VHL Family Forum

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Ocular Manifestations of von Hippel-Lindau (VHL) Disease

by Emily Chew, M.D., National Eye Institute, National Institutes of Health, from a talk presented at the VHLFA Patient/Provider Conference, May 1997, Bethesda, Maryland

Retinal angioma in the eye may be one of the earliest manifestations of VHL disease. As many as 60% of patients in some studies of large kindreds may have ocular involvement (see notes 1-7). The clinical appearance of these angiomas is a very subtle red or grayish dot no larger than a few hundred microns. As the proliferation of the vascular tumors (mostly of capillaries) progresses, secondary alterations occur to produce a distinctive clinical appearance. The blood vessels leading to and away from the tumor become characteristically dilated with marked enlargement. This tumor can lead to leakage of fluid and fatty deposits both around the tumor and in the central important area of the retina, the macula, which is responsible for the fine vision needed for reading, driving, etc. If the angiomas enlarge to an extent that the retina can be detached, hemorrhaging and scarring can occur. These can all lead to decrease in visual acuity of the affected individual. Rarely can these tumors regress spontaneously(8).

Often patients do not have symptoms as these lesions tend to progress slowly. The tumors can be detected in children and adults through the eighth decade of life on a routine exam(7,9). Symptoms such as decreased vision or a turned-in eye (crossed eye) may results in the detection of VHL in children. Decreased visual acuity can also cause adults to seek medical help and subsequent detection of the disease.

The treatment of the retinal angiomas will depend on the location and size of the lesions. Small lesions are easy to treat successfully while large lesions are notoriously difficult to treat. Photocoagulation with argon laser can eradicate small retinal angiomas in most locations (21). However, for those tumors too large or located in the very periphery of the retina, cryotherapy (freezing treatment) may be indicated. If the tumor is located on the optic nerve, the nerve that connects the eye to the brain, treatment is fraught with difficulties. Marked adverse side-effects are associated with treatment of such tumors with laser photocoagulation. Fortunately, these tumors may remain asymptomatic for long periods of time. For patients with the more severe changes such as retinal detachment, hemorrhage and scarring, the procedure called vitrectomy can be performed.(12) This involves the introduction of microinstruments under the guidance of a microscope to remove the areas of scarring and to flatten out the retina.

The importance of maintaining good visual function in patients affected with VHL depends on regular dilated eye examination (with the pupil of the eye opened with drops). For patients who are at risk of developing VHL, an annual dilated eye exam will provide important information and help maintain good vision. Good vision can be achieved and maintained in many affected individuals, especially if the lesions are detected and treated early in the course of the disease.

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Infections in Patients Treated for Brain Tumors

by Scott L. Pomeroy, M.D., Ph.D., Department of Neurology, Children's Hospital, Boston

Infections can complicate brain tumor therapy after surgery. Following the initial tumor resection, the surgical site can become infected with a variety of bacteria. Most often, the bacteria are common organisms that normally are present on the surface of the skin. This complication can begin within the first week after surgery, and is manifested by fever and by redness and/or swellling of the surgical site. This may be accompanied by drainage from the surgical wound.

If these signs or symptoms are present, it is imperative that the neurosurgeon be contacted immediately. Wound infections can spread to involve the underlying tissues or bones, or can evolve into meningitis, or even spread to involve the nervous system itself. In all of these cases, prompt attention is critical for successful resolution of the infection.

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Seeking Feedback on Dietary Supplements

Genistein, a derivative of soybeans, has been cited in reputable scientific journals as an angiogenesis inhibitor. Genistein and various dietary flavonoids are now listed for sale in several health food supplement catalogs. While there is scientific evidence that diets rich in soy foods are associated with lower incidence of prostate and breast cancer,[1] there is no data yet available to say whether soy foods might constrain the growth of VHL tumors.

It is possible that the anti-cancer effects of soy foods are related in some way to its ability to slow the growth of new blood vessels, but it is also possible that these effects are due to the influence of genistein on other biological processes. Research is still going on to understand the mechanism(s) involved. In addition to these properties, soybean products are very nutritious, rich in protein, low in fat and contain a lot of calcium. It is more cost effective to take soy as food ($1.50 per day) rather than as supplements ($5 per day).

We are seeking:

- ***Patients*** who are adding soy products to their diets or taking food supplements containing flavonoids or genistein
- ***Researchers*** interested in the effects of dietary flavonoids in general, and genistein in particular, on angiogenesis.

If you are in either one of these groups, please contact the VHL Family Alliance. We are gathering important preliminary data on the effect of natural inhibitors of angiogenesis in VHL.

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My Soybean Diet, *by Darlene S., California*

In 1994, when my husband read about the cancer-preventive effects of a soybean diet and the effect of genistein on tumor growth, we thought is sounded very much like VHL's growth of hemangioblastomas. We decided to seriously concentrate on this particular diet. We began eating, on a daily basis, moderate amounts of food that would mainly consist of tofu, tempe, soup (mostly miso) along with more cruciferous vegetables[2] (usually cut up in the soup) with a little pasta, less fat, high fiber foods, and more fruit. Not only did we lose over 30 pounds in no time, but we discovered an overall feeling of wellness.

My doctor recently said to me, "I don't know what you're doing, but keep it up! Your kidney and tumors haven't grown at all the last two years." I don't know if it's the soy or not, but I'm still eating tofu.

2. Cruciferous vegetables include broccoli, brussel sprouts, cabbage, cauliflower, Chinese cabbage, kale, mustard, rutabaga, and turnips. The beta-carotene in vegetables counteract environmental effects which can modify genes and cause tumors to form.

Imaging in von Hippel-Lindau: What Have We Learned?

by Peter L. Choyke, M.D., National Institutes of Health, Bethesda, Maryland, from a talk presented at the VHLFA Patient/Provider Conference, May 1997, Bethesda, Maryland

The screening program for von Hippel-Lindau (VHL) at the National Institutes of Health began in 1987. Ten years later much has been learned. In addition to the dramatic developments in the understanding of the molecular biology, there have been developments in clinical evaluation and management of VHL. Moreover, there have been important advances in imaging technology that make the "old" scans of 1987 look obsolete. Some things, however, remain constant. For instance, from the onset it was understood that VHL is a multisystem disorder and that any imaging strategy must take into consideration the broad spectrum of possible findings. Also, it was clear from the beginning that not all patients would exhibit all the features of VHL and in many cases imaging became focused on one or two organs. Now, ten years after our first VHL clinic it is appropriate to review what we have learned.

At the onset I would like to extend my thanks to the many patients and family members who have entrusted their films to us, or who have come to NIH to be studied. What we have learned, we have learned from you.

What Have We Learned?

It quickly became clear that a single study could not encompass all the features of VHL. Artifacts from bone limited the ability of computed tomography (CT) to be used in the cerebellum, the most common site of hemangioblastomas. Thus, MRI seemed much more appropriate in the brain. However, the ability to understand and stage hemangioblastomas was dramatically improved by the addition of gadolinium chelates that enabled magnetic resonance imaging (MRI) scans to be enhanced. Now, enhancement of brain MRIs is routine in VHL.

For spinal hemangioblastomas, CT was limited because it could only image in the transverse plane. The ideal plane is the sagittal plane and thus MRI became best suited for detecting hemangioblastomas in the spinal cord.

However, for abdominal imaging, CT was better than MRI and remains the preferred method of screening and follow-up. CT has the advantage of speed, high resolution and lower cost than MRI in the abdomen. Another advantage of CT is that there is more consistency, site to site, than with MRI.

For imaging of the scrotum, however, the best modality is ultrasound. It permits the high resolution evaluation of cystadenomas of the epididymis. Ultrasound is also very useful in the operating room where it can help guide the surgeon.

As we received more and more images from outside imaging centers and hospitals it became clear that consistency was going to be one of the most important aspects of imaging. If scans are not done in a uniform manner it is almost impossible to tell whether VHL is progressing or not.

Knowledge and expertise among radiologists also seemed to become a critical factor. Although most radiologists have heard of VHL, it is often the case that they have never personally seen a case. Fortunately, now there are references available to them, but individual expertise still determines the quality of the examination.

A final general comment is that we have learned the importance of determining the tempo of progression. VHL does not behave the same way in every-

“As we received more and more images from outside imaging centers and hospitals it became clear that consistency was going to be one of the most important aspects of imaging. If scans are not done in a uniform manner it is almost impossible to tell whether VHL is progressing or not.”

one. In some cases it is quite aggressive and requires constant follow-up but in other cases progression is slow and only periodic follow-up is needed. Thus the follow-up regimen needs to be geared to individual patients and cannot be uniformly applied to everyone with VHL.

The Central Nervous System

The most common lesion of the central nervous system (CNS) is the hemangioblastoma of the cerebellum. Most of these lesions are well recognized on MRI. Occasionally, lesions can be seen within the brainstem at the same level as the cerebellum.

In addition, hemangioblastomas can occur outside the cerebellum. The hypothalamic-pituitary axis seems to be one "hot" spot or area of increased frequency of hemangioblastomas. Subsequently we have found lesions in the supratentorial brain as well as in the retro-orbital space.

We recognized that some lesions appeared to arise outside the cerebellum and involve the temporal bone and inner ear. After one of these was removed, and was found not to be a hemangioblastoma but rather

an endolymphatic sac tumor (ELST), we became aware that many VHL patients had hearing loss and that in some cases this could be attributed to tumors arising from the labyrinth, specifically, the endolymphatic sac. Screening of this area is now routine in patients with hearing disorders.

There is disagreement about what technique is the best for detecting ELSTs. A CT scan is obtained because it shows bone erosion which is diagnostic. However, MRI is useful because it can actually detect the labyrinthine anatomy and pinpoint the extent of disease. Moreover, we believe MRI is more sensitive than CT for small ELSTs.

Pheochromocytoma

Pheochromocytomas are tumors of the adrenal gland which secrete catecholamines. These can cause patients to become very hypertensive and can result in death in severe cases. Sadly, the relationship between pheochromocytoma and VHL was not fully recognized and there have been reports of death from pheochromocytoma during anesthesia and surgery for other abnormalities.

Early recognition is thus important. We employ a combination of chemical tests and CT examinations to identify patients with pheochromocytomas. We have found that CT is very sensitive for the detection of early pheochromocytomas. It has been suggested that the pheochromocytomas in VHL are somehow "silent" but this is not correct. What can be said is that when the lesions are very small they may not elevate the catecholamine levels. With time, however, the lesions will eventually become chemically active and then finally, symptomatic. We have shown that the growth rates of pheochromocytomas in patients with VHL are almost identical to those of patients with pheochromocytomas but without VHL. Thus, it would appear that rather than being silent, pheochromocytomas in VHL are active even when small, but are detected earlier in patients with VHL due to presymptomatic screening.

Patients with VHL also have an increased likelihood of bilateral or ectopic pheochromocytomas. Ectopic pheochromocytomas are found around the adrenals and in tissues far removed from the adrenals. We now routinely scan to the level of the aortic bifurcation to reduce the chance of missing pheochromocytomas in the Organ of Zuckerkandl.[1]

There are a number of imaging modalities that can be used to evaluate pheochromocytomas. We find that CT is the best to detect lesions. The MIBG[2] study is a nuclear medicine study that is very specific for pheochromocytoma, but it is somewhat insensitive. We rely on the MIBG for finding ectopic sites of disease when the CT is negative and pheochromocytoma is suspected. MIBG is also used to assess whether the lesion should be removed. MRI can be very helpful in confirming the location of ectopic sites of pheochromocytoma and differentiating them from other potential causes of masses.

Kidney

The kidney is frequently affected in VHL by cysts and renal cancers. When we began looking at the problem of renal lesions there was some confusion in the literature regarding the importance of renal cysts. It was felt that because cysts outnumbered tumors that cysts were precursor lesions to tumors (i.e. cysts were the first lesion and tumors developed from them). This was derived from the observation of small tumors in the wall of many VHL cysts.

Extensive experience with the natural history of renal lesions using modern CT scans has shed considerable light on this. It appears that most tumors develop not from cysts but *de novo* from solid islets of tumor. Buried within the normal appearing tissue of VHL kidneys are hundreds of microscopic "islets" which are likely the true precursor lesion in VHL. We have observed that most solid tumors begin as solid tumors without a cystic intermediate. Moreover, most cysts remain cysts but can enlarge, regress or stay constant in size. A minority of lesions have both cystic and solid components. Both elements tend to grow over time, but the solid tumor component eventually becomes predominant. Thus, annual or biannual screening would seem appropriate for most patients.

Treatment of renal cancers in VHL is still controversial. On the one hand, if renal cancers are left unchecked they will metastasize. On the other hand, over-aggressive surgery will result in premature renal failure which lowers duration and quality of life. Over the past 5 years we have adhered to a policy of not removing renal cancers until they attain a size of 2.5-3 cm. A range is given to account for different growth rates. Although full analysis of this strategy is incomplete, it appears to be successful in avoiding both metastatic disease and end stage renal failure in many VHL patients.

When surgery is performed, intraoperative ultrasound has been found to be a useful adjunct. Although the surgeon is well aware of most of the surface lesions, deeper lesions and those near the surface that are hidden by scar or fat may be missed. Intraoperative ultrasound allows the surgeon to perform a more complete operation and thus prolong the response from a single surgery.

There are three major modalities in use for evaluating the kidney, CT, ultrasound and MRI. Ultrasound is a tempting choice because it is less expensive than the others and does not employ ionizing radiation. Ultrasound is the method of choice for screening children with VHL. However, several authors have shown significant limitations of ultrasound for detecting lesions as large as 2 cm. This is due to technical limitations and not necessarily due to the quality of the sonographer. CT has the advantage of cost over MRI

and the advantage of well defined criteria for "enhancement" which is the principal method by which the presence of tumors is defined. Moreover, since follow-up scans are so important, CT has the added advantage of consistency between centers.

MRI, however, has an important role in renal VHL assessment. As renal function deteriorates due to surgery, the use of CT contrast agents has become relatively contraindicated. This is because of a slightly increased risk of renal dysfunction in kidneys with pre-existing renal dysfunction. MRI contrast agents, however, have no known impact on renal function. Thus, MRI is used in follow-up studies of patients with compromised renal function.

Pancreas

In 1987 it was known that VHL was associated with cystic disease and occasional islet cell tumors. Like many aspects of VHL, while these original observations are true, the depth of our understanding of pancreatic disease has improved dramatically.

Although pancreatic cystic disease is "benign," it is not necessarily asymptomatic. We have seen examples of severe bowel and biliary tree compression due to enlarged cysts. To some extent percutaneous drainage of cysts can provide symptomatic relief. Pancreatic insufficiency manifested by diabetes or malabsorption can also be traced to pancreatic cystic disease.

Non-functional islet cell tumors of the pancreas are probably more common than previously thought. These vascular lesions can be quite subtle and grow slowly. Nonetheless, we have seen examples of metastatic disease resulting from these tumors. Interestingly, some cystadenomas of the pancreas can mimic islet cell tumors so caution must be employed. A surgical strategy for removing these lesions while retaining pancreatic function is currently being evaluated at NIH.

One side note is that the literature commonly mentions pancreatic adenocarcinoma as a feature of VHL. This tumor is commonly known as "pancreatic cancer" and usually has a very poor prognosis. We have yet to encounter a bona fide case of pancreatic cancer in VHL and this has cast some doubt on its association with VHL.

Epididymis

Epididymal cystadenomas occur in the scrotums of men with VHL. They are small masses made up of papilla of tissue surrounded by a cystic matrix. Most are asymptomatic although they may cause some vague pain or discomfort. This is one of the few "not to worry" lesions in VHL because there is no risk of malignancy. Although ultrasound can be used to help define the lesions, they are usually easily palpable and should pose no problem.

We have observed that as men age the epididymal cystadenomas tend to obstruct the rete testes, the small tubes carrying sperm away from the testicle. These are usually asymptomatic in spite of a dramatic appearance on ultrasound. It is unknown whether the lesions affect fertility beyond the normal reproductive years. Studies have shown no significant decrease in reproductive capacity in VHL.

I've printed out all you have on your website . . . thank you thank you thank you! . . . We would all like to thank you for your wonderful caring and encouraging words we have received from your hotline. . . . It has meant so much to us! -- *Kelly S., Wisconsin*

Summary

There have been significant changes in the genetics, management and imaging of VHL in the last 10 years. Experience has clarified the role of various imaging modalities for screening and follow-up. As more information is gained about manifestations of VHL with regard to specific gene mutations, it is hoped that imaging may become more targeted in the future.

Note

1. Zuckerkandl bodies, or organs of Zuckerkandl, are nodes of the sympathetic nervous system lying along the aorta. Pheos grow most commonly inside the adrenal glands, but may also grow in a number of other places, roughly along a line from the groin to the collar-bone on each side, but very rarely in the chest.
2. MIBG scanning is a nuclear medicine procedure using a radioactive isotope or tracer which is absorbed by pheochromocytoma tissue. Meta-Iodo-Benzyl-Guanidine (MIBG) is injected into the patient before the scan is performed, making the pheo stand out clearly on the diagnostic picture.

Acknowledgment

The author wishes to thank the many patients and family members with VHL who sent their films or who came to NIH and the late Michelle Filling-Katz, M.D., who began screening patients with VHL at NIH in 1987.

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Report from the Dutch Symposium

--by Joyce Graff. VHL-related abstracts from this congress are on the internet, http://www.vhl.org. [Numbers in brackets] in this article are the abstract numbers. Articles from some of the key talks will appear in this newsletter in this and subsequent issues. Medical articles based on some of these talks are expected to be published in the Journal of Internal Medicine over the coming year.

The 6th International Symposium on MEN and VHL was held at Leewenhorst Congress Center outside the sleepy seaside village of Nordwijkerhoud on the North Sea near Leiden, Holland. Gillian Houlders from England, Chris Hendrickx from Belgium, and I represented the VHL Family Alliance. We met with several members of the Dutch VHL support group, with Jeannette Bos-Mol, chairman of the group, and Joke Jansen-Schillhorn van Veen, a volunteer who organizes support groups for various conditions for Dr. Lips.

Convening the meeting, Dr. Cornelius J. M. Lips of the University Hospital at Utrecht reminded us that it was a good place to study the molecular causes of disease because the ground glass lenses that brought the modern microscope to full power were invented in the 17th century by Antonie van Leeuwenhoek, a Dutch microscopist, in nearby Leiden. Dr. Lips' genetic research began with a study of sickle cell anemia in 1975. Studying cancer is even more complex than other molecular diseases because it is a combination of promoters, inhibitors, breakdowns, repairs, and failures to repair. Just when you think you understand its cause, you realize there is yet another effect.

The easy genetics have been done -- the mapping and isolation of the highly penetrant susceptibility genes. The emphasis in genetics is now shifting from the study of inheritance to the cell biology, the functional analysis of genes, and the detection of less common susceptibility genes. We are realizing that there is a stronger influence of the environment and other modifiers. Using techniques from epidemiology, we can determine what candidate genes might be involved.

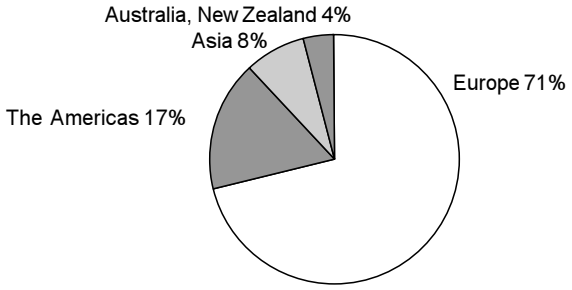


Chart 1. *Where did the attendees come from? The majority (71%) were from European countries. 40% were radiologists, 26% were clinicians.*

Dr. J. Aiden Carney, a pathologist, proposed that ***VHL might be classified*** as a multiple endocrine neoplasia (MEN). "Neoplasia" is a new growth, or tumor, arising from a single cell with a genetic flaw. MEN syndrome diseases include those which have tumors of 2 or more endocrine organs and some non-endocrine tumors as well, but the endocrine tumors dominate. MEN and VHL are both included in a loose classification of diseases called phakomatoses. This classification, described by a Dutch scientist van der Hoeve in 1925, include ones which have small spots or patches on the skin, endocrine and other tumors, and other congenital malformations.

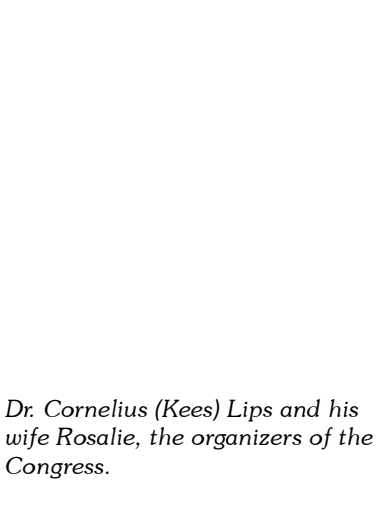
Dr. Maartje Los [228] talked about her studies of level of ***vascular endothelial growth factor*** (VEGF) in various tissues of people with VHL. The purpose of her study was to determine the nature of angiogenesis (development of new blood vessels) in VHL. Angiogenic factors (those which lead to the development of new blood vessels, or hemangiomas) are hypoxia (when there is too little oxygen, the body builds more blood vessels to bring more blood to bring more oxygen), tissue injury (where increased blood flow is needed for repairs), and vascular endothelial growth factor (VEGF). Thus the VHL protein is up-regulating an angiogenic factor and down-regulating an inhibitor of angiogenesis.

They tested ocular fluid of VHL patients for VEGF, IL-8, ET-1, and bFGF. As a control group, they used cataract patients with normal retinas. They found much higher levels at much earlier ages in VHL patients.

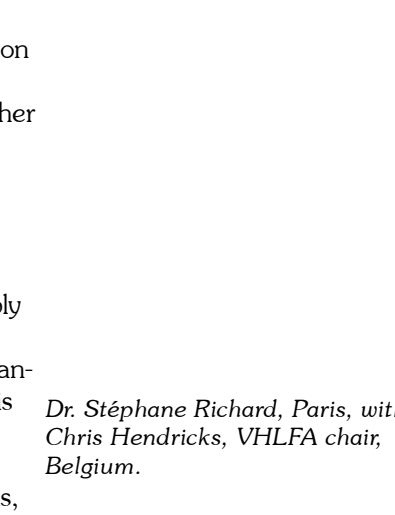
There were high levels of VEGF in renal cyst fluid, much higher than in blood. In blood and in urine, levels of VEGF, bFGF, and IL-8 were the same as the age-matched control group. Therefore it does seem that the VHL gene might be regulating VEGF expression in living tissues.

The urine samples used in this test were donated by members of the VHL Family Alliance to

Seated: Drs. Eamonn Maher, England; Klaus-Martin Kreusel, Berlin; Claudia Franz, Hamburg. Standing: Drs. Hiltrud Brauch, Hamburg; William G. Kaelin, Jr., Boston.



Dr. Cornelius (Kees) Lips and his wife Rosalie, the organizers of the Congress.



Dr. Stéphane Richard, Paris, with Chris Hendricks, VHLFA chair, Belgium.

Dr. Emil Voest while he was at the Dana Farber Cancer Research Institute in Boston in 1994.

Dr. D. Wittebol-Post [228] described her research on hemangioblastomas of the ***retina***. In the past people were sometimes diagnosed with "von Hippel's disease." We do not know how many of these people had VHL versus sporadic retinal hemangioblastoma, but presumably most of them had VHL. She and Dr. Richard agreed that multiple retinal hemangioblastomas are sufficient for a diagnosis of VHL. From the point of view of a pathologist, the retinal angiomas are identical to cerebellar hemangioblastomas, though they do not develop cysts. In peripheral tumors, treatment is generally successful. Treatment of angiomas in the central part of the vision is the most tricky, since the treatment itself can cause some damage to surrounding tissue and thus to the vision.

Dr. Gunter Janetschek [259] presented his experience with ***laparoscopic surgery for VHL*** which has previously been reported (VHLFF, March 1997). He and Dr. Neumann have now had long-term experience with partial adrenalectomy and find that this is a very good course to take, as it avoids or at least delays putting people on replacement therapy. Dr. Jane Green of Canada agreed that long-term replacement therapy sometimes causes problems. In her group of patients there is a higher rate of recurrence than in the German experience so she feels that in some families there may be a greater need for careful follow-up, but she agreed with the conservative approach even so. Dr. Neumann follows patients by watching blood pressure, symptoms, and appearance of micro-nodules on MRI.

Dr. Gerd Kempermann [260] spoke about ***ELST***. The cells from ELST look very much like those from thyroid, so ELST was often mistaken for metastasis from thyroid. It is only in the last 10 years that people have begun to understand ELST. Interestingly, the first patient described by Dr. von Hippel had an ear tumor. In the literature there are only 10 cases cited, but Dr. Oldfield's retrospective analysis identified a significantly higher number.

Whenever ELST is found on both sides, one should consider a genetic cause. It is important and often not easy to distinguish ELST from other similar kinds of tumors. It is often wrongly identified as a metastasis from thyroid, lung, breast, or kidney, or as a paraganglioma, or ceruminal gland tumor, or salivary choristoma, or plexus papilloma, or meningioma. Confirmed carcinoma of the temporal bone is very rare, and should be questioned as a misdiagnosis. Dr. Richard has 20 cases of ELST in France, 18 of which are VHL. Dr. Kempermann concluded that in cases of hearing impairment in VHL patients, ELST should be considered as the cause. CT scan or MRI in VHL patients should include the cerebello-pontine angle and the apex of the petrous bone.

Dr. Stéphane Richard [258] of Paris described the ***structure of hemangioblastoma*** of the central nervous system. There are many VEGF receptors and high concentrations of VEGF have been found around hemangioblastomas. Secondary polycythemia was found in 20% of the cases of intratentorial hemangioblastoma. In the experience of the French study, 61% of those with seemingly sporadic hemangioblastoma of the cerebellum under age 20 were in fact VHL; 50% of those under 30, and the percentages decrease with patient age. In cases of spinal hemangioblastoma, the percentages were even higher: 93% of those under 20, and 86% of those under 30 proved to be VHL. He concluded that all patients with sporadic hemangioblastoma, especially in the spine, should be investigated for VHL.

Dr. Dieter Schmidt [368] of Freiburg presented his series of ***ophthalmology*** patients with VHL. He uses fluorescein to determine which is the artery and which is the vein, and whether there is a connection between the two, in order to plan treatment so as not to compromise the blood supply to the retina. He prefers early laser-photocoagulation, though he has seen a number of untreated patients and followed the microangiomas as long as 6 years without seeing change.

Dr. Hartmut Neumann [124] of Freiburg described his work on ***genotype/phenotype correlation*** in VHL -- among people with a specific point mutation (genotype), what differences are seen in their symptoms and the course of the disease (phenotype)? The most dramatic differences are seen in the "505 mutations" (where pheos are very prevalent and kidney cancer is rare) and in the Hawaii family (where kidney cancer is very prevalent and pheos are very rare). There is an urgent need for international cooperation to compile data.

Dr. Erzsèbet Bala'zs, ophthalmologist from Debrecen, Hungary, with her daughter.

Dr. Eamonn Maher [125] of Birmingham, England, described his study of ***DNA testing*** in VHL. Mutations have been detected in 132 families (an 80% success rate) and family members who are shown not to be gene carriers can be released from regular screening. In families in whom a mutation is not detected DNA linkage studies can be used to predict carrier status in most cases. The type of VHL mutation can be used to predict the risk of pheochromocytoma with certain "missense" mutations resulting in a high risk. Screening programs can then be adjusted appropriately. A few VHL mutations may predispose to pheochromocytoma only, with no other features of VHL disease. The type of VHL mutation did not appear to determine the severity of eye involvement, but Dr. Maher reported that there was evidence that additional genetic or environmental modifying effects are involved. This means that it is not possible to accurately predict the severity of eye involvement knowing the type of VHL gene mutation. DNA analysis can be useful in cases where a clinical diagnosis of VHL disease is uncertain.

Dr. William Kaelin [126] presented his work on ***understanding the function*** of the VHL protein which has previously been reported (VHLFF, June 1997). His team has identified a new function of VHL in regulating the fibronectin matrix assembly. The consequences of this function are not yet understood. He is not yet considering environmental factors, but is looking at the possible effects of modifier genes.

Dr. David Goldfarb [127] of Cleveland reported the experience of the Cleveland Clinic and associated centers in the multi-center study of ***VHL kidney tumors*** which has previously been reported (VHLFF, June 1995). Subsequently, they have undertaken to look at the long-term survival rates of people treated with nephron-sparing surgery, with radical nephrectomy, and with renal transplants. His conclusion is that for low-grade tumors, removal of the tumors while conserving the organ is the best course of action. They found that tumors could be removed in the body, and that ex vivo ("bench") surgery was not necessary. Very few of the patients in his series had high stage disease. People with radical nephrectomy had poorer survival rates, probably also because these were the most advanced tumors. Eventually almost all patients had another tumor, but most went at least 5-8 years without need for additional surgical intervention. His team uses a goal of maintaining renal function without compromising long-term survival. They do close radiographic follow-up (every six months) and have found a very small risk of metastasis with this strategy.

Among the small number of patients who did eventually lose all kidney function, ***transplantation*** proved to be very successful. If the transplant lasts at least three years, it is cheaper than dialysis. There was some concern that immune suppression might lead to additional tumors. To study this question, they followed 32 VHL transplant recipients, 23 men and 9 women, and a control group of non-VHL related transplant patients matched by age and sex and donor, over a 48 month period. They found no significant differences between the outcomes of these two groups. They conclude that for most patients with VHL, there is no need for a waiting period between nephrectomy and transplant if the tumors in the kidney were of low stage. If there are high stage tumors, a two year waiting period is advised. The majority of VHL patients will fall into the low stage category. Live kidney donors are preferred for transplantation, but in VHL families it is important to do DNA testing on the donor to ensure that the donor kidney is not affected. When technically feasible, renal sparing surgery is the preferred approach.

Joke Jansen, organizer of the Dutch VHLFA.

At the end of the meeting an electronic voting method was used to collate the participants' opinions on some questions. This voting is not final by any means, but was an interesting ***polling of their opinions***. 40% of those present were radiologists, 26% were clinicians. See also Chart 1.

28% of the attendees had less than 5 years experience, 16% had 5-10 years experience, 36% had 10-20 years experience. Most of the questions concerned MEN, but the following questions applied to VHL.

"At what age do you recommend ***DNA analysis*** for VHL?" The consensus among those who responded was to test between ages 1 and 5 (see Chart 2). In the discussion that followed, several doctors explained that in some countries, there are efforts to create laws to prevent parents from making decisions about DNA testing of minor children unless there is material benefit to the health of the child from obtain-

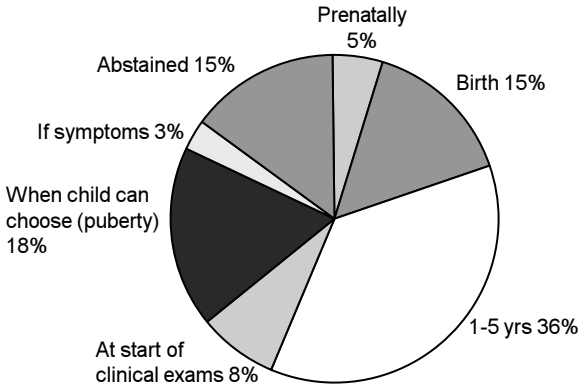


Chart 2. *Opinion poll question: "At what age do you recommend DNA analysis for VHL?" Since clinical exams begin age 3-5, the consensus (44%) was 1-5 years.*

ing this information before the child is of age to choose. The intention of this question was to determine the age at which knowing this information would most benefit the child. Dr. Neumann said that in his experience most people want their children tested at 1-5 years, and he feels that this is medically important because he has some children with serious eye problems younger than age 5.

"Should we try to protect individuals carrying mutated tumor susceptibility genes from radiation or other mutagenic exposure?" This question was poorly worded, and the voting results were unclear. From the discussion it was clear that especially for children and asymptomatic individuals of any age, the majority of those present prefer to avoid testing methods that involve radiation whenever possible, but where needed to provide clarifying information about a particular issue, the use of CT annually is warranted and agreed.

The next question was to determine whether physicians are pursuing cases of seemingly ***sporadic (random) tumors*** in the general population that can occur in these syndromes. "Are you performing DNA analysis in patients with apparently sporadic MEN1, MEN2, or VHL-like tumors?" 89% said yes, 11% said no. In the discussion, Dr. Richard said he felt that in patients with no history of genetic illness in the family, where the tumor is supposedly "sporadic" (random in the general population), if the patient is younger than 20 and has tumors in more than one organ, he feels that the patient should definitely be tested for VHL or MEN. He has seen as many as 25% of sporadic hemangioblastoma and 85% of cases of seemingly sporadic retinal angiomas prove to be VHL, and unless DNA testing is done, the patient will go undiagnosed.

"Who should ***deliver the results*** of DNA testing?" Overwhelmingly, those present felt that the attending internist or endocrinologist should deliver the news. Most of these people were from MEN, where the patient has a close ongoing relationship with the endocrinologist, which undoubtedly influenced the results. Joyce Graff stated that among the families she hears more stories of badly delivered news among internists, urologists, neurologists, etc., than among geneticists and genetic counselors. From the family perspective she would argue for genetics personnel to deliver the news. Genetics professionals are aware of and should be governed by ethical principles, such as not making directive statements about the opinion of the physician as to whether or not this person should have children. If internists and other clinicians are going to deliver this news, they need some training in sensitivity to the ethics and non-clinical issues involved.

"Most ***pheochromocytomas*** grow slowly and screening procedures are expensive. MRI may be more sensitive than measurement of catecholamines and metabolites [urine & blood tests]. Which ***frequency of screening*** do you prefer?" (see Chart 3.)

Fluids testing only every year	10%
MRI only every year	6%
Fluids testing annually...	28%
...plus MRI annually	12%
...adding MRI only if biochemical results are increased	38%
No testing unless there are symptoms	6%

Chart 3. *Testing for pheochromocytoma.*

There was consensus that patients should be followed annually, with only 6% saying that they test only when there are symptoms. Most do blood and urine testing (38%), but only 12% routinely do MRIs. 38% recommend MRI only if these chemical levels are increased in blood or urine. In the discussion, one speaker said that in 20 years he has not seen a patient who has gotten into trouble without elevated catecholamines. MRIs are expensive, and there are attempts to ration the use of expensive procedures. Dr. Neumann said that catecholamines are less sensitive, so he uses MRI, and watches blood pressure and other symptoms as well. He had one patient who died of a pheo at age 5 in the 1960's. Another said that he has seen patients with normal catecholamines who had a perceptible pheo.

"If ***one adrenal*** is affected, what is your advice about the opposite normal one?" (see Chart 4). There was consensus not to remove an unaffected adrenal gland in the hopes of preventing a future pheo. However, those present were sharply divided over whether to remove the entire affected adrenal gland, or only the medulla. In the discussion, one physician said that he has personally been very reluctant to do a partial adrenalectomy and leave some tissue that

DNA Testing for Hawaii and San Francisco families

The University of Hawaii is once again offering DNA testing for members of the Hawaiian and San Francisco families. Dr. Hsia advises that the results will not come quickly, but the cost is low.

For more information please contact Dr. Y. Edward Hsia, +1 808-983-6471, or yujen@hawaii.edu.

Bilateral adrenalectomy	6%
Total adrenalectomy on the affected side only	58%
Always partial adrenalectomy on the affected side only	36%

Chart 4. *How much of the adrenal gland to remove?*

might form another tumor. One said that he felt one could remove the entire medulla and leave the adrenal cortex; another felt it was impossible to remove every scrap of the medulla. Dr. Robert Gagel said that in the experience of the M.D. Anderson Center in Houston in following 15 partial adrenalectomies over a 25-30 year period there were only three recurrences.

In sum, it was an excellent meeting, Dr. & Mrs. Lips were wonderful hosts, and it always good to see the doctors putting their heads together over some of the more difficult issues. This group of leading experts on VHL is a warm and caring group of highly skilled professionals. The European Commission provided some funding to help doctors from Eastern Europe to attend. The setting was beautiful, and after the end of the conference a number of the attendees enjoyed a bit of touring together. Dr. Neumann played his violin at the Kurhaus (say *cure-house*), an elegant Victorian casino and spa near Amsterdam, where fashionable people used to go to "take the cure". Dr. Lips is arranging for some of the scientific papers from this meeting to be published in the *Journal of Internal Medicine* over the course of the next year. We are looking forward to the next VHL symposium in Paris in September of 1998!

When's the Next Meeting?

VHLFA Patient/Provider Conference,
Seattle, Washington, spring 1998.
Third International Symposium on VHL,
Paris, France, September 1998.
VHLFA Patient/Provider Conference,
Atlanta, Georgia, spring 1999.

My Father, Arvid Lindau

by Jan Lindau, from his presentation at the MEN/VHL Conference in Leeuwenhorst, the Netherlands, June 1997

It is thrilling to me to see what my father, Arvid Lindau, accomplished in the course of his career at work. That was a side of him I did not know during his lifetime. He didn't talk about his work at home.

He was a fun-loving person. He loved soccer, and was a referee for local soccer games for many years. He enjoyed caricatures of himself. At a shooting booth at a local fair someone put a formal picture of him over one of the targets as a joke. After the fair he bought the target, took it to his country house and enjoyed inviting friends to take shots at him.

He nearly always wore a butterfly bowtie. He was very active. His day began about 5:30 in the morning. He read three daily papers. He was active in civic affairs and held various offices in the town, and always wanted to find the best solution for society and the people. After his morning reading he had his breakfast. He avoided coffee because of the ulcers he had acquired from smoking and from a hectic lifestyle. Then he went by bicycle to the Institute of Pathology in our home town of Lund, at the southern tip of Sweden.

Arvid Lindau Photo & caricature courtesy of his son, Jan Lindau.

He had his first smoke of the day while biking. He carried three silver cases: one for cigars, one for

Standing: Jan Lindau from Sweden; seated: Hetty Neumann (Mrs. Hartmut Neumann) from Germany, and Gillian Houlders from the U.K., at the conference in the Netherlands.

cheroots, and a very small one for cigarillos to offer to the ladies. His wife also smoked a pack a day of cigarettes.

After lecturing at the institute, helping co-workers and seeing guests, he had lunch at home about 12 o'clock. He often brought someone home for lunch — international guests, students or colleagues. I met a wide variety of people that way.

About 5:30 in the evening he would have dinner at home followed by a short nap (half an hour) and then off to the evening's meetings — handball, professional meetings, or town meetings.

When he came home he would read something, usually in English, with a big cigar, and a glass of abricot or whiskey. He would read until about 12:30 and then go to bed. That was his type of life.

Beginning in 1924 he did military service as an officer and was medical chief of the southern military district of Sweden. He was extremely punctual. If a meeting was to begin, he started. If people were not there on time, he said, they must have something more important, and he accepted that. But the meeting began as scheduled.

During the war the Institute of Pathology in Lund had many refugees from Denmark and other countries. It was a very productive time for Lund, with people coming from Estonia, the Baltic, and continental Europe. It was a very prosperous and exciting time for our community, and for my father's work.

He did a lot for the students at the Institute. He was very good at raising money, and knew people who had the ability to give something. One of his proudest moments was when he dedicated a center for sports outside Lund and gave the field to the student union. It is a recreational center, and a quiet place to study. In the summer it is used as a summer camp for city children from Lund.

My father never spoke about his job, but he often took me along on his trips. "You are the young one with the quicker reactions," he would say, "You drive." To him it seemed a sensible solution. Thus by the time I was old enough to have a driving license I had already driven in six of the capitals of Europe.

His advice to me was that "you should do what you want to do every day." He told me that he was once in Baltimore with Dr. Harvey Cushing, the father of modern brain surgery, doing grand rounds, when a patient stopped them and looking at Cushing said, "Doctor, I want to thank you for saving my life."

Chapter Meetings... ...Please Join Us!

August 24, ***Bethesda***, Maryland, with Dr. Gladys M. Glenn, National Institutes of Health, re clinical care

Sept 13, ***Indianapolis***, Cindy Hunter, M.S., re DNA testing issues for VHL families

Sept 14, ***Boston***, Dr. Karol Krzystolik, geneticist from Poland, re DNA testing issues for VHL families in U.S. and Poland

Sept 21, ***New York City***, Dr. Karol Krzystolik, geneticist from Poland, re DNA testing issues for VHL families in U.S. & Poland

Oct 14, ***Chicago area***, Dr. Daniel Dalton, Northwestern University, re kidney care in VHL

For details, please contact the hotline at +1 800 767-4845 or info@vhl.org.

"Don't thank me," said Cushing, pointing to my father, "you should thank this young man here." My father said that that one moment made all the hard work of a lifetime worthwhile.

Harvey Cushing was a friend of my father's and they corresponded for many years. Lindau wrote all letters by hand, and kept no copies. I have the correspondence to him, and have placed most of it at the university library at Lund. Correspondence from him to others is scattered throughout the world.

Arvid had a number of governmental medals and decorations, but he rarely wore them. When he did, he would only wear those he thought people would be interested in. He was fond of cars, was always well dressed, and had a little dachshund. He had a fancy 1949 2-door Studebaker coupe, the only one in Sweden. He also loved motorcycles with sidecars.

At the end of his life he was scheduled for surgery and was concerned that it might not go well, so he left a letter for his wife. "Forgive me for not always being the way I wanted," he said. "Count only the bright days." Two days later he died. He has been gone now for 39 years. I miss him.

Editor's Note: Arvid Lindau was born 23 July 1892 in Malmö, Sweden, the son of a regiment doctor. After completing school (B.A. 1910) he was trained as a military officer and physician. He got his medical training in Lund (M.D. 1923, Ph.D. 1926). He was a pathologist at the hospital in Lund 1918-1933, and held a concurrent appointment as a military doctor beginning in 1924. Over the course of his career he published more than 40 papers on pathology, neurology and bacteriology.

Early in his career Lindau observed and studied a condition involving hemangiomas of the central nervous system and linked this condition to the similar condition of the retina which had been described by Dr. Eugen von Hippel of Germany. This became his doctoral dissertation work (Ph.D. 1926). He published his findings in a Swedish journal of microbiology in 1926. He was awarded the Lennmalm's prize (1929) from the Swedish Medical Society. The syndrome he described is now called von Hippel-Lindau disease.

Meet the Directors

Paula M. Sicard, Chairing the Insurance and Legal Issues Committee, has been involved with the VHL Family Alliance since its inception and is caretaker for an individual afflicted with most of the disease's known manifestations. Paula resides in Tampa, Florida, where she is law clerk to the Honorable Thomas E. Baynes, Jr., United States Bankruptcy Judge. Paula received her J.D. degree in 1986 from the University of Florida having served as Editor-in-Chief of the Law Review and President of Omicron Delta Kappa scholastic honor society. After a two year clerkship with Justice Ben F. Overton at the Florida Supreme Court, she entered private practice, specializing in commercial litigation and bankruptcy/creditors' rights. Paula was a member of the Editorial Board of the Florida Bar Journal for several years prior to her recent appointment to a three-year term on the Federal Court Practice Committee of the Florida Bar. She is also a member of the Board of Directors of the Small World Zoological Gardens, a non-profit sanctuary dedicated to the captive conservation of endangered new world primates, and is a surrogate parent to two orphaned cotton-top tamarin monkeys.

Myriam Gorospe, chairing the Research Committee, was born in San Sebastián, in the Basque region of Spain, in 1967. She grew up in Madrid, the eldest of six, with one sister and four brothers. In 1985 she entered the Universidad Complutense de Madrid, Spain, and graduated in 1990 with a degree in biology. Later that year she joined the Graduate Program in Cell and Developmental Biology at the State University of New York in Albany. After obtaining her doctoral degree in 1993, she joined the Institute on Aging of the National Institutes of Health in Baltimore. Since then she has been investigating various aspects of how cells respond to stress and to proliferative signals.

"My mother's family is affected with von Hippel-Lindau. Even though no parent was ever diagnosed, her sister and brother died of VHL cerebellar hemangiomas, and another brother and two of his children are extensively affected with the disease. I came across the VHL Family Alliance in an effort to provide some information for my uncle and cousins. I also had to translate this information, and I have since enjoyed translating a few other documents from the VHLFA (not as many as I would like, though). I think the Alliance is doing a terrific job, very relevant, helpful, sensible, beneficial and constructive. I think it is putting its efforts in the right areas. Finally, I think it is wonderfully managing the difficult task of being in intimate touch both with the families and their needs and with the intricacies and complexity of biomedical and clinical research."

To ask a research question, or to inquire about our research grants application procedures, see http://www.vhl.org and choose the Research option, or write to vhlres@vhl.org

Ellen Lydon, Chairing the Clinical Care Committee, lives in Oak Forest, Illinois, with her husband Robert and their four-year-old daughter Cristine. Ellen is a registered nurse with expertise in mechanical ventriculation. Before the birth of their daughter, she worked as an RN on an oncology unit for nine years.

Robert was diagnosed with VHL in 1995. Both Ellen and Robert were delighted to find an organization that was "dedicated to improving diagnosis, treatment, and quality of life for people with von Hippel-Lindau disease." Together they chair the Illinois chapter of the VHL Family Alliance.

Ellen's goals are to update the current list of doctors serving in each of the Clinical Care Centers, to establish some new Centers, and to develop a feedback mechanism for memers who use the services of any of these centers either as a primary care site or as a source of second opinions. She will appreciate your ideas and feedback on your own experiences. Do you find it helpful to have this list of centers knowledgeable about VHL? Have you been able to find the assistance you needed through these channels?

Gillian's Mission: to help others with VHL

by Brian and Natalie Houlders and Joyce Graff

We are sad to report that Gillian Houlders passed away unexpectedly at her home in Hampshire while in her sleep on August 4. The cause of her death is not yet known. Gillian had recently undertaken to head the U.K. affiliate of the VHL Family Alliance. She attended the Symposium on MEN and VHL in the Netherlands with Joyce Graff from the U.S. and Chris Hendrickx from Belgium. She met many of the VHL expert doctors there, and was enthusiastic in her plans for the VHL group in the U.K.

Although she ran the support group for only a short time, she touched the hearts of many of us in that time, both in England and at the Holland conference. Chris and Joyce remember her with pure admiration. A feisty lady with a delightful sense of humor, she was filled with everyday courage and unflagging good humor, and with deep love for her husband, Brian, who cared for her at home and helped in her work with the support group, and for her daughter Natalie, age 16.

Gillian had a very difficult road with VHL. Her brother was diagnosed with VHL in 1989, but the doctors didn't check Gillian until two years later. When they finally saw her scans, the doctors told her she needed surgery immediately, and had her sign a release to do whatever was required. When she woke up, she found they had removed her kidneys, pancreas, gall bladder, and spleen. "They felt that the cysts and tumors were so large that there was nothing to do but remove the organs." Today, much more is known about the management of VHL, and techniques for organ-sparing surgery are much more advanced. With early diagnosis and careful management, and with information on the latest treatment options, such a radical procedure should no longer be necessary. It is this information that Gill wanted to carry to families with VHL and to their physicians.

"I have taken over the running of this vital group because I want to prevent people going through what I have," she said. She worked tirelessly to raise awareness about the disease. Her main objective was to educate doctors and GP's (general practitioners, internists), to let them know the first signs of VHL so that treatment could be undertaken earlier.

Gill's daughter Natalie, 16, had DNA testing two years ago and does not have VHL, and Gill's three other siblings are also clear.

"She was a fighter," Brian says. She went through over 40 operations in the past six years but always bounced back like a bubble. She was a real hero. We are just grateful that she died peacefully at home and did not suffer." Gill was grateful to have such a wonderful family and friends.

We share Gill's hope for the future: "With all that has been learned in the last six years," she said, "the message to others is clear: this disease does not have to be a terminal illness. It is very treatable if you work with your medical team, find tumors early, and take appropriate action. There is more hope at this time for people with von Hippel-Lindau than ever before."

A raffle was held in the renal unit at St. Mary's Hospital, Portsmouth, in July to help fund telephone and postage costs and a British-based newsletter. Of an estimated 1800* people in the U.K. with VHL, only about 500 are currently identified. There are many more people in the U.K. who have the faulty gene, many of whom do not yet have the right diagnosis.

> "If I just save one person from going through what I have had to go through all this will have been worth it. -- *Gill Houlders*"

Gill's life, her enthusiasm, and her courage have inspired many to carry on her very important mission: to find others with VHL and raise the visibility of VHL in the medical community and the general public so that others who may not yet have a diagnosis will get the information and the treatment they need to stay healthy.

"I want to ensure that as many doctors as possible are made aware of this disease," Gill said. "Von Hippel-Lindau is so rare that most GPs are ignorant of it. If I just save one person from going through what I have had to go through all this will have been worth it."

Gillian laid a solid foundation for the VHL Support Group in the U.K. The British group is reorganizing and is looking for volunteers to join the committee and share the work. If each person can do a small amount, there will be strong support for everyone who needs it. If you can help, please contact Dora Beeforth at +44 1931 716031. Additional information will be posted on the announcement at the main number in London +44 171 681-1796 (Tel/Fax), or via E-mail at info@vhl.org.

* Calculating 1:32,000 based on projections from Dr. Eamonn Maher, Birmingham, England, on a population of approximately 60 million (Population Reference Bureau, Inc.).

One's best qualities shouldn't be measured by extraordinary circumstances but by everyday deeds. -- *Benjamin Franklin*

submitted by Joyce J., New York

Our thanks for Contributions . . .

Amy A., Louisiana
Barbara Herbert, Arizona
Kelly Heselton, Minnesota
J.H.E.J., New Mexico
Peter & Becky Lima, Michigan
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...Robert Anderson, by Michael Myers, Louisiana
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...Glenda's good checkup, by Jacky & Harold Jeter
...Jean Lima, by Becky & Peter Lima, Nancy Sagar
...Mike Murray with best wishes for his R&R. by Joyce
...Sharon Pastway, by Tania Durand, Ontario, Canada
...Tim Ross, by Dr. Michael Bell, Vermont
...Pat Stepper by Pat Kennedy, Florida
...Margaret & Grayson Smith on their 28th wedding anniversary
...E.B.T. just cuz I love you. by A. M. Baker, California
...June & Harry Wilcox's 56th wedding anniversary

In Loving Memory of . . .

...Rondo Anderson, Louisiana, by Paula Duet, Michelle Morillon
...Dorine Bender, by Pauline Howard, Beverly Nichol, Lindsay Shaw
...Michael Choiniere, by Patryce Murray
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For their gifts and services . . .

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