an active participant."

Audrey and Altheada Honored

Audrey Clifton, chairman of the North Carolina Chapter was honored for her work in growing the chapter. She has done an outstanding job of communicating with the medical community and general public in her state via newspaper and radio, as well as directly with physicians and hospitals.

The annual Minster award for Volunteer Service was awarded to Altheada Johnson of New York for her oustanding service. In addition to serving as Chairman of the Board and Chairman of the Membership Committee, she is one of the four volunteers on the Hotline Committee, answering calls for about three months each year, and attends meetings throughout the country as our representative, presenting posters and serving on panels, and generally keeping VHL and diversity visible at key meetings about genetics and cancer.

While we extend our special thanks to these two women, we also thank all the many volunteers throughout the world who make up the VHL Family Alliance, sharing themselves with others every day.

Peggy & Don Marshall, Mississippi; Terry & Barbara Redding, Florida.

Our thanks for Contributions . . .

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New VHL Handbook!

Along with this June issue of the newsletter, you will receive the latest issue of the *VHL Handbook, What you Need to Know about VHL*, basic information to families and medical teams to help people manage their health.

The Handbook is our highest priority project. Before the Handbook, it was nearly impossible for patients to find out the whole story about VHL — and nearly as hard for doctors! Thanks to a wealth of new research and publication about VHL in the past four years, there is a great deal more medical information now available, but the Handbook remains a key starting point for medical teams as well as families.

We are very grateful to the many physicians and medical research teams who have contributed to our learning over these last four years, with special thanks to our Medical Advisory Board, and to all the good questions we have received from members.

In the Handbook you will find screening guidelines for checking people at risk for VHL who do not yet have symptoms, and checking throughout the body for people who may have one or two manifestations of VHL. We have tried to be sensitive to the economics of testing. Nonetheless, there are very real reasons why MRI's are sometimes called for. The availability of imaging testing gives us the ability to see problems before there are symptoms, and in many cases this is the key to avoiding much more serious problems. If you can see and deal with kidney cancer tumors before they spread to other parts of the body, if you can see the growth rates of brain tumors and locate one that is beginning to grow at a faster rate, you have the opportunity to deal with it before there is higher risk to functions.

There are new sections on pancreas, epididymal cysts, hearing, and pregnancy. There is an expanded treatment of DNA testing, how to go about it, and where to find it. And of course there is a glossary of the terms your medical team will likely use in discussions with you, to help you understand their jargon.

Each individual will probably experience only a few of the issues described, but there is still no way to predict which ones those will be, so it is important to be watchful in all areas. Within a family, a larger number of these issues will arise at some time. Often people find that some issue which they or their doctors had attributed to stress turns up in the handbook. Understanding that it has a physiologic cause, there is more of a chance to fix it, or to keep it from worsening, and at least there is the comfort of knowing that it's not all in your mind.

Very often people call or write to say that even though it's hard to hear of all the things that could occur, it's so very much better *to know* than not to know! It's a very great relief to know that somebody understands what's going on, and that there is progress in finding the best treatment.

It's a little like playing a video game, where the character wanders around in the twisty little passages of the dungeon, going from room to room, collecting treasure. Then he steps into a dark room. Eery green eyes shine in the darkness, swords flash out of nowhere, and your character dies. But if you had known to pick up a fireball before you entered that room, if you had a map, or if you had known to keep close to the west wall, you could have survived that room and won the treasure.

That's not unlike having a rare disease like VHL. The Handbook is your map, and we share experiences to help you know, before you go through an experience, how best to survive it and maintain your health.

The Handbook is the beginning, but it's not the end! We are learning more all the time. Feel free to call or write for additional information, or for the name of some specialists in the area of concern who can consult on your particular case, review the scans, and provide some additional information to your local medical team. Having a more experienced eye looking at the scans, or getting the perspective of a physician who has experience with more VHL patients over a number of years, can make a world of difference in planning successful management of VHL.

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