VHL Family Forum

Volume 8, Number 1 ISSN 1066-4130 March 2000

Laparoscopic Cryoablation for RCC

-- *Andrew C. Novick, M.D., Chairman, Department of Urology, Cleveland Clinic Foundation*

Partial nephrectomy has become a successful form of treatment for patients with localized renal cell carcinoma (RCC) when there is a need to preserve functioning renal tissue. We recently reviewed the long-term results of partial nephrectomy[1] for treatment of sporadic[2] RCC in 500 patients managed at the Cleveland Clinic prior to 1996. A technically successful operation with preservation of function in the treated kidney was achieved in 489 patients (98%). The five-year cancer specific survival rate[3] in the series was 93%, and recurrent RCC developed postoperatively in only 8.2% of patients.

Renal cell carcinoma in von Hippel-Lindau (VHL) differs from sporadic RCC in that the diagnosis is made at a younger age, and there are usually multiple bilateral solid and cystic renal tumors. Studies have shown that partial nephrectomy can provide effective treatment for VHL patients with localized RCC tumors. People with VHL are more likely to have recurring RCC tumors; it is normal in VHL to have multiple tumors on both kidneys. Therefore VHL patients must be followed closely after partial nephrectomy so that any recurrences can be detected at an early stage when they are still localized and amenable to a second renal operation.

Laparoscopic renal cryoablation is an emerging minimally invasive treatment option for selected patients with localized renal cell carcinoma. This involves the use of a freezing probe ("cryo") to remove ("ablate") the diseased portion of the kidney. The aim of cryosurgery is to ablate the same amount of diseased renal tissue that would be removed if conventional surgery excision of the tumor were performed. The targeted diseased renal tissue is rapidly frozen in place ("in situ") with a surrounding margin of healthy renal tissue. The freezing process causes those cells to rupture and die. This devitalized tissue is then allowed to slough off over time, with new tissue forming in its place. The basic process of cryosurgery includes rapid freezing, slow thawing, and a repetition of the freeze-thaw cycle.

A primary advantage of renal cryoablation is that it can be performed laparoscopically without the need for a conventional open surgical incision. The advantages of this approach for treated patients include a shorter hospital stay, less postoperative pain, and a more rapid complete recovery.

Relatively few laparoscopic renal cryoablation procedures have been performed worldwide to date. Our Group at the Cleveland Clinic Foundation reported the initial series of ten patients in 1998,[4] and our experience now includes more than 40 carefully selected patients with localized RCC. These have all been patients with small (less than 4 cm.) solid, peripheral renal tumors not involving the central renal collecting system.

We recently reviewed our experience with laparoscopic renal cryoablation in the initial 32 patients with localized RCC who met the above criteria. All of these patients had a technically successful operation and there were no significant postoperative complications. The average operative time was 2.0 hours and the average blood loss was 67 cc. Hospital stay was less than 23 hours for most patients and the median time for complete recovery was two weeks. Renal function was preserved in all treated kidneys. Sequential postoperative MRI scans demonstrated a gradual contraction in the size of the treated lesion; in

Inside this issue!

some patients the treated lesion was no longer visible on radiological scans after one year. Twenty-four patients have undergone CT-directed needle biopsy of the cryoablated renal tumor site at six months postoperatively, and these biopsies have all been negative for cancer. There have been no cases of renal fossa or metastatic tumor recurrence with follow-up of up to three years.

Our experience demonstrates that the technique of laparoscopic renal cryoablation is reproducible and technically feasible with a low rate of surgical complications. This approach may be employed to treat VHL patients with a limited number of small (under 4 cm.) solid renal tumors on the outside of the kidney that do not involve the central renal collecting system. Laparoscopic renal cryoablation can be performed as a primary treatment for localized RCC, or for secondary treatment of isolated, small locally recurrent tumors. Notwithstanding the promising early results, longer-term clinical and radiographic follow-up of treated patients is needed to ultimately validate the effectiveness of this new approach.

1. A nephrectomy is removal of a kidney; partial nephrectomy is removal of part of a kidney.
2. Sporadic tumors are ones that occur at random in the general population, as contrasted with tumors that occur due to an underlying familial predisposition such as VHL.
3. Cancer-specific survival rates measure the number of people in the study who died from cancer. Someone for example who died in an automobile accident would not be counted as having died for purposes of this study. Thus after five years, 7% of the people in the study had died of cancer. 8.2% of those in the study had a recurrent RCC tumor, which is not unusual in VHL.
4. *Urology* (1998) 52:543-551.

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

Every penny we raise in donations from now through June will increase the number and size of this year's research grants.

Ingredients for a Good Surgical Outcome

by Emma K., Australia

I had plucked up the courage to have my annual testing. My Mum died in June at age 74 after a difficult bout with cancer, so "plucking up" is the right word. I wasn't concerned about going for the tests, just about getting the results! I was becoming more and more pleased as each result came back with a "no change" or "clear report." Smooth going so far!

Fortunately my husband and sister came with me to my last results appointment with my neurosurgeon. I really was expecting a monitoring kind of conversation, when he said that the lesion on my brain stem had doubled in size in the last year. I responded without great anxiety, "So when do you think you'll want to operate? " My brain tumors have been slow growing, so I expected him to say next year or the year after.

He replied, "Well, I thought if I went in soon you'd be getting better by Christmas Day. The final decision is yours of course, but if you leave it a year you'll be in a wheelchair." I was once again in a life-threatening position.

I picked my jaw up off the floor and asked a few questions. This would be my sixth surgery on the cerebellum since 1987. I said I'd be in touch with my decision. I left his office and said to my family in the waiting room, "Oh, s---!" My sister was great. She said, "It's alright if you need some support now -- you don't have to be strong." Having them there and hearing that was wonderful support.

As we sat downstairs in the coffee shop, in shock, waiting for our drinks to arrive, my husband said to me, "Life happens." There was not much said, as we immediatly realized the ramifications. We had all been very emotionally stretched already this year with my mother's death and dying, and we were about to begin again.

There followed a week of deep thinking, faxed questions to my doctor, discussion with family, and conversations with my VHL support team -- Joyce in Boston, Peggy in Mississippi, and Gay in Sydney. All of them had helped me a lot during Mum's illness and passing. At last I bit the bullet, girded my loins, and took the decision to have the operation.

Four weeks after the initial diagnosis and proposed course of action was suggested, I had the operation. Fortunately my surgeon operated in a hospital close to my home, so friends and family could ring me on the telephone and visit me easily. I was in a ward I knew, and some of the staff were still there from my first visit there in 1996, so it felt familiar and as "normal" as could be, given the circumstances. I returned home two weeks after the operation. The surgeon used what

he called "Frameless Stereotaxy" (see page 4) to guide him during surgery -- it was terrific for me!

I want to share with you all my preparation routine for this operation and why I believe it went so well.

The whole experience is very unsettling emotionally and it doesn't get any easier the more operations you have. How you manage the process becomes more efficient.

1. I read through all the VHL newsletters and copied out the articles "Science Isn't Enough", "Plain Talk about Stress," "Families Share Diet and Exercise Tips," and "Living with a Rare Disorder." I found them very useful and comforting.

2. I used the supplementary medicine outline from the Alliance's website.

3. I had massages and talked to wise people who understood my anxiety, not only about this operation but the sum of my experience living with this rare disease for thirty years and seeing it express itself in my father and brother, who died in 1979 and 1984, directly or indirectly of VHL.

4. I exercised very gently, walking around the block with my husband and our dog.

5. I had and have the healthiest mental attitude possible and am quietly committed to its never-ending improvement. Sure, its state of health varies depending on what's happening in my life (I am only human), but I'm mastering recognizing how I feel and managing it better.

6. I invited my sister and her family to dinner. She is my only surviving immediate family. Everyone was still grieving over the loss of Mum. I told them I realized the risks involved, and told them I was sorry, but I can't do anything about what is happening to me. My brother-in-law said that my apology was not accepted, and that they would all support me in any way they could. So for me, while it was awkward to express it, placing my emotional cards on the table was a great relief and won me some wonderful support.

The surgery was a success and the recovery is going smoothly. Here are my conclusions about why it went so well:

1. I prepared my mind and body as best I could.

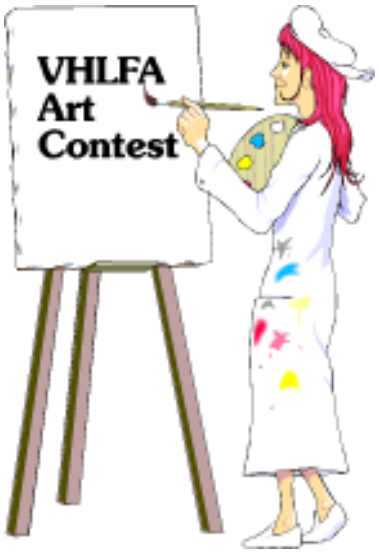
2. My annual tests picked up the change in my brain before it became violently symptomatic.

3. I go to a neurosurgeon who not only analyzes well, but had the courage to suggest operating now! This meant I was not as physically deteriorated when I underwent surgery, so I didn't have as far to come back.

4. He used the latest technology to assist him during the operation, which for me meant he used his time more effectively in planning his surgical route, getting to the tumor more accurately and quickly, and therefore spent less time in my head, which minimizes the risk of infection. It still took six hours, but he was able to go directly to the tumor. What a miraculous advance from my father's experience in 1969, before CT scans or MRI's!

5. I got lots of love and support from my husband, my family, friends, and from the Alliance.

6. The back of my head, neck and shoulders, arms and hands are numb. They change and improve daily, and I will be rehabilitating for a long time. If anyone has any suggestions, please send e-mail to the VHL discussion, vhlfa@egroups.com. I prepared myself for Christmas and practicing balancing champagne in a champagne flute, because as one friend jokingly said, "Drinking champagne through a straw is not very elegant!" We spent New Year camping with very good friends on the highest mountain in this country!



Show us your stuff!
Due May 31

Calendar 2001

We need photographs and original art for inclusion in the 2001 VHL Calendar

Thirteen artists will be included in next year's calendar.

T-Shirt

We are looking for a creative, clever, even funny T-shirt to be shown for the first time at the VHL Symposium this July in Minnesota.

Please send us your submissions. Please do not send original art, as submissions cannot be returned. Send photographs, 35 mm slides, or tiff images. Send submissions by 31 May, 2000, to:

Lisa Bonneau
4761 W. Waterbuck Dr.
Tucson AZ 85742-9629

Or send tiff images to joyceg@pipeline.com.

Frameless stereotaxy

by P.W.A. Willems[1], F. J. Hes[2, 3], C.A.F. Tulleken[1]

In the newsletter from June 1998 the treatment of hemangioblastomas was discussed in the article 'Caution Urged on Stereotactic Radiosurgery'. The authors clearly illustrated that not every VHL patient with a cerebellar hemangioblastoma is a suitable candidate for stereotactic radiosurgery. This observation was supported by a study from Adler, Chang, et al. who demonstrated that only VHL patients who present with small (<3 cm) solid hemangioblastomas without significant mass effects are reasonable candidates for radiosurgery.[4] Since microsurgical resection remains the treatment of choice for the vast majority of symptomatic cystic hemangioblastomas, we would like to present a new adjunct in neurosurgery, i.e. frameless stereotaxy or neuronavigation.

When a patient is diagnosed with an intracranial or spinal hemangioblastoma and is subsequently scheduled for surgery, it is the task of the neurosurgeon to locate this lesion and remove it. To locate the lesion the surgeon is aided by general knowledge of neuroanatomy and by the MR or CT images that have been made before the surgery. The difficulty of this task depends mainly on the size and location of the lesion. A small and deeply situated lesion will be more difficult to locate than a larger, more superficially located lesion. To assist the surgeon's orientation, especially in more difficult situations, neuronavigation has been developed.

The first reports of neuronavigation date from the mid-eighties (USA and Japan). It is now used in many neurosurgical centers around the world. The term is actually used for several types of localization instruments, which share the fact that they do not use a head-mounted stereotactic frame. Prior to the development of neuronavigation, these rigid mechanical frames were the only instruments capable of localizing a position shown on the CT or MR images. These frames are particularly useful for performing needle biopsies and inserting drains, electrodes etc. However, they are not applicable in open surgery. Neuronavigation offers a solution in open surgery.

To get help in orientation from the computer system, the surgeon needs to show the system where he is operating at that moment. To do this he uses an instrument that can be localized, or located, by the system. The system will then show the position of that instrument in the MR or CT images. Different localizing techniques have been used in the past to do this. The most popular and widely used technique is based on infrared light. Each instrument to be localized carries 2 or more flashing infrared lightsources (LED's). These infrared flashes are seen by a camera array consisting of two or more infrared-sensitive cameras. The information of these cameras is combined to generate a stereoscopic image, much like the way we use two eyes to see depth. Since the shape of the instrument is known to the system, the position of the tip of the instrument can be calculated from the positions of the LED's. Using this instrument, the positions of a number of known points on the patient's head (fiducials) are entered into the computer. The computer combines these points with their respective counterparts in the CT or MR images. It's as if the pointer is showing the computer system the position of the patient's head (this is the so-called registration procedure). From that moment on, each new location of the instrument can be shown in the CT or MR images. Thus, during the operation the neurosurgeon can see the location where he is currently operating, at that moment. Instead of infrared light, other localizing techniques include multi-jointed mechanical arms or the localization of sound bursts or electromagnetic fields. However, these variations are based on the same underlying principles.

Although neuronavigation might seem to be an ideal technique, there are a number of specific drawbacks. These drawbacks are related to the issue of accuracy. A neurosurgeon will only rely on a neuronavigation system for his orientation if the system is fairly accurate. The inaccuracy of neuronavigation is an accumulation of small inaccuracies involved with each part of the technique. These include inaccuracies in the CT or MR images, the localizing technique itself, the registration-procedure and the so-called 'brainshift'. 'Brainshift' denotes the changes in anatomy that occur after the CT or MR images have been made. Since the entire system is based on preoperative CT or MR images, displacement of tissue during the operation will not be accounted for. This effect is exaggerated when a large amount of fluid is drained, like cerebrospinal fluid from the ventricular system or tumor fluid from a cyst.

Spinal surgery presents even more problems. First, the registration-procedure is more difficult to perform since fiducials on the spinal column can only be used after they have been cleared of surrounding tissue. Secondly, the vertebrae can move a little relative to each other, which necessitates the performance of a new registration-procedure for each vertebral level. Thirdly, this registration holds true for the vertebrae themselves, but hardly for the nervous tissue within the spinal canal. In other words, the relationship between the spinal cord and the spinal column is less rigid than the relationship between the brain and the skull. Therefore, the use of neuronavigation has only been reported in spinal operations concerning the vertebrae and not in operations concerning the spinal cord.

With each operative procedure the neurosurgeon will have to decide whether neuronavigation is going to be helpful, considering the level of difficulty of orientation and the effect of neuronavigation in that specific

procedure. With respect to hemangioblastomas there are a number of possible situations. To date, the removal of spinal hemangioblastomas can not be improved by neuronavigation due to technical limitations. Brain hemangioblastomas can range from small solid lesions to large, predominantly cystic lesions. The value of neuronavigation will decrease as the lesion gets larger, since it will be easier to find anyway. And its value will decrease as the cystic component gets larger, since intraoperative emptying of the cyst will induce more brainshift.

In conclusion, neuronavigation is considered to be a valuable new adjunct in neurosurgery, known to have its own specific limitations and advantages. The technique has limited value for the large, predominantly cystic, hemangioblastomas that may occur in the cerebellum of VHL patients, but these operations are usually not that difficult. Its value is especially clear when open surgery is intended for deep-seated small intracranial hemangioblastomas. Lesions located in the brainstem still pose the biggest challenge. In these cases stereotactic radiosurgery may play a growing role.

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4. *Neurosurgery* (1998) 43:1

If I Had my Life to Live Over...

by Erma Bombeck

I would have talked less and listened more. I would have invited friends over to dinner, even if the carpet was stained and the sofa faded. I would have eaten the popcorn in the 'good' living room and worried much less about the dirt when someone wanted to light a fire in the fire place. I would have taken the time to listen to my grandfather ramble about his youth. I would never have insisted the car windows be rolled up on a summer day because my hair had just been teased and sprayed.

I would have burned the pink candle sculpted like a rose before it melted in storage. I would have sat on the lawn with my children and not worried about grass stains. I would have cried and laughed less while watching television and more while watching life. I would have shared more of the responsibility carried by my husband. I would have gone to bed when I was sick instead of pretending the earth would go into a holding pattern if I weren't there for the day. I would never have bought anything just because it was practical, wouldn't show soil or was guaranteed to last a lifetime.

Instead of wishing away nine months of pregnancy, I'd have cherished every moment and realized that the wonderment growing inside me was the only chance in life to assist God in a miracle. When my kids kissed me impetuously, I would never have said, "Later. Now go get washed up for dinner. "There would have been more "I love yous".. more "I'm sorrys"... but mostly, given another shot at life, I would seize every minute...look at it and really see it... live it...and never give it back.

Chapter News

New York -- Altheada Johnson

The NY Chapter meeting was held in November 20, 1999 at the Mt. Sinai Medical Center. Mt. Sinai is a VHLFA Clinical Care Center. The meeting was attended by: Julie McGwynn, Genetic Counselor and center contact person; Teresa Iodice, MA, PT/OT Director at the International Center for the Disabled (ICD); Bob and Evelyn Werner, Lillian White, Kathy and Stacy Richards, Joyce Johnson, Fred and Altheada Johnson.

The subject of the meeting was Relaxation Techniques. The presentation was given by Teresa Iodice. Ms. Iodice emphasized maintaining 'centeredness' while under stress, like the stress of having VHL and the guilt that parents feel when their children are diagnosed. Now, I am not a parent but I do have parents and guilt is not something I think any parent should feel about passing on VHL.

For many, VHL was not even diagnosed when children were conceived. For others, there was no knowledge that VHL could be passed on. And what if my parents had known, would I and my siblings be here today? I don't know but I am glad to be here in this world -- VHL or not. Mostly, my life has been good. I love lots of people and lots of them love me.

How do we reacquire 'centeredness' on the way to relaxation?

--Control and 'Letting Go'
--Forgiveness
--Health and well being
--Spiritual awakening
--Love and support
--Self acceptance and acceptance of others

Types of Relaxation Techniques:

-External Physical Techniques: Massage, acupuncture, shiatsu, stroking, any sort of bodily manipulation external touching.

-Physical Activity: Walking, aerobics and other sports.

-Physical/Mental/Spiritual: Tai Chi, Chi Gong, martial arts, Feldenkreis, singing and dancing.

-Mental/Spiritual: Prayer, mantra, rosary, conversation with a trusting person/God/confession/therapy, music, singing.

-Specific Techniques: Visualization, Hypnosis, Deep Breathing and Muscle contraction exercises.

Altheada's Story

My father died in 1966. He had had one operation for a tumor on his brain and was in need of another when he died. My brother died in 1969. He too had tumors on his brain. Neither of them had been diagnosed with von Hippel-Lindau (VHL) disease. All I ever remember hearing is that this was probably some condition passed along on the male side of the family. My three sisters and I thought we could put this out of our mind. A cousin pointed out that we still needed to be concerned about any male children we might eventually have. When my sisters had their children, including three boys, this unnamed tumor condition was always in the back of my head.

In 1987 things, for me, had progressed to their worst. I was unable to take one step without holding on and was in a great deal of pain. After spending two months and lots of money with two different chiropractors, treating what I thought was sciatica, an orthopedist suggested I get a CT scan. He immediately referred me to a neurologist who immediately admitted me to the hospital. After two weeks of countless CT scans, MRIs, X-rays and a nine-hour surgery I was diagnosed with VHL in 1988.

By this time, one of my sisters had given birth for the second time. She had some vision loss in one eye which had been blamed on high blood pressure. Once I was diagnosed, thankfully the doctors knew to check several other areas of my body, and suggested that other family members be checked as well. They discovered that I had a tumor on my right retina that if left untreated, could have caused blindness in that eye. It was then that we asked my sister's eye doctor if what had caused her vision problems could be VHL. He told her "no way." We have since discovered that my sister does indeed have VHL. If her eye doctor had diagnosed VHL years earlier, maybe my own problems could have been caught before they caused paralysis.

One In a Million

Being diagnosed with VHL is a very traumatic thing and I would not have been able to get through it without my husband Fred and my family. Fred and I had only been married three years when I first started feeling sick. We had just bought our first house, I was working in the outpatient department of Newark-Beth Israel Medical Center, and he had recently started working as a trainer for the United Methodist Church. He would drive me to the Port Authority to take the New Jersey Transit bus to my job. I would limp my way home on the PATH train and subway in the evenings. I had not injured myself so I just knew this would go away on its own. But it didn't.

My first hospital stay lasted three months. Fred brought dinner and ate with me every night. Mom visited during the day, and my sisters visited on weekends. We made a schedule so that their visits would not coincide, and I had visitors and home-cooked food all the time. I believe this aided my recovery.

When my doctor told me I had von Hippel-Lindau disease, and that it was genetic, I thought he had to be mistaken. I thought "Don't you know soon after you are born that you have a genetic disease?" Worse than that, I was led to believe that I was the only one in all of New York State with this condition. The sense of isolation was intense. I felt hopelessly alone, with only my family for a life-preserver. My doctor told me this was an extremely rare disease. Whenever I would have a test or scan of any kind, lots of medical staff and students would be come to observe. I would be rich if I could have charged admission. I now know of 29 other people with VHL in NY, and I am willing to bet that there are more. This disease is not as rare as people think. VHL affects so many different systems and is so different for every patient that it is easily misdiagnosed or simply not diagnosed at all.

Teaching My Doctors

Since my diagnosis, I have had three more spinal cord surgeries, one craniotomy, and laser surgery on my right eye. My condition is quite stable for now. My major task now is teaching my doctors about VHL and what I need to manage this disease. I have not run across one doctor that has not heard of VHL, but neither have I run into one outside of the U.S. National Institutes of Health (NIH) who knows how to manage this disease. How often do you scan the spinal cord, abdomen and brain? What symptoms do you need to look out for? My doctors and I would be lost without the *Patient Handbook* published by the VHL Family Alliance.

Then you have those few doctors who do not seem to want to learn. I have not quite figured this out. Are they embarrassed that they do not know everything? Do they think it is demeaning to accept information from a patient? What I want is a partner who is willing to learn from any and all sources.

Whenever I am asked by patient whether to be treated by a "familiar face" or by an expert who may be far from home, I say go to where the experts are. I feel that if I only had known then some of what I know now I would not be in the condition I am in today. My neurosurgeon knew very well how to operate on my spinal cord, but he knew very little about VHL. He admitted to me that he saw a pea-sized tumor during the first operation which he did not remove. A year later it, too, it had grown and was causing pain and damage. After a second spinal surgery, I was paralyzed.

The Family Meets With A Genetic Counselor

Finding the gene was very exciting. There is hope that a cure is not far behind but we have to be realistic. Science has known what mutation causes sickle cell

Altheada and Fred Johnson, 1999

anemia for many years, but there is still no cure. Being able to find the VHL mutation on an individual's gene is important because it can determine whether that person needs the annual screening or not. It is not a cure and does not change how VHL is managed.

I was diagnosed with VHL in February 1988. My first meeting with a genetic counselor occurred in October 1995. Once I understood that VHL is genetic and that one of my sisters had it, I immediately wanted her two children tested. My arguments were several: you do not want either of them to end up with the damage she and I had experienced. Why not find out for sure and maybe avoid all the annual testing? Wouldn't having a clear diagnosis bring peace of mind? To these arguments I have received silence. I am no one's mother, so I am sure I am not seeing things the way she does. I know, though, that she just does not want anything to be wrong with her kids.

The genetic counseling meeting was the first time my entire family got together to talk about this issue. Of my two unaffected sisters, the one who has two children agreed to the DNA test, just to make sure. My unmarried sister did not want testing. She felt, "no kids, no symptoms, why bother?" But there had to be some nagging worries. After a time she decided to be tested, and does not have VHL.

My three nephews and my niece all said that they would want to know if they had VHL. My affected sister said she had to discuss it some more with her husband. More than a year later her only son and oldest child had a brain tumor removed. This pushed my sister to have her daughter's DNA tested, which has proved positive. Knowing that she has the VHL alteration, they can now do preventive screening and hopefully see problems coming before they turn into crises.

The VHL Family Alliance

When I finally returned home in 1991 after 14 months in the hospital and rehabilitation, I had nothing to do and nowhere to go. I was and still am in too much pain to hold down a steady job. I watched TV, read, knitted or crocheted all day. I was referred to outpatient rehabilitation, and that led me to the International Center for the Disabled. There I am able to heal my spirit and share some of my knowledge as a registered dietitian through nutrition counseling with other clients. Along with several other disabled people I participated in the taping of three cooking videos. We demonstrated assistive devices, healthy cooking, shopping and eating out, all with the disabled in mind -- a first!

In early 1993, I received the first newsletter about the Alliance but I did not contact them. Several months later I received an invitation to a support group meeting in Boston. I talked to my husband and we agreed to spend the weekend in Boston. That was the first time I had ever laid eyes on anyone, other than my sister, with VHL. That trip was very special and it woke me up. Now, as Board Member, NY Chapter Chairperson and member of several different committees, I do some very productive work, mostly out of my home, for the Alliance. I answer the telephone hotline two months a year, and I watch the e-mail info account info@vhl.org

Many newly diagnosed patients feel that they are facing VHL alone that they are the only one with VHL in their universe. It is very satisfying for me to be ble to ease the panic some feel after being newly diagno ed. Doing what little I can do takes my mind off my o n concerns and allows me to feel useful and ne ded, which gives a much-needed boost to my self-esteem and self-worth. Somehow volunteering just does that. I have also attended several cancer conferences. With Fred or another family member, I pack up and go. There I am able to introduce VHL to others. Often these groups have never heard of VHL, let alone seen someone who actually has it. I feel the more we can share ourselves with others, the more likely we are to save someone else from the damaging delay a misdiagnosis can cause.

One goal of the VHL Family Alliance is to spread the word about this disease so that doctors consider it when faced with a patient with unexplained symptoms. I happen to know from answering the hotline and the e-mail account that we are reaching that goal. There are lots of people out there that get comfort just knowing we are close by. Many people that call have never talked to another individual with VHL. They feel just as I did all those years ago. Many of their stories are very similar to mine. I am so very happy that the VHL Family Alliance exists. I do not like to think where I might be without it. I have re-discovered the joy of working with and helping others, as I did when I worked with families as a dietitian. Through the ICID and as nutrition coordinator for VHLFA I use my dietitian skills in new ways.

Gene repair in rats raises hope

By Penny Stern M.D., Reuters Health

Editor's note: *As you read in the press about advances in gene repair, look for advancement of knowledge about the technology. Once there are good vehicles for delivery of repair information to all cells, then the possibility of repair of the VHL gene is more likely.*

Through the use of a novel technique termed "chimeraplasty", researchers have, for the first time, successfully repaired the genetic defect associated with Crigler-Najjar syndrome, a rare but devastating liver disease, in lab rats.

The finding may lead to gene therapies that cure other genetic diseases such as hemophilia, sickle cell anemia, [and von Hippel-Lindau disease,] according to the report published in the *Proceedings of the National Academy of Sciences*.[1]

Principal investigator Dr. Clifford Steer, of the University of Minnesota School of Medicine in Minneapolis described his team's work in an interview with Reuters Health. "We did two things that were important: one, we developed a system whereby we could go in and literally rewrite the genetic sequence in a specific gene of interest; and two, we developed a technology that would do it in the hepatocyte, the type of liver cell that controls the major defect [of Crigler-Najjar syndrome]." The syndrome is characterized by an inability to properly metabolize bilirubin, a byproduct of normal red blood cell degradation. The genetic disease features jaundice and destructive changes in parts of the brain.

The researchers created a molecule called a chimeraplast, which is based on the structure of the defective gene and "targeted to that portion of the gene with the mutation," Steer explained. When the molecule is introduced into the cell, "it tricks the cell into thinking that there is a defect in its DNA sequence for that particular gene and by tricking the cell, the cell basically repairs [what it perceives as] its own defect."

What is being accomplished, in essence, is genetic repair without having to employ techniques that require "the introduction of new genes [via genetically modified viruses] to take the place of the [original defective] genes," as is the case in conventional gene therapy, according to Steer.

"All we are doing is repairing the genetic defect in a gene that is already there," he explained. "And when you think about it, what is really the best way to do gene therapy? It would be to go in to correct the defect so that the gene is in the right position, controlled and regulated by the [appropriate] regulatory elements that would normally control that gene."

An important aspect of this technology is that "once the genetic change is made, the repair is permanent," Steer said. And although this work was carried out in an animal model, the Gunn rat – which has a genetic defect similar, though not identical, to that seen in human Crigler-Najjar syndrome – Steer "feels very confident that it's going to work in humans. It works in animal models, it works in plants, it works in bacteria, it works in any structure that has DNA in it."

The type of mutation corrected in the study involves an omission or deletion of one "letter" in a specific DNA genetic sequence. DNA is composed of basic units called nucleotides, which are designated by specific letters. These combine into sequences that "spell out" a genetic code. Changing one "letter" into another is easier than replacing a missing letter, Steer said, and in the human disease, changing rather than replacement is required to correct the defect. Consequently, "we hope that our results will be even more exciting in human beings than they were in the rodent model."

Together with his colleagues at the Albert Einstein College of Medicine in the Bronx, New York, Steer expects to submit a clinical trial application for the technique to the Food and Drug Administration early next year. "We're going to involve 3 to 5 pediatric patients already identified with Crigler-Najjar, who live in the Amish Country in Pennsylvania," Steer told Reuters Health. He commented that the Amish have a very high frequency of this disorder and that these particular children all have the same genetic defect, a mutation at a single point in the genetic code.

The majority of genetic diseases in human beings are single-point mutations, Steer explained, "so we have a technology here that can be applied to many different types of disease. The technology is here, it's here to stay, and it is very different from gene therapy."

The investigators are already developing a number of other animal models to look at potential clinical applications in disease such as Gaucher's disease, hemophilia, thalessemia, and sickle cell anemia. Though sickle cell anemia's defect originates in the bone marrow, Steer believes that the team will be able "to develop a delivery system for the chimeraplasts" that will direct them to the marrow, the site of the stem cells from which the defective red blood cells in sickle disease originate.

"It's going to be more challenging than liver, only because it's bone marrow and the progenitor cells are more difficult to deal with," he noted.

Steer emphasized that though the results achieved thus far are "very, very exciting," with potentially "broad-based application," much remains to be done. Further developing and refining the technology's seemingly limitless possibilities will "keep the medical profession busy for many, many years," he predicts.

1. *Proceedings of the National Academy of Sciences USA* (1999) 96:10349-10354.

Hormones and VHL

Question: Is hormone replacement therapy safe for women with VHL? I have read that women with either breast or uterine cancer should not use hormone replacement therapy. How about VHL women? Any input? -- *R.M.K., California*

Response compiled by Joyce Graff and Gale Lugo. It's a popular question. The family impression is that there are "caution points" around changes in hormone levels: adolescence, going on the pill, going off the pill, pregnancy, menopause, and even the "male menopause" where hormones change for men in the 40-50 age range. What people have noticed is that there seems to be a change in tumor activity around those times. Men should read this message too.

It's particularly hard to pin this down for women 18-35 because this is a time of tumor activity anyway, so what is attributable to these hormonal shifts, and what is not? We do see that women who have had little tumor activity for quite a while tend to have some renewal of activity around menopause.

There is no real data so far that would tend to agree or disagree with these impressions. There is interest at NIH in studying this, but no results to date. When they have tried to pin down information on pregnancy, many of the subjects who are willing to participate do not have sufficient documentation of their tumor status before the pregnancy to give us a real feel for how it changed. For example, someone gets pregnant and has a tumor during or shortly after the pregnancy. But do we know whether that tumor was already there at the start of the pregnancy? Do we know what size it was? Did it perhaps grow only a very small amount during the pregnancy, but it was enough to make the symptoms clinically significant? Or did it pop out of nowhere because of the pregnancy? Unless we have good scans from before the pregnancy, we don't know what to think.

Similarly, there is not yet sufficient information about hormones and menopause.

Menopause is adult-onset ovarian failure with the loss of estrogens, progesterone, and ovarian androgens. Decline in ovarian function usually begins by age 35 to 40 years. This causes a permanent state of multiple hormone deficiencies.

The long-term goals of hormone replacement therapy (HRT) include relief of existing conditions such as hot flashes; vaginal dryness; emotional symptoms; prevention of osteoporosis; prevention of cardiovascular disease, dementia, and carbohydrate intolerance. From an endocrinology perspective, it seems only logical to use HRT.

The concerns about HRT stem from concerns expressed for breast cancer patients, as well as this family impression of concern around hormonal shifts. If going on/off the pill might trigger something, might going on/off HRT also trigger somethings? Or would HRT help you avoid the shift and therefore avoid the danger? What does the breast cancer research have to tell us? While early studies warned against HRT for breast cancer patients; more recent research is inconclusive. The bottom line is: we simply don't know. We have people in this VHL community who have chosen each path. It is important that you make a reasoned decision, based on tests and actual information about your own risks.

(1) choosing HRT. Dr. R. Neil Schimke, Chief of Endocrinology and Genetics at the University of Kansas Medical Center, feels strongly that the dangers of osteoporosis are greater than any dangers of renewed tumor activity. His 6 VHL patients who are on HRT do not seem to be experiencing any significant renewed tumor activity.

(2) choosing no HRT. People who do not have osteoporosis and have good bone density test results sometimes choose no HRT. Be sure to talk with your doctor if you make this choice to evaluate your own risk factors.

(3) herbal therapy. See Nutrition information below. There are a number of women in our community who are taking these herbal supplements and seem to be doing quite well. There are two predominant isoflavones found in soybeans, genistein and diadzein. There is a substance called genistein that has been shown to reduce the growth rate of vascular tumors of the eye (research done in Heidelberg) that is also used in herbal remedies for hot flashes. Genistein can also be found in the herb Red Clover. It is also said that genistein may help in the prevention of prostate cancer, as well as other cancers. To read more on genistein go to: http://stratsoy.ag.uiuc.edu/~stratsoy/soyhealth/quantification.html.

Again, we have no significant confirming data to recommend for or against any of these paths. It's really up to you and your doctor to work out the right path for you. The most important thing is to continue your scans on a regular basis (at least every 2 years), even if you have had no significant problems for years. It's easy to get complacent if you haven't had any problems for ten years. But remember that some of the issues in VHL (e.g. kidney) are sneaky and have no symptoms until the problem has progressed quite far, and in some people kidney issues do not even begin until after ages 45-50, even though other people may experience these problems much earlier.

In the 1999 November/December issue of *Endocrine Practice*, the AACE Medical Guidelines for Clinical Practice for Management of Menopause provide recommendations for the clinical management of menopause and is intende for use by physicians to support their treatment of women's reproductive health issues.Gale Lugo, Natural Health Consultant, suggests some reading that you may find interesting about HRT and menopause: *What Your Doctor May Not Tell You About Menopause* by John R. Lee, M.D.; and *Hormone Heresy* by Sherrill Sellman. This article was based on questions from vhlfa@egroups.com, with input from our advisers.

Banning Genetic Discrimination

On February 8, 2000, at an event at the American Academy of Sciences, U.S. President Clinton signed an executive order that prohibits every federal department and agency from using genetic information in any hiring or promotion action. While this applies only to employees of the federal government, it is hoped that it will lead the way for additional legislation at the state and national level to protect other workers.

This historic action ensures that critical health information from genetic tests is not used against federal employees. The President also endorsed the Genetic Nondiscrimination in Health Insurance and Employment Act of 1999, introduced by Senator Daschle and Congresswoman Slaughter, which would extend these protections to the private sector and to individuals purchasing health insurance. Finally, the President stated his strong belief that efforts to find genetic cures for disease must not undermine vital patient protections, and he asked the Secretary of Health and Human Services (HHS) to expedite FDA and NIH reviews of gene therapy guidelines and regulations.

Fear of Misuse

Progress in genetics has helped researchers and health care providers to detect and prevent health disorders; however, it can also be misused to discriminate against or stigmatize individuals. Some employers may try to use genetic tests to discriminate against workers -- even those who have not yet or who may never show signs of illness -- in order to avoid increased costs associated with workers who are genetically predisposed to particular ailments.

In a 1996 study published in *Science*, 15 percent of individuals at risk of developing a genetic condition said that they had been asked questions about genetic diseases on job applications. Thirteen percent of the respondents reported that they or another family member had been denied a job or fired from a job because of a genetic condition in the family.

Confidentiality of genetic test results is a major concern for the public. A 1997 study by the National Center for Genome Resources found that 63 percent of people would not take genetic tests if employers could access the results -- and that almost 50 percent of people believe that most employers will ask employees to take genetic tests in the future.

Discrimination in the Workplace

This executive order, endorsed by the American Medical Association, the American College of Medical Genetics, the National Society of Genetic Counselors, and the Genetic Alliance, will:

- Prohibit federal employers from requiring or requesting genetic tests as a condition of being hired or receiving benefits. Employers may not request or require employees to undergo genetic tests in order to evaluate an employee's ability to perform his or her job.

- Prohibit federal employers from using protected genetic information to classify employees in a manner that deprives them of advancement opportunities. Employers may not deny employee promotions or overseas posts because of a genetic predisposition for certain illnesses.

- Provide strong privacy protections to any genetic information used for medical treatment and research. Under the executive order, obtaining or disclosing genetic information about employees or potential employees is prohibited, except when it is necessary to provide medical treatment to employees, ensure workplace health and safety, or provide occupational and health researchers access to data. In every case where genetic information about employees is obtained, it will be subject to all Federal and state privacy protections.

The President called on Congress to protect the private genetic information of all Americans, extending similar protections to the private sector. In 1996, the President signed the Health Insurance Portability and Accountability Act (HIPAA), which prevents group health insurers from using genetic information to deny individual health insurance benefits. The Daschle-Slaughter legislation finishes the job begun by HIPAA by ensuring that genetic information used to help predict, prevent, and treat diseases will not also be used to discriminate against Americans seeking employment, promotion, or health insurance.

At the President's request, the Secretary of Health and Human Services will instruct FDA and NIH to expedite their review of gene therapy guidelines and regulations -- to determine whether the current informed consent requirements need to be strengthened, and to ensure that information about these trials is shared with the public.

The Human Genome Research Project has made swift progress, and is on schedule to finish a draft of the human genome by April of 2000. While these advances promise great benefits, they also carry potential perils. This executive order is only one step in the lengthy process of creating the checks and balances in society necessary to use this powerful new information for good, and not for discriminatory purposes.

The National Organization for Rare Disorders provides some information of interest to people with genetic diseases at http://www.rarediseases.org See also the Institute for Health Care Research and Policy at Georgetown University, an academic effort to study

this issue from the consumer perspective, at http://www.healthprivacy.org They post concise information about proposed legislation, and suggest consumer action to assist in passing appropriate legislation. There are powerful opposition forces to legislation in this space, especially from pharmaceutical and insurance companies, so be sure when you read people's opinions that you know what their underlying agendas are.

Adaptive Technology

by Edmund D. Kiselica, Florida

Adaptive technology is the use of computer hardware and software to make the information that is accessed through a computer accessible to someone with a disability. There are many different types of hardware and software available to people with different disabilities. Here, I am going to focus on my disability, which is blindness. I became blind at the age of fourteen as a result of a VHL brain tumor. Since then I have learned a great deal about the importance and the power of computers. Without adaptive technology I would not have been able to access any of the information or powerful advantages of using a computer. There are three main categories of adaptive software. Screen reading software, screen magnification software, and reading systems.

Screen reading software is used to translate the information displayed visually on a computer's screen into synthesized speech output. This allows a blind or visually impaired person to know exactly what is presented on the screen. Jaws for Windows is the leading screen reader. It is developed by a company called Henter-Joyce. Jaws is the most powerful and flexible screen reader on the market. It works with many popular computer applications and can be customized to work with many other applications.

Screen magnification software enlarges the information displayed on a computer's screen. Typically, the enlargement is from 1 to 20 times the original size. This allows people with a wide range of visual impairments to be able to access the information they normally would either not be able to see or have great difficulty in seeing. One screen magnification program is called MAGic. It is also developed by Henter-Joyce. This product is fully compatible with Windows NT and is available in a preview edition for Windows 95/98. It is compatible with Jaws for Windows, which means that a visually impaired person can have both screen magnification and screen reading simultaneously. This is a great advantage to a low-vision computer user.

A reading system is a computer program, which allows a person to scan printed text and have it translated into synthesized speech. This allows the blind or visually impaired person to have access to printed materials that they are normally not able to read. A popular reading system is Open Book by Arkenstone Inc. This program allows a person to scan almost any printed text and have it read back to them. Open Book also allows a person to have the text displayed in a variety of colors and sizes. This lets the visually impaired person customize the way the text is displayed for optimum results.

All three of the types of adaptive technologies have allowed me to achieve independence. They have allowed me to have access to a world of information that I never would have been able to access. With the use of all these computer programs I am able to read my mail, surf the Internet, read and send e-mail, and read the bible and many other books. Adaptive technology has allowed me to overcome the limitations of my disability.

Ed liked the products so much that he recently accepted a position on the staff of Henter-Joyce. For additional information on these products, see http://www.hj.com and http://www.arkenstone.org

2000 Grants

Research donations are coming in -- more are needed to fund some exciting new research on VHL.

This year we have advertised in two biomedical journals with high visibility among physicians and scientists. Our main goal is to support the best possible research initiatives. Eight applicants from Canada, Florida, Iowa, Louisiana, Massachusetts, New York, Ohio, and Oklahoma have expressed interest in submitting grants to work on VHL and have already sent summaries of proposed work. It is likely that other investigators will apply between now and the deadline for applications April 1, 2000. We would like to fund at least two from among these applicants.

This year, we introduced two important modifications to the grants, in response to the requests of past years' applicants: The limit for funding is now up to $30,000 per year and the length of funding is up to three years. In previous years, we awarded funding for up to $40,000 per year for a maximum of 2 years.

As ever, the number and size of grants we can actually award will depend on your generosity. Donations to date will fund the basic VHLFA programs for the year. For the rest of the year, every dollar of donations will go toward research grant funding. Keep those donations coming from now through June to add to the pool of funding for research!

1999 recipients and the VHLFA Annual Report are listed in the Research Report or at http://www.vhl.org/research.

Researchers will find the application form for the 2000 Research Grants can be found at that same location.

Trichlorethylene Exposure

by Hiltrud Brauch, Gregor Weirich, Maria Anna Hornauer, Stefan Storkel, Thorsten Wohl and Thomas Bruning

Editor's Note: *As you will see in this article, it has now been shown scientifically that Trichlorethylene causes changes to chromosome 3 which can lead to kidney cancer. This includes changes to the VHL gene.*

In people who have inherited the VHL gene, there is already a "germline" (inherited) mutation in one copy of the VHL gene. These chemicals can cause "somatic" mutations (during one's lifetime) to the second copy, causing tumors to form. In people who have not inherited a germline mutation, both copies of the VHL gene can be altered, causing kidney cancer tumors to form.

Thus people with VHL are encouraged NOT to work in areas where they will be exposed to these chemicals. This constitutes a requirement for modification of the workplace under the Americans with Disabilities Act.

If you think you may have been exposed to TRI (also called TR3), contact the company where you worked at the time. All industries are required by U.S. law to have available the MSDS (Material Safety Data Sheets) papers for any and every chemical used by them, available to all employees exposed to them. If they give you trouble, the Environmental Protection Agency (EPA) should be able to assist. There are similar laws in other nations.

The development of renal cell carcinoma (RCC) has been associated with both genetic and environmental factors--with mutations in the von Hippel-Lindau (VHL) tumor suppressor gene for clear-cell RCC specifically and with long-term exposure to high doses of trichloroethylene (TRI), an industrially important solvent, for RCC generally. We investigated whether TRI exposure produces RCC through a specific mutational effect on the VHL gene by analyzing VHL sequences in the RCCs of patients exposed to high, cumulative doses of TRI.

The level of exposure for each of 44 patients with RCC who had known industrial exposure to TRI was classified according to the duration, frequency, and mode of exposure. Samples of normal and cancerous tissues were microdissected from paraffin-embedded tissue. DNA was isolated from these samples, and somatic VHL mutations were identified by polymerase chain reaction analysis, single-strand conformation polymorphism analysis, DNA sequencing, and restriction enzyme digestion. Control samples included RCC DNA from 107 patients without known TRI exposure and lymphocyte DNA from 97 healthy subjects.

RCCs of TRI-exposed patients showed somatic VHL mutations in 33 (75%) of 44 cases. The mutations were frequently multiple and accompanied by loss of heterozygosity, and there was an association between the number of mutations and the severity of TRI exposure. We observed a specific mutational hot spot at VHL nucleotide 454 in the RCCs of 13 (39%) of the patients, and this mutation was present in adjacent kidney tissue in four of these patients. The nucleotide 454 mutation was neither detected in any of the RCCs from patients without TRI exposure nor in any of the healthy subjects.

Our results suggest that RCC in patients with high, cumulative TRI exposure is associated with a unique mutation pattern in the VHL gene.

Excerpted from *Journal of the National Cancer Institute* (May 19, 1999) 91:854.

Family Feedback

After we circulated this information in the online discussion vhlfa@egroups.com, one member posted this reply: "When I showed my husband the message about trichlorethylene, he immediately went out to his company truck and brought in a can of cleaner that is used to clean electrical cables (he works for a utility company). The first ingredient was trichlorethylene. We wonder how significant that has been to his health. He seems to have such a severe manifestation of kidney tumors, 30 removed in 1998 alone! Thanks for the information!"

Many thanks to everyone who has donated this year!

There's still time to make the research grant pool even bigger! We have eight applicants so far to choose from -- help us fund at least two of them!

Disabilities and Work

The United States Congress has passed the Work Incentives Improvement Act (WIIA) in November. This means that people with disabilities who want to work will not lose vital medical benefits because of an increase in income. Americans with disabilities can enter the workforce without losing their health coverage under Medicaid or Medicare. Disabled people working jobs that include health benefits will be able to buy Medicaid coverage for expenses that their regular insurance does not cover.

For more information, contact your local Independent Living Center or state rehabilitation agency, or call 1-888-751-0077.

This issue is dedicated to:

Sheldon Marshall, Sr., father of Don Marshall, Susan McGuire and Roy Marshall.

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Continuing from page 13

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Melissa Minster & Ron Pelton on their marriage, by Joyce Graff
Erich Moan, by Margrit Lunde
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Thersa Zovart and Christin Thompson, daughters of Dave Schier, by United Fund of Filmore Township

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Brian Beaulieu, by Constance Fiala
Edna Meyer Bentz, mother of Paul Bentz, by John Bentz, Anna Hayes, Patrick Henry Elementary School Students, Eunice Konold, Linda McClusky
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Our loved ones, by John & Rina Johnson
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VHL Family Forum, Newsletter of the VHL Family Alliance
Volume 8, Number 1, March 2000, ISSN 1066-4130
E-mail: info@vhl.org; Tel: 1-617-277-5667; Fax: 1-617-734-8233
Toll-free in the United States and Canada: 1-800-767-4VHL
Editor: Joyce Wilcox Graff, 1-617-232-5946 (eve)
Adviser: Debra L. Collins, M.S., U. Kansas Med. Center, 1-913-588-6043
Internet website http://www.vhl.org
171 Clinton Road, Brookline, Massachusetts 02445-5815 U.S.A.

Postmaster: Please send address changes to VHL Family Forum, 171 Clinton Road, Brookline, MA 02445-5815.

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Purchase merchandise: (proceeds help the VHLFA!)

❑ #___Copies of *How Are You?* by Patricia Foote @ $17 each $ _____
❑ #___Copies of *Sacred Process* by Karen Koenig @ $15 each $ _____
❑ #___Copies of the *VHL Video* @ $20 each, (specify __ US or __PAL format) $ _____
❑ #___VHL Teamwork Pin in ❑ silver ($17 each) or ❑ gold filled ($27 each) $ _____
❑ #___Copies of Pierre Jacomet's CD of Bach's Goldberg Variations @ $12 each $ _____

VHL Symposium registration (see page 16 for information)

Prices include breakfast and lunch on session days, dinner Friday evening, and handout sets.

❑ #___Basic Science Day only @ $70 per person $ _____
❑ #___Track 1: Full Symposium Thursday thru Sunday @ $225 per person $ _____
❑ #___Track 2: Physician Track Friday thru Sunday @ $ 180 per person $ _____
❑ #___Track 3: Family Track Friday thru Sunday @ $ 170 per person $ _____
❑ #___Companion dinner tickets Friday evening for people not attending the sessions + $ _____
❑ #___Add $35 CME certificate fee if credits are desired + $ _____
❑ #___Subtract $20 per person if ordered before June 28 - $ _____
❑ #___Subtract $20 for second person in family ("spouse discount") - $ _____

Payment Method:

❑ Enclosed check, payable to the VHL Family Alliance ***TOTAL:*** $ _____
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Send this form to VHL Family Alliance, 171 Clinton Road, Brookline, MA 02445 USA
Canadians, send donations to VHLFA Canada, RR 1, Renfrew, ON K7V 3Z4 Canada

Conference 2000!

This year's Medical Symposium, to be held at Phillips Hall on the campus of the Mayo Clinic, July 20-23, 2000, promises to be a very exciting meeting. Mayo will award 25 CME's to registered physicians who attend all sessions.

We have designed the meeting in three "tracks" to meet the needs of attendees with varied backgrounds in medical terminology and genetics.

Track 1 begins Thursday, with the biomedical researchers sharing their research with one another, and will assume a familiarity with biomedical concepts and terms. People not prepared for this level of technical language are encouraged to begin on Friday morning. A summary of the highlights of Thursday will be presented on Sunday.

Physicians not familiar with molecular genetics are invited to begin on Friday morning, with discussions of the state of research on genotype/phenotype alignments being done in several countries. Family members who have attended previous national meetings may wish to attend this session.

Families are encouraged to begin Friday morning with "VHL 101," an introduction to the terminology and concepts you will hear during the meeting. If you have never before attended a conference, we strongly suggest you attend this orientation session.

Beginning Friday afternoon, all three tracks converge and all remaining sessions are open to everyone.

Hotel space is reserved at the Kahler Grand (1-507-282-2581, $75/$85), and the Rochester Marriott (1-507-280-6000, $119/$129). Reservations must be made by June 28 to qualify for these conference rates. Call 1-800-767-4VHL or 617-277-5667 for a conference brochure, or see http://www.vhl.org/conf2000 ***See you there***!

Agenda

Thursday, July 20, 2000 8:30-5:30
Basic Science Day (Track 1 begins here)
8:00 Breakfast
Welcome: Hugh C. Smith, M.D.
Keynote: Corey Raffel, M.D., Pediatric Neurosurgery, Mayo Clinic
Structure of the VHL Gene and Protein
Function of the VHL Protein
VHL-regulated Gene Expression
Understanding and Controlling Tumorigenesis
Toward Gene Therapy
6:30 - Welcome Reception
Friday July 21, 2000 8:00 am - 12 pm and Lunch
Track 2 begins: Genotype/Phenotype Alignment, 8 am-12
7:30 Breakfast
Genetic Changes: Cause and Effect
Understanding Genotype/Phenotype Alignments
Finding All VHL Mutations
12:00 Lunch
Track 3 begins: VHL 101, 8:00 am - 12 pm
7:30 Breakfast
Introduction to Terminology and Concepts
12:00 Lunch
Friday July 21, 1 pm - 5 pm and Dinner (all tracks)
General Session: VHL Care in the New Millenium
Keynote: Dr. Virginia Michels, Genetics, Mayo Clinic
Creating Partnerships; VHL Clinical Care Centers
Ethical, Legal, and Social Issues
6:30 - Conference Dinner
Saturday July 22, 2000 8:00 am – 5:00 pm (all tracks)
Optimal Clinical Care
7:30 Breakfast
Keynote: W. Marston Linehan, M.D., U.S. National Cancer Institute
Clinical Research Programs; Clinical Issues
Preserving Organ Function: Adrenals
Achieving a Diagnosis; DNA Testing
Preserving Organ Function: Kidney & Pancreas
Hemangioblastomas of the CNS and Retina
Stereotactic Radiosurgery for Hemangioblastoma
Sunday July 23, 2000, 8:00 am to 1:30 pm (all tracks)
7:30 Breakfast
Keynote: Jay Platt, GySgt USMC, retired, Cartersville, Georgia
Tumor Localization and Assessment
Radioactive Plaque Therapy for Large Eye Tumors
Innovative Eye Treatments and Clinical Outcomes
Progress in Research (Summary of Basic Science Day)
Symposium Consensus Meeting; Closure
Adjourn until Padua, Italy, in 2002!

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

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