VHL Family Forum

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The Human Genome has been Sequenced, Now What?

by Virginia Michels, M.D., Department of Genetics, Mayo Clinic[1]

When I see people in my office with VHL or other genetic disorders, and we go through tests and scans and plans for the next evaluation, at the end I always ask if there are any questions. Lately everyone has the same question: What's going to happen now that the human genome has been sequenced? So I thought that today I could give you some of my impressions of how the sequencing of the human genome will make a difference for medicine.

There are some gaps in the sequence, and some proofreadings and checks to do, but the consortium has announced that for all practical purposes the genome has been sequenced at least to some level. Although this is not a magical breakthrough, it's a major breakthrough, and it has happened very quickly since the researchers first decided that instead of simply finding genes one by one, there should be a concerted effort to sequence it all. It is hoped that this will move things forward faster. I'd like to give you some idea of the work remaining, and how I hope this will affect clinical care in the coming years.

The gene for VHL is on the short arm of chromosome 3. We can't see that gene under the microscope, it's too small. So let's look at a chromosome (see Figure 1), and dissect what's really in it, so that you have some understanding of what the scientists have been doing and where it is leading us.

To understand how this is all done, imagine these coils being unraveled into strings, and the molecules spelling out words. The molecules comprise a code of letters, not just eight or ten letters long, but thousands or tens of thousands of letters long. In spite of the very long length of the "word", each of those base pairs are made up of only four different letters: AGCT, which stand for adenine, guanine, cytosine, and thymine, the four bases on DNA. When you sequence a gene you learn the exact sequence of these letters. Obviously it took very sophisticated science to sequence the entire genome. But when you're done, now what do you do with it? Does it automatically tell us everything about how the genome functions? Very definitely not.

The next step is called "Annotating the Genome." This important job is to take this very long and complicated sequence, which is about three billion letters long, and start to make sense out of it. Here's one example, a very simplistic example of what the scientists have to do. Try reading the sentence:

T heca thidun dert hec hair.

(Yes, it's in English). If we know where to start and stop each word, we can make better sense of it:

The cat hid under the chair.

All we had to do is move the spaces. But in this example, it was relatively easy. We know what a cat is, and a chair, but what if we didn't know? What if we moved the spaces and got a sentence like this one?

The snurb hid under the fump.

It may look like a sentence, but we still don't know what a "snurb" is, or a "fump".

The new buzzword for this annotation process is proteomics. We're going to move from genomics to the protein that the genome encodes.

The gene in the cell unravels, and the DNA code makes a messenger RNA code, and in most cases this makes a protein. If all goes well, we get a normal healthy protein. So we talk about the VHL protein, and the other proteins that interact with the VHL

continued on page 2

Inside this issue!

Figure 1: *Structure of a gene*

protein. If the process does not go well and the genetic material is altered, then we get an altered protein, and it may not work. Our job now is to understand what alterations occur in the proteins so that we understand what is really causing the disease and why things are not working as they should.

This is a diagram (see Figure 2) of the VHL protein and how it acts with hypoxia inducible factor (HIF). If the VHL protein isn't working right it affects some other proteins and the cell begins to think it isn't getting enough oxygen. So it starts to make some new blood vessels to bring more oxygen, and vascular tumors begin to form. The VHL protein interacts with a number of other proteins and enzymes, each of which also has to be normal for this process to work.

If we know all this , if we know what the VHL protein is, why do we need the entire human genome? We have learned a great deal about the VHL gene from the researchers who have presented for the past two days of meetings in Rochester. But we know only 5-10% of human genes, and there are estimated to be somewhere between 30,000 and 100,000 human genes. Among those other 90-95% of genes that we don't yet understand, I can almost guarantee you that there are some other genes that will impact the function of the VHL protein. As we understand more about those influences on VHL, we are going to learn more and more about this disorder. We heard about one just yesterday from Dr. Maxwell (see inset). As we learn more about what the rest of the genome is doing, it will make a tremendous difference for VHL.

To make this more clear, and to help you understand why better understanding can lead to better treatment, I want to provide a classic example for which Goldstein and Brown won a Nobel prize some years ago in medicine. It has become a classic example, and it's another disorder that we've all heard of: arteriosclerosis, or hardening of the arteries. We've all heard that elevated cholesterol levels is one of the factors that can predispose us to hardening of the arteries. These investigators found that there was a LDL receptor that has to be formed appropriately in the cell, similar to the little notch that HIF-1 fits into in Figure 2, but shaped more like a little pit. This LDL receptor protein has to find its way to the cell membrane, it has to enter the little pit. If this process worked well, the receptor would bring cholesterol into the cell as a particle called LDL cholesterol, and process it. However, if the LDL receptor wasn't working well and didn't bring the cholesterol into the cell, the cell got confused and said "We don't have enough cholesterol, we'd better make some more!" (Does that sound familiar? It's like "We don't have enough oxygen, we'd better build some blood vessels.") So it's the same kind of problem as in VHL -- there are some abnormal signals going on because of a lack of the appropriate feedback.

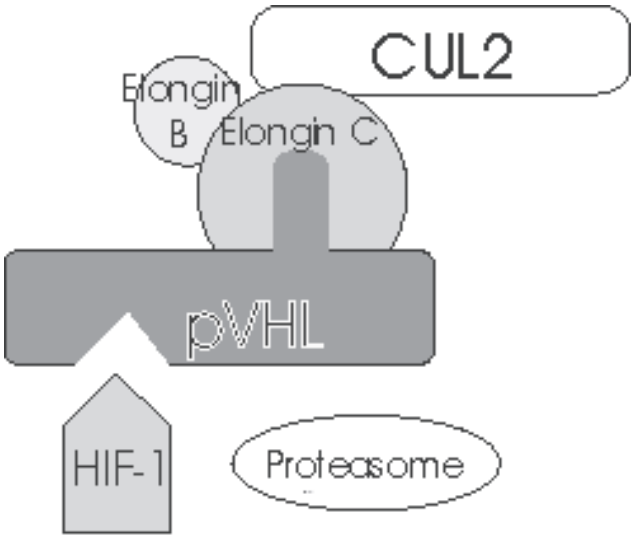

Figure 2: *pVHL attracts and degrades HIF-1 molecules, thus regulating the levels of HIF-1 in the cell.* Nature, *Vol 399 (1999) 203-4.*

So one could say that if we were going to treat this disorder, maybe we'd better find a way to get that protein back into the cell, or get it into the cell so that it gets into the pit, or make sure that the process works right. Yes, that would have been one approach. But if that were the only approach, we'd still be looking for those answers, and we still wouldn't have any treatments for this disorder. But instead the investigators widened the scope of their inquiry. They tried to find out what else was going on -- what other proteins are active in this process? And they found some of these other proteins, such as the enzyme HMG CoA Reductase. Next, researchers found some medications, some of the statin drugs, that turn off that confused enzyme that was making more cholesterol that was clogging up the arteries. These medications essentially tell that enzyme to stop making cholesterol . This has proven to effectively lower many people's cholesterol into a range where they are no longer at risk for arteriosclerosis.

So the more you understand, the broader you widen the circle of understanding of all these proteins and how they interact, it gives us more and more treatment options. I do believe that the same kind of thing will happen with VHL and other genetic disorders. The more we know, the better chance we have that somewhere along the pathway, along the chain of events that occurs during this process in the cell, we will find something that will be effective. Maybe it won't be effective for each complication, but we will chip away at the problem and will find medications that will be effective for some of the challenges in VHL.

Dr. Maxwell on HIF-1

De. Patrick Maxwell of Oxford University in England showed that the VHL protein (pVHL) regulates a substance known as the hypoxia-inducible factor (HIF-1). He explained that four billion years ago there was very little oxygen in the atmosphere. As photosynthesis went on, the levels of oxygen in the atmosphere increased, and organisms needed a mechanism to protect themselves from conditions of too much or too little oxygen.

When you are at high altitudes, oxygen is low. When you are wounded, additional oxygen is needed by the wounded tissues for healing. And when a cancer tumor is growing, it needs more oxygen to support the high rate of growth of the cells.

Otto Warburg won a Nobel Prize for his demonstration of the high correlation between growth rate of the tumor and availability of oxygen. When oxygen is low, we see the levels of HIF-1 in the cell begin to rise. HIF-1 has been shown to activate a number of important genes that are important in vascularization of tumors during conditions of low oxygen.

It looks like pVHL normally targets HIF-1 for destruction so that HIF-1 will not continually activate these genes (see Figure 2.) Just as we know that VEGF is needed for tumor growth, we now know too that oxygen is necessary to support that growth. Perhaps by doing something to inactivate HIF-1 in the cell we could also constrain the growth of a new tumor. There are probably other important proteins that are regulated by pVHL which might also separately be targeted by therapies to limit tumor growth.

Additional reports from the Basic Science Day can be found on the VHL website, www.vhl.org/conf2000

Another thing that is important to remember is that a particular gene can function a little bit differently in different cells. So a gene that works one way in a brain cell might have a different role in a pancreas cell. You can readily see how this relates to VHL. When that gene is not working right in the brain, we get a hemangioblastoma which is not a malignant tumor, and when it's not working right in the kidney we know that it can cause a malignant tumor. We also know that malignant tumors generally are made up not just one abnormality. There are many different genetic changes that contribute to the development of the cancer. For someone in the general population it takes even more events to accumulate before that person gets a malignancy. If we understand more about how all the genes work, we might be able to find out why the same VHL gene in the brain does not cause malignancy, and take that factor and somehow use it to treat the kidneys and keep the kidney tumors benign and non-cancerous. Wouldn't that be a wonderful breakthrough?

Here's another example. We really don't understand why a small VHL hemangioblastoma may sometimes sit quietly in the cerebellum for years, but then one day it begins to grow. It becomes a bigger lesion, perhaps with a cyst. If we can begin to understand through the Human Genome Project what proteins are being expressed and what genes are being turned on, and why these tumors are suddenly being "activated", maybe we could find a marker, something that might be identified through a blood test, that would indicate when a tumor is going to start to act up. Perhaps then we would know when to treat it before it grows. Or maybe if we could find such a marker, we might be able to devise a medication that would halt that next step and keep the tumor quiet and prevent it from growing.

I am hopeful that in the next decade these advances will move the whole field of genetics forward. Our understanding of genes, of the proteins they make, and how they interact, will be like a snowball. It starts very small, but as you roll it along the ground, it gets bigger and bigger, faster and faster.

Similarly, our accumulated knowledge about the VHL protein and its associated proteins and enzymes will eventually lead to some major breakthroughs in the new millennium for treatment of VHL disease.

1. Based on her talk at the VHL Symposium, 21 July 2000

Dozens of new genes in tumor blood vessels

In the August issue of the journal *Science*, Scientists at Genome Molecular Oncology in Framingham, Massachusetts, in conjunction with researchers at Johns Hopkins University in Baltimore have identified dozens of new genes involved in angiogenesis, the building of blood vessels. "This gives us a whole bunch more of potential targets for cancer therapy," Brad St. Croix of Johns Hopkins told Reuters, "but it is going to take several years to figure out which of these are going to be useful." This underscores Dr. Michels' point above that in broadening our knowledge of genes and how they interact we will discover many new possibilities for impacting tumor growth.

Reported August 18, 2000, by Reuters and CNN.

Pansies for Hope

Hope sees the invisible,
feels the intangible and
achieves the impossible.

Help achieve the impossible!

Give to advance research on VHL!
see page 15

Consensus Meeting

The Fourth International Symposium on von Hippel-Lindau, July 20-23, 2000, in Rochester, Minnesota, consisting of 180 assembled researchers, physicians, and members of affected families from 17 countries agreed on the following conclusions from the meeting:

DNA testing in childhood

Genetic testing for VHL in early childhood is justified **(a)** because of early age at onset, and (b) because of availability of treatment. It is still the choice of the individual family whether to perform DNA testing in childhood. However, all untested children must be considered to be at risk for VHL, and preventive screening is essential.

A genetics professional should be involved prior to any DNA testing (children or adults).

This symposium strongly disagrees with the misuse of DNA status information by insurance companies, employers, or others. DNA status information should be used only for the medical benefit of the patient and in any research to which the patient has agreed.

Prevention

Based on data from NIH, people with VHL are advised not to smoke, and to reduce their exposure to second-hand smoke.

People with VHL should be alerted that there is evidence (Brauch et al) to suggest that exposure to Trichlorethylene and associated substances may accelerate VHL. Confirming evidence is needed before recommendations can be made.

Families in Japan have a significantly lower rate of eye tumors than people with similar genotypes in other parts of the world. This may prove important for prevention.

Adrenal

Dr. Green recommends beginning screening from age 3-4

There is compelling evidence (Lenders et al) that Plasma free metanephrines (PFM) is the most sensitive and specific test for pheochromocytoma. We are encouraged by these results, and believe that PFM can be a useful adjunct to existing testing methods. Standards for children still need to be established.

Guidelines for drawing blood and submitting samples for analysis to NIH or Mayo Clinic can be found through http://www.vhl.org/pheo

Clinical neurochemistry laboratory procedures for laboratories interested performing this test are available at http://www.catecholamine.org

Because very small tumors can be identified in this manner, it is important to have a threshhold for watching/operating on tumors.

Adrenal-sparing surgery should be the standard of care for people with VHL.

Organ-sparing adrenal surgery should be performed laparoscopically whenever possible.

Kidney: When to Operate

The "3-cm. Rule" is still the guideline for watching kidney tumors. This is based on data from centers worldwide, which does show considerable variation. There is still some small risk of metastasis (less than 1%) which should be disclosed to the patient. Any relevant familial variations should be taken into account.

Pancreas

Screening of the pancreas is important. Tumors may be observed up to 2-3 cm.

Surgery to drain of cysts should only be undertaken when needed to manage pain.

Organ sparing surgery is preferred when surgery is necessary.

We are encouraged by early results, and would like to see continued evaluation of PET to assist in distinguishing neuroendocrine tumors from cystadenomas.

CNS

Risk of spontaneous hemorrhage of spinal lesions is very low (0% in Sarkar study).

Need for a retrospective study of CNS lesions treated with stereotactic radiosurgery with longer follow-up, to rule out periods of quiescence and evaluate danger of longer-range complications.

Presymptomatic screening for brain and spinal cord lesions is critical to maintaining health and function, to monitor growth rates and make informed decisions about course and timing of action.

An appropriate program of screening and counseling has been proven to dramatically reduce morbidity, fatality, and anxiety among people with VHL.

Review of Screening Guidelines

We reviewed the Screening Guidelines in the *Handbook* and suggested the following changes, underscored, for consideration of the Medical Advisory Board and possible inclusion in the next revision of the *Handbook*:

From Conception

· inform obstetrician, communication among doctors

From birth

· inform pediatrician of family history

Ages 2-10

· annual physical & neuro assessment by pediatrician informed about VHL (BP, neuro, nystagmus, pupil)

Beginning about age 3-5

· eye exam with indirect ophthalmoscope or better

· test for elevated catecholamines in 24-hour urine, or with plasma free metanephrines or 24-hour urinary fractionated metanephrines where available

Note: The age to begin screening was reduced from 4-6 to 3-5 based on data from several participants indicating more eye and

pheo involvement in young children than had previously been thought. Earlier treatment of eye lesions can save vision; many reported data that pheos are best treated in their early stages of development, before they become sufficiently active to cause heart and vascular complications or have a pheo incident provoked by a minor accident.

Ages 11-19

· every 6 months, eye exam

· annually, physical with informed pediatrician

· include baseline scrotal examination in males*

· test for elevated catecholamines in 24-hour urine, or with plasma free metanephrines or 24-hour urinary fractionated metanephrines where available. This test should be performed before any surgery, or if pregnant.

· ultrasound of abdomen, including ovaries in females

· every two years: MRI with gadolinium of brain and spine. Annually at onset of puberty or before and after pregnancy, or before any surgery.

Note: There was a discussion whether to keep or omit the scrotal check since action is not taken unless there is rupture. It was decided that as good ongoing practice for all men for the early detection of testicular cancer (analogous to breast self-examination in women), and as a baseline in case of any questions, this manual check should remain. Ultrasound only if deemed necessary.

Age 20 and beyond:

· eye exam with indirect ophthalmoscope

· quality ultrasound

· at least every other year, CT of abdomen w w/o contrast, but NOT during pregnancy, including review of any possible APMO's in females[1]

· ultrasound preferred during reproductive years

· physical exam by informed physician

· test for elevated catecholamines in 24-hour urine, or with plasma free metanephrines or 24-hour urinary fractionated metanephrines where available

· every two years: MRI with gadolinium of brain and spine (and before and after pregnancy)

· audiometric exam. If hearing loss, tinnitus, vertigo, then add MRI of Internal Auditory Canal.

Requests for presentations in 2002

Please include APMO's[1] in the screening, to serve as a baseline in case of gynecological questions.

Please report all genotype/phenotype information to the French VHL database (available through www.vhl.org/research). Grouping this data in a consistent format will give everyone a larger pool of data on which to base research.

We need a study of factors contributing to earlier versus later metastasis of kidney tumors: Specific mutations? Modifier genes? Other characteristics? There seem to be familial variations in time-to-metastasis.

We need a retrospective study of CNS lesions treated with stereotactic radiosurgery with longer follow-up, to rule out periods of quiescence and evaluate danger of longer-range complications.

We need a study of the effects of hormone shifts or hormone levels in women (adolescence, pregnancy, going on/off the pill, menopause). If a protocol can be written to gather data from women in a consistent way, the women of the VHLFA will gladly participate in such a study.

We need more information on the implications for people with VHL of the Swedish study on mobile phones and brain tumors. In that study it was said "that the use of cell phones can cause brain tumors, especially if one is already predisposed toward tumors." Does this imply that people with VHL are at increased risk with mobile phones?

1. Adnexal papillary cystadenomas of probable mesonephric origin (APMO) are the female counterpart to the benign cystadenomas found in men with VHL. They are benign, but can be mistaken for other more threatening tumors in this area that occur in the general population. More information is needed to distinguish the two and prevent over-treatment.

"Health is not static; it is normal to lose it periodically in order to come back to it in a better way." -- *Andrew Weil, M.D.*

It's all in your Head

I have lived with VHL for many years. I lost my left eye. I had extreme pain in that eye nut I am not sure I could say it was directly related to the VHL angiomas in the eye or the side eye complications that they caused. I also had pain after a kidney surgery -- much of this was due to the way things were healing and went away over time. I know everyone is different though.

One thing that I do know…. Pain is never imagined, it is very real to the patient -- what ever the cause. I went through literally hell a few years ago feeling pain in my back and legs. I was told in an indirect way by a couple of doctors that the pain was in my head. Unfortunately I believed it for a while. I later found out that I had a tumor in the spinal cord with an associated cyst. This was diagnosed by a Neurologist who realized that VHL could manifest itself this way and sent me for an MRI. I guess my point is -- never let any one say the pain is not real. Even if it is panic related, it still hurts and I am sure there are things that can be done to assist in that. -- *Elizabeth B., Alabama*

Teamwork for Health

"It was great to meet all the folks at the conference. As the locals would say here in Alabama, you threw one 'humdinger of a shindig!' I've remarked to several of my colleagues that it was the first time I had ever been to a conference where researchers, doctors, health care professionals, and patients were all attending the same sessions and contributing — the synergy was remarkable. My compliments to all the organizers for your remarkable skill in keeping such a wide variety of people moving in the same direction." — *Michael Brown, O.D., Veterans' Administration, Huntsville, Alabama*

78 health care professionals and 101 family members gathered in Rochester, Minnesota, on July 20-23 to learn from one another about VHL, and to share ideas for improvements in diagnosis and treatment.

Thursday was devoted to Basic Science, understanding the mechanics of what goes on in the cell: how the normal VHL protein (pVHL) influences normal biology, and how the lack of pVHL causes tumors to form. It's like solving a large and complicated puzzle. The good news is that many of the puzzle pieces are already known, and others are falling into place. (See website for the Basic Science Summary).

While 75 people began their attendance on Thursday, most began on Friday. Health care professionals were encouraged to attend the genotype/phenotype alignment presentations on Friday morning, while the families, especially those attending a meeting for the first time, were encouraged to attend "VHL 101", led by Joyce Graff. There were 34 people in the class. The first half of the class was spent introducing ourselves and telling our VHL stories. That was a learning experience in itself, as there was a broad spectrum of experience represented in the room. We passed out copies of the *Handbook*, reviewed the highlights of what the doctors would be discussing in depth, and went over some of the scientific terms that would be used. At the Annual Meetings previously held in the United States, VHLFA asks the presenters to aim their talks at a well-informed lay audience, and to keep the language appropriate for that group. The purpose of a Symposium, however, is to allow the health care professionals to talk with one another, so at this symposium there were no constraints on the scientific language.

At each Symposium the assembled participants work together to move our collective knowledge about VHL forward. At the Honolulu Symposium in 1996 we asked that in future, the reports from the various countries should try to present their findings to show characteristics associated with particular mutation types. For a specific mutation (*genotype*), what disease characteristics (*phenotype*) do they find? While the new people were in the VHL 101 class, the health care professionals and more experienced family members listened to the genotype/phenotype alignment reports from France, Germany, Japan, Italy, Netherlands, and the United States. Dr. Frederik Hes reported more insertion mutations in the Netherlands than in the U.S., and a preponderance of CNS hemangioblastomas.

Altheada Johnson of New York, retiring Chairman of the Board, opening her award -- a VHL blanket. See page 16 for a full shot of the blanket.

After eating lunch together, the two groups joined beginning Friday afternoon and were together for the next two days. Dr. Virginia Michels set the tone of the meeting with her keynote address (see page 1). Joyce Graff explained what a Clinical Care Center does, providing backup and second opinions for local doctors less familiar with VHL. Even the CCC's don't know everything, so they have the Expert Centers to rely on in dealing with tricky issues: US NIH, Freiburg, Paris, Jerusalem, and Tokyo.

Dr. Karol Krzystolik from Poland and Dr. José da Rocha from Brazil told us about their relatively new studies of VHL in their countries. For 4 and 3 years respectively they have worked to identify and provide appropriate treatment for people with VHL. There are dramatic differences in the health of the people diagnosed with symptomatic lesions, and those diagnosed early through DNA diagnosis. Dr. Krzystolik's experience has led him to believe that it is important not to wait for people to come with symptomatic lesions, but to identify people early, before there are symptoms, and work with them in a program of prevention.

Tom Rodenberg, an attorney from Kansas, shared with us his experiences as the family negotiator with health insurance carriers in a large family with VHL. Patricia Rasmussen spoke about the importance of making sure your wishes are clear on paper and with your family so that in a case where you may be unable to speak for yourself for a time, you can be sure your wishes will be carried out. The best instrument for

Chris H. came from Belgium, Rhonda S. came from Malaysia.

most people is a "health care directive or power of attorney" which enables your chosen friend or relative to speak for you whenever you are temporarily unable to do so. Tom and Patricia both advised us to educate ourselves, meditate on it, take the necessary steps, and remember to change it as circumstances change in the future. Forms are available at doctors' offices and hospitals.

Dr. Catherine Stolle (http://www.med.upenn.edu/~gdrs/) gave an excellent overview of the process of DNA testing, which will be made available in a future newsletter. Getting a DNA test is in part a fairly routine laboratory test, like any other blood test. But the test is not the biggest part of the process of determining your VHL status. After you get the results, then the real questions begin.

On Saturday morning Dr. McClellan Walther of the U.S. National Cancer Institute (NCI) delivered the keynote address, describing the work of his group on kidney cancer. Kidney cancer is rising sharply, up 30,000 cases per year in the U.S.. It accounts for 12,000 deaths each year, and there are 200,000 people alive with a history of kidney cancer. NCI has been studying the changes in chromosome 3 associated with kidney cancers, establishing genetic diagnoses for kidney cancer, and identifying targets for therapy.

A link has now been established between smoking and kidney cancer. Smoking also increases the risk of other cancers, but VHL patients who smoke were found to have faster-growing kidney tumors compared to nonsmokers. They studied 53 VHL patients with 117 kidney tumors over 3 years, and the smokers had significantly shorter tumor doubling times than the nonsmokers. People with VHL are therefore advised not to smoke, and to reduce their exposure to second-hand smoke.

NCI has worked out a strategy of "resetting the clock, not curing" kidney cancer. They wait until one of the tumors reaches a size of 3 cm., and then they remove all the tumors they can see, "shelling out" the tumors, with a thin (1-2 mm) margin. They have generally been able to do this with minimal loss of kidney function. So far, following 52 patients over 1-17 years, there have been no metastases. The number and position of the tumors is unimportant, the strategy is working. See also page 12 for a less invasive experimental approach.

Six physicians reported on ***clinical research programs*** in their countries, calling out some interesting differences from one country to another.

Dr. Gladys Glenn of NCI described their clinical program, studying families with various kinds of familial kidney and pancreatic cancer. Pancreatic islet cell tumors tend to spread to the liver, and they have had some good results from infusing liver cells with chemotherapy. Dr. Taro Shuin found that Japanese patients have more of the rarer tumors (e.g. liver, pituitary, skin), and cases where age of onset is not typical. Dr. Giuseppe Opocher reported that in Italy they now check all people diagnosed with renal or pancreatic cancer for the VHL mutation. His clear conclusion is that an integrated clinical approach improves the quality of health care, helping people identify the various clinical specialists needed to treat the problem.

The series on ***Clinical Issues*** began with two physicians reporting improvements in diagnosis and treatment for adrenal tumors. Dr. Jacques Lenders of the Netherlands described a new test for pheochromocytoma (reported in VHLFF 7:4, December 1999), Plasma Free Metanephrines (PFM). This test is not yet widely available, but it is not expensive to implement. The laboratory procedures to be followed in doing the test are now available on the internet at www.catecholamine.org and any laboratory that wants to do the test is invited to obtain them. In tests conducted so far this test has been found to be more specific (100%) to pheochromocytoma than any other test, and more sensitive (99.3%) than any other. In a test among 131 patients the test missed only one very small tumor in a person with VHL. The test is currently offered for about $230 by Mayo Clinic, with additional labs coming online rapidly.

Dr, Geoffrey Thompson noted that the first surgical resection of a pheo was done at the Mayo Clinic in 1927, and the patient lived to the age of 93. Untreated pheos are often first discovered at autopsy: 75% of those recorded at Mayo died suddenly, one-third during or shortly after childbirth. He is looking at PFM testing, and finds CT the best imaging modality for finding pheos. He prefers laparoscopic surgery unless the situation is tricky. If the pheo is too close to the vena cava or main artery, or if it is malignant, he prefers open surgery. Posterior adrenalectomy often

L to R: Vicki Couch, Dr. Virginia Michels, Peggy Marshall, and Kelly Heselton introduced the speakers and kept the meeting running smoothly.

leads to chronic pain, bothersome numbness, and weakness in the oblique muscles of the back. He finds that while laparoscopic surgery takes a bit longer operation, there is less pain and more patient satisfaction.

Dr. Walter Hall of the University of Minnesota described his work with intraoperative MRI. He has a special operating room and an Interventional MRI system designed for intraoperative use. He finds that it allows him to do surgery more safely, since the MR can calculate within 14 seconds a comparison to previous images, determining for example whether something seen on the image is the same tumor seen before surgery, or something caused by surgical trauma. He has had particular success with glioma. He can do "functional imaging" to map motor, voice, or memory areas of the brain just before putting the patient to sleep. This marks areas to avoid in dissecting the tumor. They have limited but positive experience with hemangioblastoma. He invites inquiries. 612 624-5108 or hallx003@tc.umn.edu

Dr. Hartmut Neumann, whose work in "preventive medicine" with VHL was recognized by the insurance providers of Germany in 1999, has turned his focus to finding undiagnosed cases of VHL throughout Germany. He did a nationwide study of 270 patients with symptomatic pheos. 100 had inherited conditions, including 76 with VHL, 17 with MEN2, and 6 with NF1. Of those under age 10, all had VHL mutations. Between ages 11-19, 60% had inherited pheos, and all but one had VHL mutations. He is hoping to do a nationwide study of other aspects of VHL to find what the penetration of VHL is in each of these issues.

Dr. Jane Green described her work over the last 20 years with families with VHL in Newfoundland. In this remote part of Canada there are large families (12-15 children). In the first family they studied in 1982 there were 24 affected members, 10 of whom were already deceased, 10 with blindness in one or both eyes, many with neurological disabilities or anxiety. Through a systematic screening program, 84 tumors were identified in the first few years. As their understanding of VHL increased, more VHL families were referred to them and entered the screening program. While these families had severe disease in 1982, in the last 20 years there have been only four more deaths, and four more blind eyes. 150 tumors were treated successfully, 3 renal sparing surgeries, two people on dialysis, and one renal transplant.

She finds that a clinical screening program allows earlier diagnosis and treatment. Genetic testing allows more efficient screening, since you can target the right people for conscientious follow-up. She therefore feels that genetic testing for VHL in early childhood is justified, both because of the early age of onset on pheo and eye problems, and because there is now effective treatment to prevent the worst consequences of these occurrences.

She has done extensive cost comparisons for the Canadian government. Just from the perspective of the health care system, the cost of management of VHL with screening is lower than the cost of management of symptomatic disease. More than that, the societal cost of managing a family with early deaths and disabilities is great than the cost of health maintenance.

Three talks focused on ***preserving organ function*** in the kidneys and pancreas. Dr. Walther presented the work NCI is doing on pheochromocytoma, which occurs in VHL, MEN2, NF1, and other familial conditions, as well as sporadically and outside the adrenal (extra-adrenal carotid body tumor). They have 12 patients with adrenal tumors which were not functioning for several years, which they have chosen to watch until they begin producing hormones or until the patient is planning a pregnancy.

Dr. Pascal Hammel of the Francophone VHL Study Group shared his work on the pancreas. Now that there are better strategies for CNS and kidney tumors, neuroendocrine tumors of the pancreas are becoming relatively more important. 75% of VHL patients in France have pancreatic lesions. In 7% of the cases, pancreas is the only affected organ. There are usually no symptoms. Of 153 tumors, 10% were islet cell tumors, and 10% were neuroendocrine tumors (NET), and the rest were benign tumors or cysts. NETs sometimes cause pain (compression or acute pancreatitis). CT or MRI can identify them, and scintigraphy can be used to confirm the diagnosis.

Dr. David Goldfarb reported experience with partial nephrectomy at the Cleveland Clinic. They have found that conservative surgery leads to longer survival and better quality of life. They use 3-dimen-

Welcome, Henrietta!

Henrietta was born in Sweden on Saturday, July 22, while her father, Mikael, was attending the VHL Symposium, 7000 miles away in Rochester, Minnesota.

"I've been aware of the fact that VHL runs in my family ever since I was a child. My father died from a VHL related brain tumor in 1961, when I was three. But not until last year, when my five year old daughter got a tumor in her eye, did I start to really look in to what VHL is. The Family Alliance, has been of immense value to me -- and my daughter. The tumor was very near the optic nerve and her vision was 10% in that eye. The doctors in Sweden were insisting on laser treatment, which would have ruined the central vision. Through the Alliance I got in contact with a German professor, Michael Foerster, who managed to save my daughter's eyesight! Prof. Foerster operated, using a partly new technique, and today no one can see a trace of the tumor in her eye! She is wearing an eye patch over the good eye to make the bad one work harder, and she is up to 80% vision."

"My wife and I decided that I should come even though the baby was due to arrive, because of the importance of this information to myself and my family. It's been a wonderful experience!"

sional volume rendered CT to ensure identification of all existing tumors of resectable size, and a detailed assessment of the vasculature, the kidney tissue, and the collecting system. It is a non-contrast integrating information provided by arteriogram, venogram, IVU, and 2-D CT that produces a 3-5 minute video showing the location of kidney relative to ribs, spine. It helps to predict what will be encountered in the operating room, and removes the need for preparatory films. Just as NIH is using heat (Radio Frequency Ablation), Cleveland is using a freezing probe to destroy kidney tumor tissue, which can be done successfully laparoscopically. They have now treated 34 tumors less than 4 cm. in 32 patients, most of which are RCC in older patients (mean = 65.4 years) who required an average stay of 1.8 days, 15 minute procedure, and 2 weeks to normal activity. At six months there was no evidence of cancer. This may be a possible treatment for some VHL patients.

Five physicians presented their findings on ***hemangioblastomas of the CNS and Retina***. Dr. Atom Sarkar of the Mayo Clinic talked about the 31 VHL neurosurgical patients treated at Mayo. Two-thirds of them had some lesion in the kidney, pancreas, or adrenals. They found that incidence of spontaneous hemorrhage of spinal tumors was very low (0%). Not all spinal tumors require removal.

One-fourth of all their VHL patients have some lesion in the spine. He noted that before operating on the spine it is critical to understand what involvement

The Symposium was held in Phillips Hall at the Mayo Clinic.

there is in the cerebellum. If there is a mass effect in the cerebellum, and you release the pressure in the spine, the brain could herniate into the spine and cause a fatal accident.

Dr. Tung Nguyen of the U.S. National Institute for Neurological Disorders and Stroke (NINDS) described the research he has been doing to learn more about the natural history of CNS lesions, in hopes of being able in future to predict which of the various small tumors we can see on medical images is likely to grow and when. Because of the potential complications from treatments, they do not want to operate until it is truly necessary, until there is some kind of neurological compromise. If we could predict which tumors were thinking about growing, we could possibly use less risky therapies such as stereotactic radiosurgery or gene therapy to inactivate these tumors before they got to a symptomatic size. In his analysis of 88 patients, symptomatic lesions grew faster than asymptomatic lesions. 26% of the tumors studied grew in two "phases," with intervening periods of quiescence. Of tumors treated with stereotactic radiosurgery, 90% of the lesions stabilized, shrank, or disappeared, leading to the conclusion that this is a useful therapy for tumors that meet its criteria for success. But even if a tumor shows no growth over a 3-year period, is it really inactivated, or is it a growth plateau? We need to refine the criteria for evaluating these tumors.

Dr. Nguyen is looking for more indicators of the readiness of a tumor to grow, including possibly checking the levels of VEGF in the blood. He is also examining other factors that might cause tumors to grow. One area of inquiry is hormones. They have found a progesterone receptor in hemangioblastomas. There is some suggestion that pregnancy or puberty can accelerate tumor growth.

Dr. Mika Niemelä of Finland reported his study using interferon alpha to treat hemangioblastomas (hBs) of the CNS. He found no decrease in size of existing hBs, but no new hBs during the treatment. One patient had a new lesion 9 months after the therapy ended.

Dr. Hélène Dollfus of the Francophone VHL Study Group studied the natural history of VHL tumors of the retina over time among 240 patients ages 6-71 years. She found that most activity occurred during ages 10-19, with the number of new hB per year decreasing with the age of the patient. She finds that the period of greatest sensitivity to eye damage is 15-30 years. The larger the number of hBs, the greater the risk to the vision. Her study also identified that patients with more pancreatic manifestations tended to have less retinal involvement.

Dr. Hiroshi Kanno of Japan described 43 cases of hB 1975-2000, 13 of whom have VHL. He found that the monoclonal antibody against vhl protein (VHL40) reacts to both mutated and wild type proteins of vhl gene. Sporadic hBs have the same protein expression as VHL-related ones.

Sunday morning ***Jay Platt*** of Georgia (see article page 13) shared with us some inspiring stories from his 2160 mile hike of the tough mountainous terrain of the Appalachian Trail. More than a physical effort, it was an exercise in commitment which taught him many life lessons, which he shares in his new book.

Dr. Peter Choyke of the diagnostic radiology department of the NIH shared his experiences with uses of ***imaging in VHL diagnostics***. He said that ultrasound is particularly well suited to children because it doesn't matter if they wiggle or squirm, it's like a movie.

Ultrasound can be used intra-operatively, even on a laparoscopy probe, to avoid the possibility of removing healthy tissue. Intraoperative MRI is also an important tool. Radio frequency ablation can be used to cook tumors of the kidney, but is less likely to be useful in the pancreas, and is not useful in the adrenals as it would make the pheo angry.

Telling the difference between a cystadenoma and a neuroendocrine tumor is not easy — it's a judgment call. It is easy for radiologists in the field to overreact to these tumors. Location is important, especially in the pancreas. Positron emission tomography (PET) is a radioactive technique that measures the sugar uptake. It is still expensive and not yet widely available, but it shows you what is metabolically active in the body, so it is very useful in differentiating the neuroendocrine tumors from cysts. The contrast dye is excreted into the kidney, so structures in the kidney are hard to see.

In general he feels it is best to choose the method that is best for you and stick with it. If you move from one modality to another, you don't know whether it's

Jon Tobin (volunteer crew member from Minnesota), Mikael E. from Sweden, and Deb C. from Michigan enjoy getting to know one another over dinner.

you that changed, or the difference in technique. He stressed the importance of regular screening, and doing good analysis at the first sign of symptoms. He advised patients to advocate for themselves, and to go to centers with the best equipment, and maintain consistency in your medical imaging records. Imaging provides early detection, and early detection means better outcomes. He also stressed the importance of communication — all the doctors involved need to understand and communicate with one another.

If you have a reaction to contrast, it is usually to ionic contrast. Non-ionic is more expensive, but causes less reaction. Another technique to lower reaction is to slow down the rate of injection. Talk with the doctor about an anti-emetic agent. Dr. Choyke has found gadolinium to be the safest contrast agent he has dealt with — it's more expensive, but it adds a great deal to the scan and enables him to look for areas that are active. Contrast uptake is not specific for tumors, but it is very helpful in VHL.

There was a question whether open MRI's are as good as the closed ones. He said that three years ago he would have said no, but today, especially if you require sedation to go through a closed MRI, the open ones are probably okay. It takes longer, but the result can be as good especially if it helps you avoid sedation.

Dr. James J. Augsburger of the University of Cincinnati and Dr. Klaus-Martin Kreusel from the Free University of Berlin, Germany, shared their experiences with *radioactive plaque therapy* for large eye tumors. They choose this modality when dealing with larger tumors, extrapapillary locations, with persistent progress of the tumor or its secondary abnormalities. Ruthenium brachytherapy (Rub), involves suturing a ruthenium plaque to the globe of the eye. The German team has now treated 35 angiomas in 32 eyes. All angiomas were destroyed, and all eyes were preserved, but vision was not always preserved. There are still questions whether the plaque therapy may

induce other cells to mutate and form future angiomas. Both stressed that the truly "best therapy" is pre-symptomatic screening and maintenance of small lesions with laser therapy, as the larger the tumor, the higher the risks of any procedure.

Four physicians shared their experiences with ***management of retinal angiomas.*** Dr. Helmut Buettner of the Mayo Clinic; Dr. Emily Chew of the U.S. National Eye Institute (NEI), Dr. Michael Gorin of the University of Pittsburgh; and Dr. Kreusel from Berlin.

Dr. Buettner reviewed the monitoring and maintenance of small lesions with laser, and larger tumors with cryotherapy. Earlier treatment is preferred, as cryo causes more scarring and more vision impairment. Dr. Chew's research shows that VHL eye tumors have been shown to have genetic alterations of the VHL gene. Under the microscope, they are identical to VHL hemangioblastomas of the CNS. She is testing drugs that block VEGF production as a way of limiting the vascularization of VHL tumors, and are using these therapies as well for diabetic retinopathy. Some of the retinopathy drug trials are now in Phase 3, and these may prove useful for VHL as well.

Dr. Gorin reported his work using fluorescein potentiated argon laser (FPAL) to treat 55 angiomas in 25 eyes of 17 individuals, with very good success. He stressed the importance of treating very small lesions because they are trivial to treat at that stage, and much more difficult to control when they are larger.

Following the review of Thursday's Basic Science presentations, Dr. Adrian Harris from Oxford, England, shared with us the preliminary findings of his ***clinical trials*** with the anti-angiogenic drug SU5416 from Sugen. This drug must be administered intravenously, three times a week in the doctor's office. There will be an oral form next year, and oral drugs from two other drug companies as well.

SU5416 is one of many new drugs that target Vascular Endothelial Growth Factor (VEGF). It has been shown to be in high supply in cancer tissues, growing a blood supply to feed the cancer tumor. It is therefore a very good target for a drug that wants to stop cancer tumors.

SU5416 blocks the receptors on the surface of the blood vessel that respond to VEGF. Instead of actually lowering the levels of VEGF, SU5416 reduces the sensitivity of the blood vessels to the VEGF signals. At this time they are working only with patients whose cases cannot be treated with standard treatments. Results to date have been very mixed, with no dramatically positive results to report. The drug does not seem to be effective in shrinking or stopping the growth of well-established tumors. Ultimately, we will probably need a combination of multiple drugs to work on the same tumor simultaneously with multiple strategies.

Another possible strategy is to target the over-production of growth hormone. Just as families report rapid progression of lesions in adolescence and pregnancy, there are drugs used to treat over-production of growth hormone in pituitary tumors — somatostatic analogs — which are being used successfully in treating diabetic retinopathy, where growth factor synergizes the angiogenesis and makes it worse. He is in fact treating one patient with a somatostatin analog.

He underscored the importance of depositing tissue with the tissue bank. It is critically important to research to have tissue material to test new drugs in the lab to determine which ones are most helpful with particular tissue types.

There is a new test using a positron emission tomology (PET) scan with an antibody that picks up VEGF. You inject the tracer, it is soaked up by VEGF, and then lights up on the scan to indicate the amount of VEGF in difference parts of the body. This test is in the process of FDA approval now. He expects it will be used for every cancer patient, and also for VHL patients.

The VHL protein has now been shown to be an important factor in the regulation of a number of important proteins in the body and play a role in angiogenesis: PDGF beta, Endothelin1, Adrenomedullin, TKF alpha, TGF beta, Nitric oxide synthetase, COX2 prostaglandinsurokinase receptor, and PAK — all of which may be potential targets for therapy. There are drugs in cancer therapy trials for all of these. Drugs blocking VEGF are the highest priority, but we should not ignore other pathways. Because it is difficult to shrink well-established blood vessels, this may be an argument for treating lesions at earlier stages, or to use a combination of multiple drugs. We need more information on dosage and long-term safety. Prospects are very optimistic, and within the next 3-5 years we will have a great deal more information about how to proceed.

Mark Your Calendar!

U.S. Annual Meeting
Palo Alto, California
June 22-24, 2001
Co-sponsored with
Stanford University Medical Center
Chairman: John R. Adler, Neurosurgery

Fifth VHL Symposium
Padua, Italy, 2002
co-sponsored with the University of Padua
Chairman: Giuseppe Opocher, Genetics

Cooking Tumors to Zap Cancer

From an article by Bonnie Flock, Clinical Center News, *June 2000, National Institutes of Health*

Using radiofrequency (RF) energy to "cook" and kill cancerous tumors without affecting surrounding healthy tissue may provide an alternative to surgery for patients with kidney and other cancers, according to Dr. Bradford J. Wood, a clinical investigator with the Clinical Center's Diagnostic Radiology Department. Dr. Wood presented his research at the 25th Annual Scientific Meeting of the Society of Cardiovascular & Interventional Radiology, held this spring. This work was reported to the VHL Symposium by Dr. McClellan Walther.

"Preliminary results look promising for this technique, which is being used on tumors throughout the body, including painful tumors and cancers of the kidney, adrenal, liver, prostate, and bone," said Dr. Wood.

RF energy is fed to the tumor through a very small needle with an electrode on the tip. The needle is inserted into the tumor under imaging guidance, such as CT scan or ultrasound. The electrode generates heat up to 100 degrees Celsius. After 10 to 12 minutes of continuous contact with the tumor tissue, the RF energy "cooks" a 1-inch to 2-inch sphere, killing the tumor cells. Larger tumors an be treated by cooking overlapping spheres. The dead cells are not actually removed, but become scar tissue and eventually shrink. Typically, the outpatient procedure is performed while the patient is lightly sedated, and the patient may go home hours later, usually feeling no pain.

RF ablation is a modification of electrosurgery or electrocautery, which has been around at least since the 1920's, according to Dr. Wood. It is finding a niche in cancer treatment, which increasingly is being customized for each patient based on the size, location, and type of tumor.

Early results from a multicenter study that included the Clinical Center look promising: of 21 kidney tumors treated, 14 (67 percent) were no longer visible on x-ray 5 months after RF treatment. One patient remains cancer-free 18 months after treatment. For kidney tumors 3 centimeters or less, 11 of 14 (79 percent) showed no activity on follow-up.

"Most of these smaller tumors were in patients with recurrent, hereditary kidney tumors. For these patients, RF may provide an effective, minimally invasive option that spares normal kidney and prolongs function," said Dr. Wood. The renal ablation procedure is sometimes referred to as "RITA".

In a related Clinical Center study of tumors of the adrenal glands, 10 of 15 tumors (67 percent) showed no active disease, while the remaining patients had some tumor visible on follow-up imaging. All patients treated had x-ray evidence that most of the targeted tumor was killed by the treatment. No major complications were seen. Results are preliminary with only short-term follow-up.

In another preliminary study, RF ablation provided effective short-term pain control in 21 of 24 painful tumors. RF could eventually be an option for inoperable patients who have not responded to conventional methods, are on high-dose sedating pain medicine, or have had maximum allowable radiation, according to Dr. Wood.

"RF is less expensive, safer, and generally easier than surgery," said Dr. Wood. "However, without randomized, prospective trials and long-term results, RF is not an alternative to surgery at this point. Surgery remains the proven treatment of choice for most solitary or small liver tumors."

Collaborating with Dr. Wood on this research are Drs. Tito Fojo, Mac Walther, Steve Libutti, and Christian Pavlovich of NCI. "It is still early, but we are optimistic," said Dr. Mac Walther at the VHL Symposium. "Patients are responding very well to the therapy. We need longer-term follow-up before we can say with certainty that VHL kidney tumors treated in this way will not come back."

More information, pictures, and video of this work can be found at the following website: http://www.cc.nih.gov/drd/rfa/.

> "Optimism is essential to achievement and it is also the foundation of courage and true progress. --*Nicholas Murray Butler*"

Happy Birthday to Vic!

This issue is dedicated in honor of Victor A. Nichols on his 90th birthday, by his family and friends.

"I have been acquainted with VHL several times over the years.

I have lost six people near and dear to me with VHL. We lost a sister-in-law in 1935, 18 years old. A twin daughter in 1968, 29 years old. Our oldest son in 1975, 39 years old. A grandson in 1985 at 26 years old. My wife in 1985 at 70 years old. A grandson in 1987 at 24 years old. A daughter, the other twin, in 2000 at 61 years old.

We did not know about VHL until 1987 when one of my grandsons was in the hospital and one of the doctors found out. My contribution for all families with VHL is HOPE."

A Time to Walk

by Jay Platt,[1] Georgia

What's one trait that the truly successful share? Although some might argue that it is their background, education, or status, I disagree. Rather, I believe that if you were to study the lives of anyone who's made a mark in this world, you'd find one common denominator that exists -- it's their attitude, particularly, their attitude of perseverance.

They quite simply refuse to give up. They are overcomers. They continue when others quit. As a result, they've been able to rise to the top of their respective fields.

Without a doubt, one of the greatest examples of perseverance is none other than Abraham Lincoln. If you want to learn about someone who simply refused to quit, look no further.

Born into poverty, Lincoln was faced with defeat throughout this life. Over the years he lost eight elections, twice failed in business, and suffered a nervous breakdown. Although he could have quit many times, he didn't, and because he didn't, be became one of the greatest presidents in the history of our country.

Or look at Thomas Edison, who invented the incandescent light bulb, but only after over 10,000 unsuccessful attempts. A famous story recounts the time a young reporter asked Edison how it felt to have failed so many times, in his quest to create the light bulb. How was he able to go on? Edison replied, "I haven't failed 10,000 times, I've discovered 10,000 ways that won't work."

While those are great examples of perseverance, what about you? How's your attitude? Are you one of the ones that get going when the going gets tough or do you instead roll over and give up? Do you have bulldog determination, or is retreat always an option for you?

These are important questions to ask yourself and then answer honestly. I firmly believe that of all the characteristics one needs to be successful in life, a 'never quit' attitude is one of the most important. It's what keeps you going when almost every fiber of your being wants to quit, or when others say 'it' can't be done. Unfortunately, far too many people don't possess this type of attitude. As soon as they get knocked down, they throw in the towel. They never realize their true potential because they quit as soon as things get tough.

My wish is that people would realize that there is light at the end of the tunnel. It doesn't matter how many times you get knocked down as long as you get back up. After each rain storm there's always a rainbow, but to see it, you've got to first go through the storm. The secret is sticking around long enough to see it come to pass.

Although I was already a strong believer in the importance of attitude before my thru-hike, hiking the trail reinforced in me the vital role a proper attitude plays. I never would have made it without it.

The entire trail was difficult at times, but some parts were definitely harder than others. For me, the White Mountains of New Hampshire and particularly Mt. Madison, tested my attitude to the fullest.

My first day there, while coming down what was basically the face of a cliff, I suddenly had a dizzy spell and slipped and fell sideways. I began to tumble down the mountain until a tree broke my fall. I slammed into a sharp branch that was just a few inches off the ground. My head hit is full force in the area of my left temple, and I blacked out momentarily.

> "A 'never quit' attitude is what keeps you going when almost every fiber of your being wants to give up, or when others say 'it' can't be done."
>
> *-- Jay "Patch" Platt*

Eventually, I regained my awareness and slowly stood back up. To say it scared me would be the understatement of the century. Shaken at the thought of how close I'd come to a fatal fall, it took several hours from that point for me to make my way down the mountain.

That night was a time of some serious self-reflection. For the first time since I'd begun the hike, I questioned what I was doing and why. Was I even physically able to accomplish such a feat? Plenty of people were telling me that the answer to that question was no. Maybe they were right. After all, here I was with one eye and a brain tumor, going up and down what at times was downright treacherous terrain.

It was time for a gut check. Was all this attitude stuff that I was always telling others about for real? After thinking for awhile I realized that by completing my hike I had a great opportunity to set an example for others to follow. I realized that by not quitting, even though it was hard, I might one day inspire others to continue during their own tough times. At that point I made the decision that no matter what I wasn't going to quit. I would persevere to the end! I just didn't know how hard it would get . . .

1. As excerpt from Jay's new book, *A Time to Walk: Life Lessons Learned on the Appalachian Trail,* his hike of 2,160 miles from Maine to Georgia. He is donating $5 from the purchase of each copy of his book, to support research on VHL. See page 19 for ordering information. In July, Jay was elected to the Board of Directors, to be Spokesperson for the VHL Family Alliance.

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Gifts that Keep on Giving . . .

Please do some special shopping this season in the VHL store. All the profits from sales in our store go to support the VHL Family Alliance programs and research.

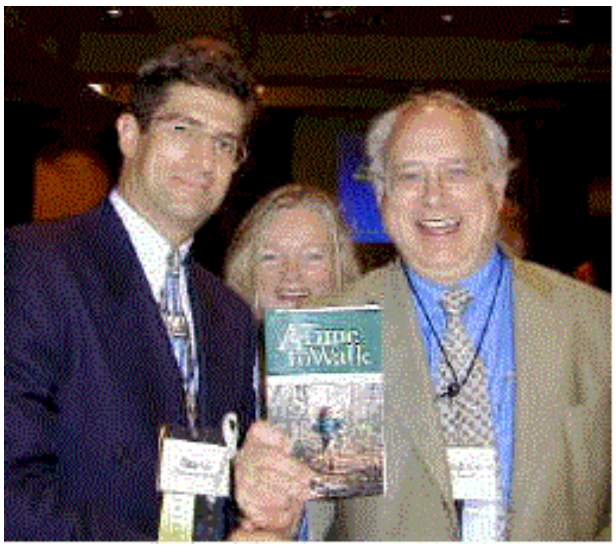
Kathy Braden of Indiana, Vice Chair of the Board, models our new Millennium T-shirt: white with blue, yellow, and black design by Tracy Abraham of Ohio, winner of this year's T-shirt design contest.

Damon Graff presents our new Caring T-shirt, white with brown ink, designed by Altheada J. of New York. Its text reads: "One day I met another person with VHL…We talked, shared, cared, compared, cried, laughed and learned…Pretty soon we felt in control of VHL…We could help ourselves and others, too."

The Board presented to Altheada a beautiful all-cotton lap blanket with a woven design featuring the VHLFA logo, honoring her completion of six years of service on the Board. You can have one too!

Jay Platt introduced his new book, *A Time to Walk* (see page 14). Dr. & Mrs. Neumann took an autographed copy home to Germany. Jay is donating $5 from the sale of each book to support VHLFA.

Please see page 15 of this issue, or the VHL store on our website, for additional items. Patricia Foote's book How Are You? on taking charge of your own health care, and Karen Koenig's beautiful and inspiring poems, and Pierre Jacomet's award-winning piano performances also benefit VHLFA.



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