VHL Family Forum

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New from the Laboratory of Immunobiology

by Berton Zbar, M.D.

One of the major goals of our research program has been to identify the changes in the gene (mutations) that produce VHL. We have identified mutations in 85/114 (75%) of VHL families. This area of mutation research has provided an enormous amount of new information about VHL. I will summarize this information in this article.

Perhaps the most striking observation is that there appear to be three types of von Hippel-Lindau disease. VHL type 1 is the commonest form of the disease and is characterized by a tendency to develop tumors in the eyes, brain, spinal cord, kidney and pancreas. VHL type 2 is less common. VHL type 2 differs from type 1 in that affected family members may develop pheochromocytomas. VHL type 2 is further divided into types 2A and 2B. Individuals in families with VHL type 2A develop pheochromocytomas, but not kidney cancer (this type of VHL is uncommon). Individuals in families with VHL type 2B develop pheochromocytomas and kidney cancer. (see Table 1)

This classification was based on studies of the mutations in a large number of VHL families. Families with more than 25 affected individuals were particularly useful in identifying what tumors occur and what tumors do not occur with particular mutations.

The spectrum of tumors that occur in a particular VHL family can be described as the *phenotype*.[1] One major result of our work is that we now know what types of tumors accompany particular VHL mutations. For example, a mutation at position 505 in the VHL gene that changes the DNA building block T to C is associated with VHL type 2A, that is eye, brain and adrenal tumors but not kidney or pancreatic tumors. For another example, a mutation at position 712 or 713 in the VHL gene that changes the DNA building block C to T, or G to A, is associated with VHL type 2B, that is eye, brain, kidney, adrenal and pancreas tumors. From the mutation in the VHL gene, one can make informed predictions as to which tumors will develop in a particular family. We are gathering together mutation data from families from research workers in the U.S., Great Britain, Europe and Japan. This information when combined with *phenotype* will be useful to investigators trying to predict disease manifestations.

One of the most striking observations to emerge from studies of mutations of the VHL gene involves the finding of exactly the same mutation in families that are not thought to be related. This situation can come about in two ways: (1) the mutation has occurred several times in the population; (2) the families with the identical mutation are in fact related, they have a distant common ancestor, but are unaware of this fact.

We have had examples of both situations in our studies. There are 14 families in Germany and 2 German families living in Pennsylvania that have the identical VHL mutation.

> “Each VHL family should keep a record of the mutation identified in their family. This information will be valuable to future generations of family members.
> -- *Berton Zbar, M.D., Lab. of Immunobiology*”

The evidence suggests that these families have a common ancestor with a VHL mutation. There are families with VHL from several different countries that have the identical 712-713 mutation. The evidence suggests that this mutation developed independently in these populations.

This information is published in the December 14, 1994, issue of *Human Mutation.*

1. ***Phenotype:*** The entire physical makeup of an individual: hair, eye color, and in VHL, the types of tumors present in the family.

Table 1
NCI classification of von Hippel-Lindau disease

Type	Clinical Characteristic
1	without pheochromocytoma
2	with pheochromocytoma
- 2A	without renal cell carcinoma or pancreatic cysts
- 2B	with renal cell carcinoma and pancreatic cysts

Inside this issue!

We're so Excited to meet you in Boston!

Sign up now -- see page 15!

♥ ♥ *Dedicated to improving diagnosis, treatment, and quality of life for people with von Hippel-Lindau disease* ♥ ♥

DNA Testing for von Hippel-Lindau

Research versus Clinical Testing

by Joyce Graff and Peggy Marshall

There are two kinds of laboratories: research labs and clinical testing labs. A clinical testing lab is like the one where your doctor sends your routine blood and urine samples, with the exception that in the case of DNA testing it takes a laboratory with special knowledge and equipment, and with special "DNA probes" which can be used to check for mutations in the VHL gene itself.

There is only one *clinical laboratory* in the United States at this time equipped to do DNA testing for the VHL gene, at Johns Hopkins Hospital under Corinne Boehm.[1] At least one additional lab is expected to open up later in 1995. A clinical lab is set up to receive samples for testing, apply the tests, and return the results to the doctor in a short and predictable period of time, with a report which the doctor can discuss with you.

You may have heard of research labs which collected samples and worked to identify the VHL gene. The two most prominent of these in the United States were at Harvard University/Massachusetts General Hospital under Dr. Bernd Seizinger, and at the National Cancer Institute under Dr. Berton Zbar.

A research laboratory is an experimental environment where samples are collected only when they are needed to further research. Results can take years — finding the mutation in the gene of the Hawaii family took a total of twenty-seven years.[2] Research labs do the work that makes the clinical work possible, and then they go on to the next project and turn over the day-to-day work to the clinical labs like that at Johns Hopkins.

With DNA testing comes a lot of conversation, helping to determine how best to get the information needed to test a particular individual, and then interpreting the results. It is best to have a geneticist near you to hold those conversations with you face-to-face. Few of us understand genetics, and even most doctors are not well trained in understanding or explaining genetics. It is best to work with a specialist — a geneticist or genetic counselor — who can meet with you and help you to understand the process and the results.

A research lab is not staffed to explain the concepts to you, or handle all the questions that you need answered. Please help us protect the time of the research laboratories so that they can continue with the very important research work which we are hopeful will soon lead to new therapies for VHL.

Obtaining Useful Results from your Research Samples

Many people submitted blood samples in the past to one of several research studies which led to the finding of the VHL gene. Research testing does not cost the subjects money, so if results can be obtained from these research samples, that would be the first choice. However, since the gene was found in June 1993, *none of the genetic research studies are taking new participants.* So if you had not previously submitted a sample, you cannot obtain results from a research lab.

Dr. Seizinger's samples, which were part of the Harvard/Mass. General Hospital set of samples, led to the discovery that the VHL gene was on chromosome 3. The most recent paper from this team[3] includes a detailed acknowledgment to "the VHL families in the United States, Canada, and Europe for their participation in our studies," including a listing of the many physicians and genetic counselors who helped provide "VHL family blood and tissue samples and clinical information." In addition, this group is notifying the appropriate genetic counselors when they identify specific mutations.

If someone in your family previously participated in the studies under Dr. Seizinger, you should contact the physician who collected the samples, or your genetic counselor, to see if they have received any new information regarding Seizinger's department. If not, please ask them to follow up.

"*A research lab is not staffed to explain the concepts to you, or handle all the questions that you need answered. Please help us protect the time of the research laboratories so that they can continue with the very important research work which we are hopeful will soon lead to new therapies for VHL.*"

If someone in your family previously participated in the studies under Dr. Berton Zbar at the National Institutes of Health, then you can ***write*** to Dr. Zbar and ask if he has identified the mutation area in your family's VHL gene. If he has useful results to share with you, he will send a letter with the information the clinical lab will need to do the testing:

Dr. Berton Zbar, Frederick Cancer Research Institute, Laboratory of Immunobiology, Building 560, room 12-71, Frederick, MD 21702, Fax: 301-846-6145

This applies only to families who have previously submitted samples to Dr. Seizinger or Dr. Zbar. They are not accepting new families into their studies, nor new members of participating families. However, information on any one member of your family will give you the information you need to test other family members in the clinical lab.

If you receive such a letter, you would then present this letter to the clinical lab to obtain testing.

Other research labs

If you had sent samples to another research team, you should write and inquire whether they have identified the particular mutation area in your family's VHL gene, so that a direct test can be done.

Even if you are not able to obtain this information from the research team you dealt with, all is not lost. Because of the methodology developed, primarily by Dr. Zbar and Dr. Maher, there are a number of options for testing which will be explained to you by your local genetics team.

How do I find a geneticist or genetic counselor?

Begin with your doctor, or with the medical center where you normally go. Inquire in the departments of obstetrics or pediatrics. If they do not have an associated

geneticist, they will know where to find one which is acceptable under your health plan.

If you are near one of the Clinical Care Centers listed on page 8, that would be a good choice.

Clinical DNA Testing for VHL

DNA testing is currently done at only one lab in the United States, at Johns Hopkins Hospital in Baltimore, Maryland.[1] Samples can be sent by mail. The approach to this lab should be made by a physician — a geneticist or family doctor — who can work with you locally and explain just what the information means.

Genetic analysis does not yet work for every VHL family.

The first step is to identify the particular modification in the VHL gene which is unique to your own family. This is best done with a blood sample from someone who already has a clinical diagnosis of VHL.

If you have not previously participated in Dr. Zbar's research, you can send to the clinical lab a sample from a family member who has a clinical diagnosis of VHL. The lab will say whether or not they can "see" the mutation area in this sample.

If yes, then other samples from your family can be sent for a simple "direct test." The VHL gene is a long gene. Many different kinds of mutations or flaws in this gene might occur, any one of which results in the VHL gene not functioning the way it is supposed to function.

It's as if the VHL gene were a chapter in a book. One sentence is wrong in that chapter. It could be any sentence, and the sentence might have been changed in any of a number of ways, but the chapter is not perfect. In a particular family, however, that same change is copied faithfully down through the inheritance of that family. So if we know, for example, what the particular change is there in the DNA of the parent, we can go straight to that same area and check for that particular change when we check the child. This is called a "direct test." (See also the June 1993 issue of the *VHL Family Forum*.)

If not, then the lab may request additional samples from other members of your family, to assist in determining where the mutation area is, or whether there is a group of "flanking markers" (associated genes and patterns) which is commonly associated with VHL. This kind of "linkage analysis" is described in the March 1993 issue of the *VHL Family Forum.*

If they are unable to do DNA testing yet for your family, please let us know and we will notify you if additional research studies open up which might make it possible for your family to obtain testing.

A Word of Caution

Please note that there are concerns about the misuse of DNA testing information by insurance carriers and employers. Before doing DNA testing on any family member who does not have a clinical diagnosis of VHL it is a good idea to make sure they have employment, health insurance, and life insurance in order.

The National Organization for Rare Disorders (NORD), of which we are a member, is collecting stories from individuals and working to make it illegal to use this information wrongly — perhaps to exclude people from coverage, or to discriminate in hiring and promotion. For example, a child who tests positive may be classified as having a pre-existing condition for insurance purposes -- even before birth.

Teamwork
for
Health

Please join us in Burlington!

The agenda for the Annual Meeting is very exciting, packed with great information, and lots of time to schmooze with other people with VHL. See page 13.

But what would make it really special is if ***YOU*** would come! We need ***your*** participation to make the conference complete.

Book your ticket now!

Register on page 15!

See you in Burlington!

April 29-30, 1995

* Pre-planning for next year: tentative dates for the 1996 conference are June 17-22, 1996, in Honolulu, Hawaii, held in cooperation with the University of Hawaii at Manoa and the John A. Burns School of Medicine.

Be alert for any signs of misuse of this information, and keep us and NORD informed of any problems you encounter. We will be happy to answer your questions and concerns.

National Organization for Rare Disorders
100 Route 37, P.O. Box 8923
New Fairfield, CT 06812-8923

1. Clinical testing labs for VHL also exist in England and Germany. Choose the lab closest to you:
U.S.: Ms. Corinne Boehm, DNA Diagnostics Laboratory, Center for Medical Genetics, Johns Hopkins Hospital, Baltimore, MD 21205, Tel: 1-410-955-0483; Fax: 1-410-955-0484.
England: Dr. Eamonn R. Maher, Clinical Genetics, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, U.K., Tel: 44-223-216446, Fax: 44-223-217054.
Germany: Dr. Hiltrud Brauch, Labor für Molekularpathologie, Klinikum rechts der Isar, Trogerstraße 32, D-81675 München, Germany, Tel: 49-89-4140-4592; Fax: 49-89-4180-5215.

2. This work was begun in 1977 by Drs. Lamiell, Hsia, and Salazar. See Go RCP et al., *Am J. Hum. Genetics*, **36:**131-142 (1984). Their identification and investigation of this particularly large VHL family helped to spur genetic research on VHL. Ironically, the particular genetic mutation in this family was not identified until 1994.

3. Dr. Jean M. Whaley et al., "Germ-Line Mutations in the von Hippel-Lindau Tumor-Suppressor Gene are Similar to Somatic von Hippel-Lindau Aberrations in Sporadic Renal Cell Carcinoma," *Am. J. Human Genetics*, 1994 **55:**1092-1102.

Questions and Answers about DNA Testing

by Corinne Boehm, M.S., with Peggy Marshall, Mississippi

Peggy assembled a list from the hotline volunteers of commonly asked questions about DNA testing and passed them to Corinne Boehm, head of the DNA Diagnostics Laboratory at Johns Hopkins Hospital in Baltimore, the single DNA testing lab in the United States at this time.

1. Why do I have to go through a genetic counselor? Isn't genetic counseling for people who are having babies?

Having your test request made by a genetic counselor increases the likelihood that you will be educated about the process of DNA testing you are undertaking and will therefore be making an informed decision about whether to pursue DNA studies. As many individuals who have requested DNA testing have become aware, technology is not yet available that allows an individual to simply send off a blood sample for VHL testing and receive a simple "yes" or "no" answer.

This is because DNA testing for VHL is, in most cases, *not* performed by testing for the VHL mutation (called a *direct test*) but rather by tracking the inheritance of the mutation by using DNA markers near or within the gene (called *linkage analysis*). This requires a testing process that includes multiple family members and careful review and analysis of medical records on all individuals who are said to have VHL and are included in the study.

Most genetic counselors have a good understanding of linkage analysis and therefore are able to take a pedigree and determine which family members may be necessary for a successful study. They also consider it their responsibility to communicate the process of linkage analysis to either an individual or several family members and to coordinate the shipping of all the needed samples. Most non-geneticist doctors do not know enough about linkage analysis to explain it to you.

In summary, our desire for referrals to be made by a geneticist is to assure us that you are receiving the best information available about DNA testing and that you understand the process of the testing, including its benefits and potential pitfalls, before becoming committed to the process . . . i.e., that you are given the opportunity to make an informed decision about whether you want to pursue VHL testing given its limitations. The desire for the laboratory to have the referral made through a genetic counselor has nothing to do with child-bearing. However, if you feel a need to discuss reproductive options, a genetic counselor is also a good person with whom to do so.

2. Why do I have to send blood if Dr. Zbar has my blood stored?

Fresh samples are requested to make sure the interpretation of the test results is as accurate as possible. For purposes of maximizing accuracy in testing procedures, licensed clinical laboratories such as ours are required to develop and adhere to a quality assurance program. One way we can be most certain of the accuracy of our results is to receive a blood specimen directly. The more hands a sample passes through, the greater the chance that there will be a misunderstanding of who a sample was derived from. Therefore, we request a new blood sample whenever possible to help ensure the accuracy of the test result.

3. Do we have to pay for each blood sample sent? For example, a mother has VHL and wants her three children checked. Do they pay a separate fee for each individual? How many family members have to send blood samples?

Yes, there is a fee for each sample that we receive whether or not the person whose sample is being analyzed will receive diagnostic information. Unless we already have on file or from Dr. Zbar the map required for a direct test, we will need to study multiple people to do linkage analysis. The cost for us to make a VHL diagnosis for one person will be greater if we need to study blood from eight family members than if we need to study blood from only four family members. It is impossible to predict how many samples will be needed. Indeed it is even impossible to predict if a diagnosis can be made before a family is studied. Genetic counselors who understand the concepts behind linkage analysis will be able to tell you how many samples will likely be needed in your particular situation. This depends on who wants test results and what the family structure is.

> *"Most non-geneticist doctors do not know enough about linkage analysis to explain it to you."*

4. What if only one member in a family "seems" to be affected with VHL? What are the chances of the gene mutation being found?

Given current technology, the chances that a VHL mutation will be found is only about 15%. Therefore, when only one member in a family seems to be affected with VHL, the likelihood that other family members will be able to receive useful diagnostic information from a DNA test is about 15%. Linkage studies are not possible in families in which only a single individual has VHL.

5. Can a parent request DNA testing for their adult children, or is that an individual decision?

The decision about whether to pursue presymptomatic testing for VHL is a very personal one and something that each person must make for him or herself. Within a family there are likely to be some individuals who want presymptomatic testing and others who do not; this is normal even though sometimes it is difficult to understand why somebody would make a decision which is different from your own.

For this reason, a parent cannot request DNA testing for an adult child. Similarly, the question is often debated

Altheada to Speak
ICD, New York, June 1
1:30 - 3:00 pm

Altheada Johnson of our Board of Directors, who also chairs our New York Chapter, will present a seminar on von Hippel-Lindau disease June 1, 1995, at the International Center for the Disabled, 340 East 245th Street, New York, NY.

Altheada, a registered dietitian, has been actively involved with ICD since 1991. Spinal surgery in 1989 left her unable to walk. Many of you have met her on the VHL Family Alliance hotline. Individuals with VHL, their families and support personnel, are welcome.

The seminar is free, but pre-registration is requied to

whether a parent can request DNA testing for a child. For some inherited disorders, guidelines for testing specify that a parent may not request presymptomatic testing in a child; rather, testing for a child must be deferred until the child is of an age that s/he can make an informed decision about whether s/he wants such testing. Currently we offer presymptomatic testing for children when requested by a parent because we feel that the information gained from DNA testing can affect medical treatment (that is, screening). However, this decision is one that is often debated by the genetics community.

6. What is the procedure for having DNA testing?

I recommend that the procedure you follow is to contact a genetic counselor who is close to your home and tell him or her that you want presymptomatic testing for VHL. You may need to make this person aware of the fact that our laboratory performs such testing. By working with a genetic counselor you will be working with someone who is educated in linkage analysis and therefore will be able to best help you with the testing process. You can obtain a list of genetic counselors in your area from the National Society of Genetic Counselors, 233 Canterbury Drive, Wallingford, PA 19086.

7. Should I go through my health insurance company for the testing?

The question of whether to pursue payment for VHL DNA testing through an insurance company is a personal one. I do not feel I am in a position to answer this question as well as many others would be, but it is definitely worth checking into.

> *"Within a family there are likely to be some individuals who want presymptomatic testing and others who do not; this is normal even though sometimes it is difficult to understand why somebody would make a decision which is different from your own."*

Asking the Insurance Company to Pay for Genetic Testing

— Joyce Graff, Massachusetts, from me personally, not the opinion of the Alliance

There are concerns about the potential misuse by insurance companies of genetic information. This is of concern to all families affected by genetic indicators of potential problems, the number of whom increase with the finding of every new gene. As Dr. Francis Collins likes to say, soon we will all have some pre-existing condition. Clearly the system of "pre-existing conditions" needs to be changed.

Meanwhile, my son and I did ask our insurance company to pay for the DNA testing. He already had a clinical diagnosis of VHL, so it didn't add any information that the insurance company didn't already know. If, however, you are testing children who do not have any symptoms, you might want to simply write a check.

The Bottom Line is: *Never lie to your insurance company.* Lying is grounds for them to terminate your policy. However, at the same time, don't volunteer any information they haven't specifically asked for. ❑

Join the Fun!

The VHL Family Alliance is now On Line with Rock Online!

If you have access to a computer and a modem you can participate in the Fun! Rock Online is a new Internet service providing information and Rock and Roll music over the Internet, and a number of entertainment opportunities and person-to-person discussion groups.

The VHL Family Forum Online provides an area to post messages that other VHL Alliance members can respond to. Vital information can be posted for all to read. The idea is to learn from each other in a fun environment. All areas of topics are covered. "Chat" live by typing messages to one another in an online "chat lounge" every Sunday between 7 pm and 9:30 pm Eastern U.S. time. Talk anonymously with others if you wish. Get to know other members and *Rock Online!*

Schedule April-June, Sundays, 7-9:30 pm:

7:00 - 9:30 pm New York time
First Sunday of month: Focus on parenting issues
Second Sunday of month: Young People's Forum
Third Sunday of month: Coping skills Forum
Fourth Sunday of month: Open Forum

To access VHLFF Online:

Dial with your computer 1-212-647-8660
or Telnet to MAGIC.WEBB.COM
Choose VHL Family Forum from the forum menu.
For technical assistance, call 1-800-ROCK-WEB.

We are experimenting with two services

Please help us evaluate which you prefer.

The VHL BBS at 1-212-222-4724 costs only your telephone connection charges. There is only one phone line, so your visit time will be limited. You may post messages, read messages, and download files from the library. Access is via dial-up telephone only. This is a charitable service of the United Methodist Church.

The VHLFF at Rock Online (1-212-647-8660) uses the same bulletin board software, so you have only one method to learn. There are more phone lines, but after an introductory time you would pay a monthly fee for connection. If you already have Internet access, you can connect without charge via Telnet or the WorldWide Web.

In either case, it's *your messages* that will make it successful! Please try both and see what you think.

Medical Information Online:

VHL Family Alliance medical information is also available on Web servers through OncoLink and the National Society of Genetic Counselors Web Services. Details are posted in VHLFF Online, or by writing to vhl@pipeline.com. See our URL at the bottom of page 12.

These services are new and evolving. We will appreciate your participation and feedback.

Many thanks to Fred Johnson, Rick Werner and Debra Collins for help in the startup stages. Now it's up to ***you*** to participate and make the discussions interesting!

Hints for the BBS:

Call or write for complete instructions.

There is a Main Menu with a number of choices. Ask to select a Forum. The name of our Forum is VHL.

Read messages, Write messages, or check the Library.

When in doubt, press <Return> or <Enter>.

Have fun! ❑

VHL France

by Mireille Proux, President, VHL France

It is with very great pleasure that we announce the formation of VHL France, an affiliate of the VHL Family Alliance in France. We are delighted to join with the many other national groups in providing support to other VHL families in France and in spreading information about VHL in France and French-speaking countries.

You asked me to share our experience with VHL — I say "our" because my husband and two children are affected. In 1983, at the age of 34, my husband underwent brain surgery after six months of suffering. The diagnosis was delayed. The tumor was in the cerebellum, the cyst had grown to the size of an orange, and emergency surgery was followed by five weeks in a coma. My husband came out of the coma with paralysis on his left side. A long, very long period of rehabilitation brought him through to complete recovery with no disability. This is a great message of hope to share with other VHL patients with this kind of lesion, — with a lot of strength of conviction on his part and the loving support of those around him, he achieved a full recovery.

At a medical check-up in 1987 they found a retinal hemangioblastoma near the optic nerve of the left eye of my 15-year-old daughter. According to the first doctor, there was only an unfortunate coincidence between my husband's surgery in 1983 and the retinal lesion of my daughter. According to a second doctor there was almost certainly a relationship between these two events, but he would need to do further investigation.

In June 1988 my husband had his left kidney removed.

When at the end of 1988, my son, then 15 years old, was also found to have a retinal lesion in the periphery of one eye, there seemed to be no further doubt that this was a hereditary condition, but what? They had still they had not identified the disease in question. We began a lengthy journey from doctor to doctor. Since I work in the medical press, I began to do my own research among the published journal articles, and found my way to Dr. Stéphane Richard who has since joined the VHLFA Clinical Care Program (*see page 8*).

Peggy and Mireille.

Michel and Alexandre.

After a series of tests on Peggy, Alexandre and Michel, in April 1994 my husband had an operation on his right kidney to remove a series of small lesions. We are very glad to be in touch with Dr. Richard these last two years, and follow a regular schedule of check-ups consisting of:

- every three months an eye examination, with laser treatment if necessary to control new hemangioblastomas.
- once a year an MRI of the spine and brain
- once a year a renal scan for my husband and two children.

I am now convinced based on our experience that there exists in France, and perhaps in other countries as well, a lack of knowledge of this disease which leads to delayed diagnosis and sometimes grave consequences. I also believe that access to helpful and complete information can help people manage their health and avoid the advanced stages of this disease.

This is why my husband and I have decided to form this association. Dr. Richard has agreed to serve as medical advisor to our group, and four other eminent physicians have joined our Medical Advisory Board.

I hope that with the association of all the VHL societies which exist we can mobilize this information within and beyond our respective national territories.

We are delighted that VHL France will be mentioned in the *VHL Family Forum,* and are pleased with the brochure "Qu'est-ce que le VHL?" in French which announces our partnership.

Please convey to all the members of the VHL Family our sincere wish that this will be without doubt a year rich in progress on VHL.

Copies of "What is VHL?" are now available in English, French, Spanish, and Portuguese. Other languages are in preparation. This article translated from the French by Joyce Graff. ❑

New Strategies in Early Detection and Treatment

Summarizing an article by Nicky Karsdorp, Arthur Elderson, Dienke Wittebol-Post, et al, University Hospital Utrecht, Utrecht, The Netherlands[1]

The University Hospital, Utrecht, has periodically screened members of a large affected family since 1976. Three family members had already died when the disease was first named in the *proband*, the initial patient studied, the fifth of nine children. (See Figure 1) His father had died of metastatic renal cell carcinoma at age 55. Hospital records of two of his sisters indicated that they had died of cerebellar hemangioblastomas at 39 and 32 years respectively. Twenty-three family members underwent screening, (the primary patient's six other siblings and their 18 children, nieces, and nephews) of whom 9 were found to have VHL.

Four have angiomas of the eye, thirteen have renal lesions, four have pheochromocytomas, four had pancreatic lesions. Liver cysts were found in two patients. Small cystadenomas in the epididymis were found in two patients, and a cystadenoma in the broad ligament in one patient.

In the eye, "the finding of twin vessels may be an early diagnostic sign of the disease." Twin vessels are where a tiny vein and a tiny artery are paired near the optic disk. "Twin vessels can also be found in the normal population," but while they occur in 5.5% of the general population, they occur in 64% of people with VHL.

In the kidney, "CT scanning is found to be more reliable than ultrasound in distinguishing renal cysts from renal cell carcinoma." However, the Utrecht team recommends using annual ultrasound for most follow-ups, to reduce the exposure to radiation. Radiation is known to cause genetic mutation, which may be associated with the transformation of normal cells into tumor cells.

This group advocates a conservative approach to treatment of kidney tumors. "Only solid and progressively growing lesions with a diameter of more than 3-4 cm. should be surgically removed. Partial nephrectomy is an attractive alternative and has produced favorable results. . . . If bilateral nephrectomy is indicated, kidney transplantation is a reasonable option in the long run." However, the risk of developing any cancer is increased in people whose immune system is suppressed. "One may speculate whether immunosuppression enhances the development of VHL lesions." [p. 165]

Diagnosis of pheochromocytomas remains tricky.[2] This group recommends refraining from treating pheochromocytomas until they become chemically active, or until the tumor shows steady growth. "However the behavior of pheochromocytoma remains unpredictable; biologically inactive pheochromocytomas may suddenly become dangerous." This is especially true under markedly increased stress, such as any kind of accident or surgery. MIBG scintigraphy[3] is important to find any pheos which may occur outside the adrenal glands.

"VHL is a potentially malignant disease, which requires careful family screening. CNS hemangioblastoma and renal cell carcinoma are the most treacherous." For a person who carries the VHL gene, regular lifelong screening is required to maintain health by ensuring timely and appropriate treatment. "Clear oral and written information has to be provided to the families about clinical symptoms, signs, complications, treatment, prognosis, and inheritance of the syndrome. Early recognition may prevent patients' and doctors' delay.

> *"For a person who carries the VHL gene, regular lifelong screening is required to maintain health by ensuring timely and appropriate treatment."*

"The disease can greatly impact a family's sense of physical and emotional well being. Recently, VHL family members have initiated the publication of the *VHL Family Forum* to share experiences and information. This newsletter will facilitate communication among patients, close family members, and health care workers and contribute to care for families."

1. Nicky Karsdorp, Arthur Elderson, Dienke Wittebol-Post, Ronald J. Hené, Jaap Vos, Michiel A. M. Feldberg, Adriaan P.G. van Gils, Johanna Jansen-Schillhorn van Veen, Thea M. Vroom, Jo W. M. Höppener, Cornelis J.M. Lips, "Von Hippel-Lindau Disease: New Strategies in Early Detection and Treatment," *American Journal of Medicine*, **97:**158-168, Aug 1994.
2. See Graham, "The Many Masks of Adrenal Involvement," *VHLFF,* December 1993. See also Neumann et al., *N.E. J. Med.,* 329:1531-1538 (1993).
3. A nuclear medicine test for pheochromocytoma. See Graham or Neumann articles in footnote 2. ❑

Figure 1: Pedigree of the family. American Journal of Medicine, 97:159, August 1994.

Finding People with VHL

-- Joyce Wilcox Graff, Co-Chair

One of our primary goals is to improve diagnosis of VHL, so that people will obtain a correct diagnosis as early as possible. This means not only working toward better methods of diagnosis, but also raising consciousness of VHL among health professionals and the general public, to increase the likelihood that a diagnosis of VHL will be considered as an option.

In the past two years the Alliance has grown from a seedling of an organization into a strong tree with far-reaching branches. In this issue you meet our newest affiliate, VHL France. We now reach more than 3400 individuals with VHL in twenty countries. Most of these people already knew they had VHL. But there is a growing number of people newly diagnosed.

More health professionals today are aware of VHL than ever before. Two physicians called recently to thank us for our information, which finally solved mysteries they had been wrestling with for two to five years -- their patients have VHL. Just in the last two months we have spoken with five affected people who learned for the first time the name von Hippel-Lindau. In some cases, it is clear that VHL had been in the family for generations, without the right diagnosis. In two cases, like the one on page 6 of this issue, this may prove to be the first case of VHL in the family.

The number of identified individuals affected with VHL is rapidly increasing. Thirty years ago few people would have believed there were even a dozen in each country. Registry projects in England (Dr. Eamonn R. Maher, Cambridge), Germany (Dr. Hartmut Neumann, Freiburg) and France (Dr. Stéphane Richard, Paris) and examination of registered cases of hemangioblastoma and kidney cancer have found hundreds of previously undiagnosed cases of VHL. The geneticists' estimates of one in 38,000 people are looking more and more probable.

There are estimated to be 7,000 people with VHL in the United States alone. That's more than three times the number estimated to have a diagnosis today. Once people obtain a correct diagnosis they can obtain the information and assistance they need to manage their health. Please

Renew your Membership -

Renew Hope Together we can

make VHL a manageable disease, and find a cure.

We need your help.

Clinical Care Centers

For additional information, please contact Susan Warnick, R.N., 16 Ridge Lawn Road, Reisterstown, MD 21136. Tel/Fax (410) 526-6858. Maryland . (= new since December)*

Canada: *Memorial University of Newfoundland, St. John's, Newfoundland.* Jane Green, M.S., Medical Genetics, Tel: 709-737-6807; Fax: 709-737-3374.

France: Sainte-Anne Hospital, Paris. Stéphane Richard, M.D., Neuro-oncology, Tel: +33-1-4586 2406; Fax: +33-1-4565 8728.

Germany: *Albert-Ludwigs University Hospital, Freiburg.* Hartmut Neumann, M.D., Nephrology, Tel: +49-761-270-3363; Fax: +49-761-270-3245.

****Netherlands:*** *University Hospital, Utrecht.* Dr. Cornelius J. M. Lips, Dept. of Internal Medicine. Tel: +31-30-509-111; Fax: +31-30-518-328.

United Kingdom:

England: *Addenbrookes Hospital, Cambridge.* Eamonn Maher, M.D., Tel: +44-223-216446; Fax: +44-223-217054.

****Wales:*** *University Hospital, Cardiff.* Dr. Diana Wheeler, Institute of Medical Genetics. Tel: +44-222-743922; Fax: +44-222-747603.

United States:

California: *University of California, San Francisco.* Siobhan Geary, R.N., Neurocutaneous Clinic, Tel: 415-476-3338; Fax: 415-476-7965.

Hawaii: *Kapiolani Medical Center, Honolulu.* Y. E. Hsia, M.D., Tel: 808-956-8331; Fax: 808-956-5518..

Illinois: *Northwestern Memorial Hospital, Northwestern University, Chicago.* Maureen O'Connor, R.N., Daniel Dalton, M.D., 312-943-5353; Fax: 312-908-0376.

Iowa: *University of Iowa Medical Center, Iowa City.* Ann Muilenberg, Coordinator. Tel: 319-356-2674; Fax: 319-356-3347.

Kansas: *University of Kansas Medical Center, Kansas City.* Debra L. Collins, M.S., Tel: 913-588-6043; Fax: 913-588-3995.

****Maryland:*** *Johns Hopkins Medical Center, Baltimore.* Jill Hennessey, M.S., Medical Genetics, Tel: 410-955-3122; Fax: 410-955-0484.

Massachusetts: *Lahey Clinic, Boston.* John Libertino, M.D., Urology, Tel: 617-273-8420; Fax: 617-273-5246.

***Michigan:** University of Michigan, Ann Arbor. Wendy R. Uhlmann, M.S., Molecular Medicine & Genetics. Tel: 313-763-2532; Fax: 313-763-7672.

Minnesota: *Mayo Clinic, Rochester.* Mary Kelly, Clinic Coordinator, Tel: 507-284-8198; Fax: 507-284-0161.

New York: *Albert Einstein Medical College of Medicine/Montefiore Medical Center, Bronx.* Robert D. Burk, M.D., Tel: 718-430-3720; Fax: 718-918-0857.

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

****Ohio:*** *Cleveland Clinics, Cleveland.* Dr. Andrew C. Novick, Dept of Urology. Tel: 216-444-5584; Fax: 216-445-7031.

****Texas:*** *Baylor College of Medicine, Houston.* Michael Frazier, B.S., Manager, Genetics Clinic, Texas Children's Hospital. Tel: 713-770-4280; Fax: 713-770-4294.

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

Crisis and Opportunity

by Amy J, Arkansas

I assume how you feel about this disease depends upon your perspective of where you are with it right now. In this newsletter I've read about many courageous people who are battling various and sundry ailments and medical problems, large and small, with positive attitudes that buck them up and help keep them fighting. But while you're in the middle of a prolonged battle, it's hard to keep your spirit and your energy up.

Until a year and a half ago, I didn't know I had VHL. I had a brain tumor removed in 1984, when I was 25, but after a year of being misdiagnosed, the actual surgery went smoothly enough. I have since learned — by my husband reading my old records — that my neurosurgeon suspected I had VHL and was monitoring other tumors and cysts in my brain, kidneys, and spine, but he didn't tell me about it. when I did question a pathology report that I read I was told not to worry — that if something ever did come up — and it wasn't likely — he'd make sure that it was taken care of before it caused me discomfort. I was on my own and still basically young and care-free, so I accepted that. For nine years I remained disease-free, and I marvel at the joy of that now. I seldom thought about illness, aside from dutifully getting a yearly MRI, which I considered a necessary chore.

In fact, I was beginning to lag behind on getting an MRI every year, and it had been a year and a half since receiving my last scan when my world fell apart. The past year and a half has been the year from hell. No sooner have I barely recovered from major or minor surgery, than I have needed surgery for something else. In the interim there have been more MRIs and tests. All this has been a real eye-opener, and I feel sadder and wiser for it. Although I know now that my life will never be normal, and I'll be living with an illness for the rest of my days, knowledge is power. I know that I'm a fighter, and now I know for certain that I'm a survivor. Still, this constant coping with medical issues has worn me down, not to mention depleting our finances to an alarming level. And does one ever get over the underlying subconscious feeling of being frightened and vulnerable?

I had just returned from a vacation in February, 1993, when I experienced those old familiar feelings that I recognized from my first tumor — loss of balance, coordination, general fatigue, handwriting problems, dizziness, and the like. Unfortunately, my husband and I had recently moved to my home state of Arkansas, and no one else here in the medical profession is very knowledgeable or experienced in VHL . . . so by the time I went back to my neurosurgeon at Georgetown University Hospital in Washington, D.C., I was in pretty bad shape, having seizures, and unable to walk. After an intensive operation and lots of physical and occupational therapy, I began relearning to walk and write over the summer.

If I can't exactly dance or race-walk anymore, I have figured out other things I can do for exercise and pleasure. And I was lucky; it didn't affect my job — I'm still an editor, and my company has been very supportive throughout my absences for surgeries and recovery. My job allows me to do a lot of work from home anyway, which is fortunate. As soon as I was strong enough, I went to the Cleveland Clinic in the fall for much-needed partial nephrectomy of my left kidney. Immediately after surgery I was told that I needed a partial nephrectomy of the right kidney, too. When I went back to have this operation after the holidays, my left kidney was discovered to be blocked. Thus began six months of minor operations and shunts and tests, and the possibility of having it removed altogether. We were on a first-name basis with everyone at the Cleveland Clinic and adjoining hotel whether we wanted to be or not! A last-ditch effort this spring by my wise and valiant surgeon saved me from another surgery and removal of the kidney.

It is now months later and I've had four more MRIs because my spinal tumors are acting up. I'm going back and forth to doctors in Texas and Maryland. All these appointments and check-ups, with the exception of the MRIs and tests for my eyes, must be done out of state, since the local doctors aren't confident in treating me and I'm not willing to be a guinea pig for educational purposes when it comes to surgery. We're building a strong medical team out of state, and I have several local doctors who are go-betweens and pinch-hitters when necessary. After a few tries, I'm finally lucky enough to find a family practitioner willing to learn about VHL, and help me keep on track for various tests while monitoring the ever-growing file. But my husband still spends hours on the phone and pores over the latest information he can find. I read it all too, but not in the detail that he does.

So life goes on, as you know. I intellectualize that I have been lucky because the outcome of these surgeries has been favorable. But I resent being told how "lucky" I am, unless this statement comes from another VHL warrior or someone who is dealing with or has dealt with a serious illness.

In Chinese calligraphy the character "ji" means both crisis and opportunity. I view having VHL this way. For all the negatives that this disease provides, it also grounds me to the reality of what is important in my life. It emphasizes the importance of the pure value of living each moment in acute awareness and appreciation for what I do have and can accomplish. And like so many others dealing with an illness, I am grateful for the loving support of family and friends. ❑

Ask the Experts

Examining the eyes of young children

"I have VHL. My nine-year-old son is therefore at 50% risk of having VHL. I took him to an ophthalmologist requesting that he be screened for VHL. The ophthalmologist checked his eyes without dilating them and assured me he did not have VHL. I questioned the accuracy of the test, since he had not dilated the eyes. He said that in young children the eyes are so clear that it is unnecessary to dilate the eyes to see the retinas and that this examination was sufficient. Is that true, or should I see another ophthalmologist?" — *Ann B., Massachusetts*

We sent this question to two experts in VHL:

"It is true that in young children the media of the eye are usually clear enough that the central area of the retina including the optic nerve, the macula, and the major blood vessels can be seen clearly without dilation. The peripheral areas of the retina, however, cannot be seen totally without dilation and for this reason I would recommend dilation for a baseline examination, particularly in view of the family history of VHL. Small lesions of VHL might only be able to be seen through dilated pupils and lesions in the peripheral area of the retina likewise may only be observable through dilated pupils." — *Jerry Cavallerano, O.D., Ph.D., Beetham Eye Institute, Joslin Diabetes Center, Boston, MA.*

"I do not think that the child had adequate screening evaluation for VHL. It is very important to perform a dilated fundus examination to adequately study the retina. I have found retinal angiomas in children's eyes as young as five years of age. It has been reported even earlier than this. Since retinal angiomas can be very tiny, one must carefully study the fundus both at the slit-lamp and with indirect ophthalmoscopy. Although the child may be free of the disease as far as the ocular examination is concerned, I would not be satisfied without a dilated examination and a very careful study." — *Robert B. Welch, M.D., Associate Professor of Ophthalmology, Johns Hopkins University School of Medicine, Baltimore, Maryland.*

"I agree with Dr. Cavallerano and Dr. Welch. In the Freiburg VHL study (Germany) we found the majority of retinal lesions in the periphery. Many of these patients had no central retinal angiomas. Blindness occurred mainly in childhood and youth, underscoring the need for careful investigations in young patients or relatives at risk. Yearly follow-up seems to be extremely useful in these young people. -- *Hartmut P. H. Neumann, M.D., leader of the Freiburg VHL study.*

Could Carpet Fumes cause VHL?

"All 8 rooms of our new home were carpeted within 2 days in December of 1973. When we moved in shortly after, we noticed odors for more than six months. I became pregnant with Tim in July of 1974 after living in the house for 8 months. Tim was born in March 1975, weighing six pounds.

"When Tim was 14 years old, our optometrist discovered a hemangioma in his right eye. An ophthalmologist suggested further investigation through CT scans of the abdomen, pelvis, spine, and brain, which led to a diagnosis of von Hippel-Lindau. Tim's two sisters, my husband and I have all had thorough CT and MRI testing which proved to be negative. They say that Tim is a 'new mutation.' Could this genetic disorder be caused by carpet fumes?" — *Cindy M., Wisconsin*

"You pose a very interesting question. I will ask Dr. Virginia Michels to respond. I spoke yesterday with Dr. Nina Ahmad of Wills Eye Hospital in Philadelphia, and she told me that we just don't know enough yet to say yes or no. It could be, and then again it might have nothing to do with it. It could have been any number of things, and the effect could have been on the sperm rather than the egg, since the sperm, nearer the surface of the body, are more accessible to environmental damage. The scientists are working on the genetics research to obtain better answers; meanwhile, just try not to blame yourself.

"There is a kind of randomness to genetic changes which is designed into reproduction in order to strengthen the species as we evolve, and to ensure diversity. In addition, there are simply errors which occur at a very low frequency, but with all the millions of replications it takes to make a human being, it is a miracle that there are as few errors as there are. The best example is from telecommunications. When you send data over a telephone wire, it's really a series of zeros and ones. An "A", for example, is 1000001. If 1000001 passes intact over the wire, you see an "A" on the screen. If it's 1000010, a subtle swap in one sequence, then you see a "B". If it's 100001 (dropping out only one zero) it's an exclamation point.

"The genetic code is represented as a sequence of elements represented by the letters ACGT, but it's the same principle. The VHL gene is a recipe for a protein. If the code is transferred intact, the right protein is made in the body. If something happens — a couple of letters in the code get swapped, or one drops out — then the protein is not made correctly. The intended protein did not get formed (it's not an "A") and some other protein did get formed (it's a "B").

"These errors do occur periodically and we don't understand why. It may be that Tim is the first one in the family, and it may be that one of you in fact has the flawed gene but no clinical symptoms. Since VHL has "widely variable expression," it is possible for someone to have the faulty gene and have extremely minor effects. The only truly reliable test is a DNA test.

"Your conjectures about what environmental influences might have been at work are certainly useful, we just don't know enough yet to prove or disprove it. I'll add it to the pile of conjectures from other people, and we'll see what commonalities come up. Keep those theories coming!" — *Joyce Graff, Co-Chair, VHL Family Alliance*

"We have no evidence that carpet fumes or formaldehyde acts as a mutagen at this time. People working in certain medical laboratories are exposed to formaldehyde over more prolonged periods and there has never been any evidence that this causes inheritable mutations in humans." — *Virginia V. Michels, M.D., Mayo Clinic, Rochester, Minnesota.*

Gamma Knife also does Brain Surgery

First let me say I applaud you and the others at the VHL Family Forum for your volunteer efforts in helping the people who have von Hippel-Lindau disease. The world could use more people like you.

We at Elekta are dedicated to improving the treatment and quality of life for patients with a number of neurological diseases and disorders. One of our primary products is the Leksell Gamma knife¨.

I would like to correct the impression left by your article

Robot Does Brain Surgery [*VHLFF,* September 1994]. Let me just say, the most elegant solution to a given problem is almost always the "simplest" solution. In the case of the Neurotron 1000, they are trying to use a very complex device, a robot, to perhaps achieve what Elekta already does with the Gamma Knife. Our GammaPlan multiple isocenter dose planning system can conform the dose to almost any lesion shape and in almost any cranial location. The Gamma unit delivers this dose with no moving parts and no software! If history is any predictor of the future, the long term reliability and accuracy of any device like the Neurotron 1000, which is very software intensive and has a large number of moving parts, will be several levels below what will be required by the neurosurgical community.

The Leksell Gamma Knife has treated more than 25,000 patients worldwide with proven accuracy, long term reliability and efficacy.

I hope the clarification of these points will be of interest to your readers. — *Stanford W. Miller, Director of Marketing, Elekta Radiosurgery, Inc., Atlanta, Georgia.*

Editor's Note: *There is a lively on-going debate in the medical community over the pros and cons of Gamma Knife versus Linear Accelerator. Owners of one always feel theirs is far superior to the other. From what we have gathered, though, the most important factor is the knowledge and experience of the team planning the treatment and driving the machine, especially their experience with hemangioblastoma versus other kinds of tumors.*

"It should also be stated here that the efficacy of focused irradiation, whether it is delivered with gamma-knife or other approaches, has not been established. In fact there are differing opinions of its utility even among those who are using it." -- *Edward H. Oldfield, M.D., Chief, Surgical Neurology Branch, National Institute of Neurological Disorders and Stroke, Bethesda, Maryland.* ❑

The Veteran

by Dru K., Florida

I am a Veteran . . .
But not one of wars between people and their countries . . .
I am a Veteran of the wars of life . . .
The battle of . . . Hate
The battle of . . . Love
The battle of . . . Youth
The battle of . . . Growing Old
The battle of . . . Education
The battle of . . . Health
The battle of . . . Ignorance
The battle of . . . Racism
The battle of . . . Friendship
The battle of . . . Trust
The battle of . . . Financial Security
The battle of . . . Lonliness
The battle of . . . Depression
The battle of . . . Sanity
The battle of . . . Just Remaining Strong
Yes,
I am a Veteran,
But first I am a human being.

Introducing our Medical Advisory Board

There are thirteen medical professionals listed on page 14 who may not always be very visible to you as readers, but who are very visible to the members of the Board of Directors. They very generously lend us their expertise as consultants on difficult questions from members, in the writing or reviewing of material for this newsletter, in presenting or helping design presentations for our annual meeting, and in advising us on various aspects of our programming. We continue here the introductions begun in the September issue. We have purposely sought out people with depth and breadth of experience with VHL — people whose formal training has been enriched by working with a number of patients with VHL over a number of years.

Eamonn R. Maher, B.Sc., M.D., M.R.C.P., Cambridge, England

Dr. Maher is University Lecturer in Medical Genetics at Cambridge University and Consultant in Medical Genetics at Addenbrooke's Hospital, England. A graduate of the University of Manchester, Dr. Maher has a special interest in the clinical and molecular aspects of familial cancer syndromes, particularly von Hippel-Lindau disease. He has a large clinical practice in cancer genetics which serves a population of approximately 2 million people. In addition, Dr. Maher and his colleagues provide a national service for advice on the clinical management and screening, and molecular genetic testing for VHL disease.

He has participated in almost 100 scientific papers and books including "Clinical features and natural history of von Hippel-Lindau disease" (*Quarterly J. Med* 1990 **70**:1151-1163) , "Identification of the von Hippel-Lindau disease tumour suppressor gene" (*Science* 1993 **260**:1317-1320), and a book *A Practical Guide to Human Cancer Genetics* (with Dr. S. V. Hodgson, Cambridge University Press). Dr. Maher and his research group were actively involved in mapping and isolating the VHL gene and are continuing to investigate the molecular genetics of VHL disease.

Dr. Maher will be a featured speaker at the Second International Patient/Provider meeting on von Hippel-Lindau in Boston, April 1995.

Virginia V. Michels, M.D., Minnesota

Dr. Virginia Michels has been Professor and Chairman of the Department of Medical Genetics, Mayo Clinic, Rochester, Minnesota, since 1990. A graduate of Marquette University, magna cum laude, she received her medical degree from the Medical College of Wisconsin in Milwaukee and completed postgraduate fellowships in Milwaukee and at Baylor College of Medicine.

She serves on the Technical Advisory Committee for Newborn Metabolic Screening of the Minnesota State Health Department, and has served on the medical advisory board of the National Tuberous Sclerosis Association 1987-1992.

Dr. Michels has lectured widely on her area of primary research, inherited cardiovascular disease, including visiting professorships in Okinawa, Japan, and Prague, Czechoslovakia.

Bernd Robert Seizinger, M.D., Ph.D., New Jersey

Dr. Seizinger is the Vice President of the Oncology Drug Discovery Department, and Director of the Department of Molecular Genetics and Cellular Biology at the Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey.

After completing postdoctoral research fellowships in Neuropharmacology at the Max-Planck-Institute in Germany, and in Neurology and Genetics at Harvard Medical School, it was while he was working in the Neurogenetics Laboratory of the Massachusetts General Hospital under Dr. James Gusella that he began investigations into von Hippel-Lindau disease. These and related investigations led to major advances in the genetics of VHL, of Neurofibromatosis, and of acoustic neuroma. He was awarded the Junior Investigator Award of the National Neurofibromatosis Foundation. It was his team, working in collaboration with physicians and researchers throughout the country, and with the generous donation of samples from VHL families, which narrowed the location of the VHL gene to the short arm of chromosome 3.

Dr. Seizinger has published 86 peer-reviewed publications, including "Von Hippel-Lindau disease maps to the region on chromosome 3 associated with renal cell carcinoma" (*Nature* 1988 **332**:269-270), "Genetic flanking markers refine diagnostic criteria and provide new insights into the genetics of von Hippel-Lindau disease (*Proc Natl Acad Sci USA*, 1991 **88:**2864-2868), and "Germline mutations in the VHL tumor suppressor gene are similar to somatic VHL aberrations in sporadic renal cell carcinoma" (*Am J. of Hum Genetics* 1994 **55:**1092-1102)

Edward H. Oldfield, M.D., F.A.C.S., Maryland

After obtaining his medical degree at the University of Kentucky Medical School Dr. Oldfield completed two years of general surgical residency at Vanderbilt University Hospital, and a year as a neurological registrar at the National Hospital for Nervous Disease, Queens Square, London, before entering neurosurgical residency at Vanderbilt University Hospital. After finishing his neurosurgical residency he spent one year in private neurosurgical practice before joining the staff in the Surgical Neurology Branch of the National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health, Bethesda, Maryland. He has been the Chief of the Surgical Neurology Branch, NINDS since 1987.

For the past several years he has supervised the neurosurgical care of patients with von Hippel-Lindau disease at the National Insitutes of Health.

As the head of the Surgical Neurology Branch he has developed laboratory and clinical research programs devoted to increasing the understanding of the biology of central nervous system tumors, including those associated with von Hippel-Lindau disease, pituitary tumors, syringomyelia, spinal arteriovenous malformations, and other forms of cerebral vascular disease. Clinical initiatives have included the introduction of gene therapy for CNS tumors and the use of recombinant immunotoxins for certain types of brain tumors. He has particular experience with the surgical removal of hemangioblastomas from the cerebellum, brain stem, and spinal cord. He introduced the investigation of vascular endothelial growth and permeability factor (VEGPF), previously known as vascular permeability factor (VPF) in central nervous system tumors, including the demonstration of greatly increased production of the VEGPF in hemangioblastomas associated with VHL (*J. Clinical Investigation* **91**:153-159, 1993) The result of that investigation suggested that the basis of the development of these very vascular tumors was linked to the production of excess VEGPF, a growth factor that specifically acts on endothelial cells. More recently he and his colleagues have linked the development of hearing loss in patients with VHL to a rare form of tumor of the inner ear, low grade endolymphatic sac carcinomas, which will be reported in an upcoming publication. ❑

What's Cooking?

-- Altheada Johnson, New York

The Florida Chapter is preparing what we think will be a very special fund-raising cookbook. What will make it special is the contributions of members from each of the fifty states, and from each country around the world!

Because we want our cookbook to be truly representative, we want YOU to give us one or more of your favorite recipes to feature in the book. The book will have 10 different food categories including Appetizers, Main Dishes, Cakes, Cookies and Desserts, Breads and Rolls.

All recipes will be separated into categories, so please write each recipe on a separate sheet of paper. The deadline for contributions has been extended to June 20, 1995.

The completed book will cost $10. Each recipe you contribute will allow you $1 off the purchase price of the book (up to $5). We are anticipating a great demand for the book. You may want to order one or more for yourself, and others for gifts and special occasions.

With *your* recipe, it will be wonderful!

Please mail or fax all contributions to:

Mrs. Gale Lugo
1990 Harmon Avenue
Winter Park, Florida
32789-5306 U.S.A.
Tel/Fax: (407) 628-1504

VHL Conference, April 29-30, 1995, Burlington, MA

Invitation to Fellowship & Learning

Central Nervous System Symposium

— Stephen R. Freidberg, M.D., Dept. of Neurosurgery, Lahey Clinic, Burlington, Mass.

The Second International Patient/Provider conference on von Hippel-Lindau disease to be held in the Boston area in April 1995 will focus on the multidisciplinary management of this complex disease. This, of course, involves the expertise of neurosurgeons, urologists, ophthalmologists, otologists and geneticists.

Dr. Peter Dempsey, Department of Neurosurgery, Lahey Clinic, will chair a symposium on central nervous tumors. He will stress the indications and techniques of surgery for brain and spinal cord tumors. When is surgery indicated? How often should patients receive MRI scanning in the absence of clinical worsening? Is it sensible to merely follow asymptomatic tumors in critical locations with clinical examination and scanning? There will probably not be unanimity of opinion among the panel but we should arrive at a consensus answer to these important questions.

In addition to a discussion on the surgical management of VHL, there will be discussions of important new avenues for treatment and diagnosis by Dr. Haring Nauta, University of Texas, and Dr. Jay Loeffler, Brigham & Women's Hospital. Radiosurgery is the delivery of high dosage radiation energy to small volume lesions in critical areas of the nervous system. This is done with the patient in a stereotactic frame. The radiation dosage is delivered with the assistance of an elegant program that reconstructs the brain, the tumor, and important neural structures such as the optic nerves and brain stem. Multiple radiation beams can be tried on the computer. The critical structures are avoided. Normal brain receives very low dose and the tumor receives a high dose of energy.

The exciting development of Magnetic Resonance Imaging (MRI) and Magnetic Resonance Angiography (MRA) has revolutionized the diagnosis of VHL disease. With these techniques accurate diagnosis of brain and spinal cord lesions can be easily made, the patient can be easily followed and angiography can frequently be avoided. Dr. Andrew Mancall, neuroradiologist at the Lahey Clinic will discuss the latest in MRI techniques.

Dr. Peter Black, Brigham & Women's Hospital, will discuss an innovative Cerebrospinal Fluid Shunting system for the treatment of hydrocephalus.

Ms. Hetty deVroom, representing Dr. Edward Oldfield, will discuss the recent discovery of an endolymphatic cyst seen in VHL patients. This can be a cause of hearing loss.

I'm going to Boston!

The nervous system symposium at the Patient/Provider Conference will provide a state of the art review of basic surgical management and techniques as well as new innovative diagnostic and therapeutic approaches. ❑

On behalf of the Lahey Clinic, I wish to welcome the VHL Family Alliance and its members. The conference program's agenda and renowned participants should make this a truly memorable and exceptionally educational event. I would encourage any member who is able to attend to do so, as it should be well worth their time and effort.

I also invite fellow medical professionals to partake of this truly unique opportunity to learn about a hereditary cancer syndrome.

I am pleased that we at the Lahey Clinic can assist by serving as a host site and in helping to further awareness of VHL and support for individuals and families affected by VHL.

-- John A. Libertino, M.D., Chairman, Institute of Urology, Lahey Clinic

> *"So far we have people coming from Canada, France, England, and at least twenty states.* ***We need you too!*** *"*

As Dr. Alfred Knudson says, in the last ten years von Hippel-Lindau disease has gone from being an "obscure medical curiosity" to one of the most important diseases for the study of cancer. As we learn more about VHL, scientists are learning more about how cancer develops in everyone. There are exciting improvements to report in the area of genetic research as well as in diagnostics, imaging, and treatment.

We are pleased to present Dr. Eamonn R. Maher from Cambridge University in England, and Dr. W. Marston Linehan, Chief of Urologic Oncology at the U.S. National Cancer Institute, who will present the latest developments from their genetic research on VHL.

The Lahey Clinic Medical Center, the Beetham Eye Unit of Joslin Diabetes Center, and many other physicians and institutions in the Boston area have contributed their expertise to this two-day program on von Hippel-Lindau disease. Dr. Andrew Novick is coming from Cleveland to present his recent findings on kidney treatment.

Dr. Philip Reilly, a neurologist who also practices law, and Richard Saltus, President of the Marfan Syndrome Foundation, will speak on legal and ethical issues around DNA testing.

There will be lots of opportunity to ask questions and engage in dialogue with the medical experts as well as the families themselves who are living with VHL.

We need you — individuals, families, and medical professionals. We need to benefit from your experience and expertise. We need your questions to enrich the presentations. We need the benefit of your knowledge and experience to round out the program.

The key to success at this Second International patient/Provider Conference is ***your participation.*** We need to learn from you. We want each of you to know that you are not alone with VHL, that there are people who care and who can help.

We sincerely hope that you will enjoy your stay in the Boston area and will want to come again. We look forward to seeing you in Burlington!

-- Laurel Newson and Joyce Graff, Co-Chairs, International Meeting ❑

This issue is sponsored *in memory of Mrs. Clare L. Nelson, beloved mother, grandmother, great-grand-mother, sister and friend; and Grand-mother of Stacey Regal O'Hare who has VHL.*

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In Honor of . . .

...Chad Erickson, by Aunt Audrey
...Lois Erickson on her recovery, by theBoard ...Lois Erickson and her enthusiasm for the VHL Family Alliance, by Audrey Tobin
...Damon G. on his promotion
...Joyce Graff on her new job, from her friends at Digital Equipment Corporation
...Joyce Graff on her birthday, by June and Harry Wilcox
...Lonzo Hayes, by Donna Ellington
...Patti Kohlen, by Dr. Charles Wilson

In Memory of . . .

...Benjamin Apher, by Rachael Morgenstern
...Mrs. Brumback by June & Harry Wilcox and Joyce Graff
...Richard A. Cohn, M.D., by Sidney & Dorothy Cohn
...Mrs. Doris Comin, from June & Harry Wilcox, Margaret & Grayson Smith, and Joyce Graff
...Mme Monique Delmas, by Didier Delmas
...Burnice Wayne Chambers, by Sherri C. Doyle
...Frank Warren Graff, by Joyce Graff
...Mrs. James B. Green, by June & Harry Wilcox
...Mr. & Mrs. Lonzo Hayes, Sr., by Peggy & Don Marshall
...Franklin B. Hege, by Marian F. Hege
...Judy Hindman, by Fred & Nancy Hindman
...Richard Hinton, by June & Harry Wilcox
...Robert Oscar Hurt, Jr., from Margaret & Grayson Smith and Harry & June Wilcox
...Mary Margaret Kampmeier, by Audrey Tobin
...Karen Koenig, from her "other family"
..Aaron Linker, by Brian & Susan McGuire
...Harry A. Marshall, by Brian & Susan McGuire
...Sheila Pipkin Phelps, by June & Harry Wilcox and Joyce Graff
...Roy O. Rhuda, by Brian & Susan McGuire
...Wesley Rhuda, by Brian & Susan McGuire
...Howard & Shirley Stert, by Ben & Judy Kohlen

with our thanks for Donations & Assistance from ...

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United Methodist Ch, Board of Church & Soc
Dr. Charles Wilson, California

... and from all the Members of the VHL Family Alliance

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Toll-free in the United States and Canada: 1-800-767-4VHL 171 Clinton Road, Brookline, Massachusetts 02146 U.S.A.

Membership, Feedback and Order Form

Name: _____

Address: _____

_____

Please renew your membership!

City: _____ State: _____ Zip: _____

Country (if not USA)_____ Fax: _____

Phone (home): _____ Phone (work): _____

❑ My employer will match my contribution. I have enclosed the appropriate forms.

All Members receive 3-4 issues of the Forum during the year, and one copy of each Alliance publications. Free subscriptions are available where the dues are a hardship.

❑ Audio version available if needed for a handicapped member

I am a ❑ VHL patient ❑ VHL family member ❑ Supporting Friend

❑ Professional (physician, nurse, dietitian, social worker, etc.)

❑ My occupation is _____

❑ I am interested in participating in a local support group

❑ ***Membership*** *($25 per mailing address, $35 for medical professionals)*

❑ ***Tax-deductible donation*** *to support the work of the Alliance*

❑ *1994 Conference audio tapes (7 tapes) #__ @ $40* $ _____

❑ ***T-shirts*** *#__Small #__Medium #__Large #__XL* $ _____

❑ ***Sweatshirt*** *#__Medium #__Large #__XL* $ _____

❑ ***Sacred Process,*** *poems by Karen Koenig #__ @ $15* $ _____

Total membership & materials **$ _____**

Second International Patient/Provider Conference on VHL:

Friday evening April 28 thru Sunday April 30, 1995, Burlington, Massachusetts (near Boston)

Burlington Marriott Hotel, (800) 371-3625 or (617) 229-6565, fax (617) 229-7973.

Call the hotel to make reservations, $80 per room, for 1-4 adults and two children. Cribs available. Licensed day care for children is available near the hotel. The hotel has a pool (no lifeguard). If there is sufficient request, we may arrange for child care in the hotel, with parents sharing the cost. Please tell us the names and ages of the children for whom you would like to have licensed child care in the hotel if available.

_____

_____

What in particular would you like to learn at the Conference? Tell us so that we can make sure it is available to you.

_____

_____

Conference Registration

❑ Conference Registration _____ @ $95.00 $ _____

Registration includes breakfast & lunch Saturday & Sunday, and a set of handouts. Please plan to join us for breakfast.

❑ Discount for Spouse Subtract $20 from second registration $ _____ (-)

❑ Earlybird Discount For registrations postmarked by April 7 $ _____ (-)

Total conference registration: **$ _____**

Attendees from outside the U.S. may pay on-site. Please send the form so we know you're coming!

In Honor Of . . . donations (minimum $5 each):

I am enclosing a donation ❑ In Memory Of ❑ In Honor Of ❑ OK to list in VHLFF

Honoree's Name _____

In Honor of Occasion: _____

Please send card to (name and address) _____

_____

Return to: VHL Family Alliance, 171 Clinton Road, Brookline, MA 02146

In Britain, send to VHL Patient and Relative Contact Group, 114 Longfield Rd, Littleport, Ely, Cambs CB6 1LB
In France, send to VHL France, 87, rue de la République, 95240 Cormeilles-en-Parisis, France
In Italy, send to Alleanza VHL, Loc Malvicina, 19, 15066 Gavi (AL), Italy
In Australia, send to VHL Family Alliance, 2/51 Musgrave St, Yarralumla 2600, Camberra, ACT, Australia

Greetings to Everyone in the Family

Don and I have a very special request that we hope each of you will take to heart and give serious consideration. We have spent the last year helping in every way we could to spread the word about the VHL Family Alliance. We realized early on the need for fund raising so that all our goals could be achieved. We have many special programs in progress to support our growing VHL *Family*. While all of our talented labor comes from dedicated volunteers, there are still things which cost money.

The *toll-free telephone line* that provides a great measure of support for many different needs, is in most cases the first contact a new VHL patient, family member or professional has with our *Family*. Do you remember how alone you felt the first moment you heard you had VHL?

The *patient packets* includes the *VHL Handbook*, Family Tree, recent VHL Family Forum newsletter and informative brochures along with a personal invitation to join in our *Family*. We continually receive compliments that our packet is the most professional, informative and contains the most current VHL information. Do you remember how difficult it was in the beginning to find any VHL information?

The *support meetings* and international conferences have brought all of us together into a large caring and sharing *Family*. Do you remember how hard it was to accept this rare disease and then to find out there are others all around us that are walking in our shoes and needing a tender ear and a story to share?

The Clinical Care Centers are a growing network of caring medical professionals sharing information to take the best possible care of you and others. Do you remember how hard it was to find a physician who knew about VHL?

The VHL *Family* Alliance provides a tremendous support and information system, which brings us to the point of our request. We need your help to reach out with telephone support, brochures, handbooks, newsletters, support meetings, and education. We also need to begin to be directly involved with research, both participating in and funding new research.

Each of us has friends and family members who could be very interested in helping our Family. Sometimes all it takes is a little explanation and encouragement. You can even do your own fund raising in your local community. Bake sales, yard sales, auctions, craft sales, raffles, and sponsoring sporting events, can help raise money to keep our Family healthy. Don and I have had great success in our small community with a spaghetti supper, craft sale, and raffle -- enough to fund two issues of the newsletter from Mississippi alone.

Many of us need to renew our membership for this year and along with that may consider a monthly donation. If everyone on our mailing list sends in their dues we can fund our education programs. If everyone puts in another modest donation, we can offer a research grant this year.

Let us all be active in our Family and work together and make a difference in the lives of others! If we can be of help in any way, or if you have any ideas to share -- call us!

We are looking forward to seeing you in Boston in April!

-- *Don & Peggy Marshall, Miss.*

Have you renewed your Membership? Please do it today!

Please join us for the Annual Meeting, Boston, 1995!

VHL Family Forum
Newsletter of the VHL Family Alliance
171 Clinton Road
Brookline, MA 02146

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