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Foundation Announces 1998 Research Awards

The National Neurofibromatosis Foundation has announced the recipients of its research awards for the academic year 1998-1999. The awards are as follows:

The Feinberg Family Research Fund Award

Dr. Suzanne Brill
Harvard Medical School/MGH
Two Year Young Investigator Award
Project Title: "Functional Analysis of NF1 In Drosophila"

Dr. Brill will study in the fruit fly model the role of the NF1 protein as an "integrator" of two very significant signaling pathways, namely Ras and cyclic-AMP. The work is expected to help us better understand why a gene defect (NF1) causing tumor growth also leads to significant deficits in learning and memory. Another important goal of Dr. Brill is to identify other genes which may act as modifiers of the NF1 gene and cause the manifestations seen in the disorder.

The Marcy and Richard Horvitz Family Fund Award

Dr. Gerald Cox
Harvard Medical School/Boston Children's Hospital
One Year Grant
Project Title: "Genetic Mapping of Familial Schwannomatosis"

The project is designed to identify the gene suspected to cause Schwannomatosis, a variant form of NF associated with changes in the NF2 gene.

The Mark B. Wallner Foundation Award

Dr. Jeffrey Field
University of Pennsylvania
One Year Grant
Project Title: "The Role Of Pak Protein Kinases in Neurofibromatosis"

Dr. Field's study is designed to determine the cellular events that contribute to the development of neurofibrosarcomas. He has developed a new way of blocking the growth of neurofibrosarcomas. His experiments should pinpoint the precise signal in the cell that causes this blockage. Once the mechanism is known, the information is expected to be useful in the development of drugs which can be used to treat neurofibrosarcomas and neurofibromas.

Dr. Michele Mazzocco
Johns Hopkins University-Kennedy Krieger Institute
One Year Grant
Project Title: "Specification Of The Cognitive Phenotype of NF1: Cognitive Correlates Of Mathematics And Language Skills"

The study proposed by Dr. Mazzocco is designed to identify the early cognitive and academic difficulties specific to children with NF1. The results are expected to create a specific profile of learning disability in children with NF1 and the processes underlying these difficulties. Such a profile will have important implications for effective intervention and treatment.

The Keller Research Fund Award

Dr. Andrea McClatchey
Harvard Medical School/MGH
One Year Grant
Project Title: "Investigation of NF2 Function Using Cells Derived From NF2 Mutant Mouse Strains"

Dr. McClatchey will study the function of the NF2 protein in the mouse model to determine what role it plays in the signaling pathway that determines cell growth and differentiation. She suspects that the role of the NF2 tumor suppressor and the family of proteins to which it belongs play a much more important role in human cancer development and progression than suspected.

The Texas NF Foundation Award

Dr. Luis Parada
University of Texas, Southwest Medical Center
One Year Grant
Project Title: "An In Vivo Model For The Malignant Phenotype of Type 1 Neurofibromatosis"

Dr. Parada will conduct experiments with mice carrying both the NF1 and p53 gene defects. His aim is to learn from these experiments how malignant tumors develop when the two mutant genes interact in the animal model.

The Barrie and Faith Sommerfield Family Fund Award

Dr. James Weston
The University of Oregon
One Year Grant
Project Title: "The Role Of SCF In Mouse Melanocyte Precursor Migration"

In this basic science project Dr. Weston seeks to develop a better understanding of how cells in very early embryonic development lead to the eventual formation of café au lait marks and neurofibromas.

Scientists Meeting In Colorado Report New Advances In Both NF1 And NF2

(Ed. Note: "The NNFF International Consortium For The Molecular Biology Of NF1 and NF2", now in its thirteenth year, is a worldwide collaborative effort of all leading laboratories in NF1 and NF2. It is sponsored and managed by the National Neurofibromatosis Foundation. The Consortium meets annually and is widely hailed for having accelerated the progress in NF research.)

by: Dr. Bruce Korf
Harvard Medical School/ Boston Children's Hospital
Chairman, NNFF Clinical Care Advisory Board

The NNFF International Consortium For The Molecular Biology of NF1 and NF2 met for four days during June in Aspen, Colorado. The meeting was chaired by Dr. Neal Copeland (National Cancer Institute). It was attended by 103 investigators from the United States and Europe.

The first session was devoted to the clinical and molecular genetics of neurofibromatosis and was chaired by Dr. Bruce Korf (Harvard/Boston Children's). The meeting began with an introduction to the Department of Defense/US Army Neurofibromatosis Research Program provided by the program head, Col. Irene Rich. Col. Rich reviewed the history and administration of the program, and announced a new request for proposals for additional funding of neurofibromatosis research. Recently, the Department has approved funding of a pair of natural history studies, one for NF1 and one for NF2. These upcoming studies were described by the principal investigators, Dr. Bruce Korf (Harvard/Boston Children's) for the NF1 study and Dr. William Slattery (House Ear Institute) for the NF2 study. Both studies are intended to collect data on the patterns of growth of neurofibromatosis-related tumors in preparation for eventual clinical trials.

Three talks focused on the molecular genetics of NF1. Dr. Klaus Scheffzek (Max Planck Institute, Germany) described the three-dimensional structure of the GAP protein and the structural basis for its interaction with RAS. Scheffzek has recently been successful in obtaining a crystal form of the RAS-NF1 GAP-related domain and described the structure of the association of the NF1 GAP-related domain with RAS.

Through this work, several amino acids that are critical to the binding of Ras were identified. Many of these correspond with known mutations in individuals with NF1; others are candidate sites for mutation. Dr. Ludwine Messaien (University of Gent, Belgium) reported on her experience with screening 38 patients with NF1 for mutations using a multi-step approach. One was found to have a balanced translocation, and none was found to have a large deletion. Additional mutations were found with the protein truncation assay (17 mutations) and by heteroduplex analysis (3 mutations). Interestingly, four mutations were found to reside within exons and yet lead to exon skipping. Overall, mutations were found in 21/38 patients. Several poster presentations also described progress in NF1 mutation analysis.

It has been hypothesized that mutation of both copies of the NF1 gene might underlie the pathogenesis of neurofibromas, although this has been difficult to prove, in part due to admixture of normal and tumor cells in benign neurofibromas. Dr. Margaret Wallace (University of Florida, Gainesville) examined cutaneous and plexiform neurofibromas for loss of heterozygosity of NF1, finding this in 2/15 cutaneous tumors and 5/12 plexiform neurofibromas. Loss of heterozygosity was also found in 3/5 malignant peripheral nerve sheath tumors. Dr. Eduard Serra (University of Barcelona, Spain) presented a poster showing evidence for loss of heterozygosity for NF1 in some neurofibromas. These results provide support for the hypothesis that NF1 functions as a tumor suppressor gene; those tumors not found to have loss of heterozygosity are presumed to have mutations in both NF1 alleles, although these mutations have not been identified.

The second session was chaired by Dr. Andre Bernardts (Harvard/MGH) and focused on the cell biology of NF1. Bernardts described the phenotype of *Drosophila* NF1 knockout mutations. The flies tend to be small and exhibit learning defects. Increasing levels of cAMP rescue the flies from the phenotypic effects of NF1 mutation. Dr. Yi Zhong (Cold Spring Harbor Laboratory) continued the story of the *Drosophila* NF1 mutants, concentrating on the learning defect. The phenotype is similar to that produced by mutation in the rutabaga locus, involved in the adenylyl cyclase pathway; Zhong presented evidence that NF1 in *Drosophila* may function through that pathway in its effects on learning. Dr. Gihan Tennekoon and Dr. Jeffrey Field (both University of Pennsylvania) presented data on the activity of RAS pathways in Schwann cells. There are multiple pathways through which RAS exerts an effect on transcription. Ha-RAS activity in Schwann cells leads to differentiation, acting through the Raf/Mek/Map kinase pathway. The PI-3 kinase pathway appears to be involved in the inhibition of apoptosis of Schwann cells. Proteins in the Rho family lead to changes in Schwann cell morphology when activated. Another protein involved in Ras signaling is Pak 1. Dominant negative Pak mutants inhibit Ras-dependent transformation of Schwann cells. Dr. Laura Klesse (University of Texas, Southwest) described the role of RAS pathways in neuronal differentiation and survival. The Raf/Mek/Map kinase pathway appears to be involved in neurotrophin-induced differentiation but the PI-3 kinase pathway is required for survival, as for Schwann cells. Dr. Jeffrey DeClue (National Cancer Institute) reported finding activity of the EGF receptor on malignant peripheral nerve sheath cells in culture as well as on benign neurofibromas. Growth of the malignant cells in culture is EGF-dependent. Dr. Wade Clapp (University of Indiana) reported on his study of RAS signaling in hematopoietic progenitor cells. Mouse *Nf1* ^{-/-} hematopoietic stem cells demonstrate abnormal proliferation in response to cytokines and activation of the Raf/Mek/MAP kinase pathway. It is hypothesized that the NF1 protein functions to modulate this pathway, and its absence leads to abnormal activation. Dr. George

Mashour (Georgetown University) reported increased secretion of angiogenic factors from Nf1^{-/-} Schwann cells, including an angiogenic factor Midkine (MK). Interestingly, MK was found to be expressed at increased levels in skin from individuals with NF1, regardless of whether it was adjacent to a neurofibroma. This suggests the possibility of using MK expression as a diagnostic marker, an idea that is being subjected to further test. Dr. Jonathan Epstein (University of Pennsylvania) presented his work on the origin of the cardiac defect in Nf1^{-/-} mice, presenting evidence for abnormal epithelial-mesenchymal transformation. Dr. Camilynn Brannan (University of Florida, Gainesville) presented a poster proposing the alternative explanation that cardiac development is retarded in Nf1^{-/-} mice, leading to a discrepancy of development of the heart and the rest of the animal.

The next session, chaired by Dr. James Gusella (Harvard/MGH), was devoted to the molecular genetics of NF2. Gusella provided a summary of current understanding of the function of merlin and other ERM proteins. Dr. Vijaya Ramesh (Harvard/MGH) reported that merlin co-localizes with actin filaments in cellular projections and membrane ruffles, similar to other ERM proteins. She described a protein NHE-RF, involved in Na⁺/H⁺ exchange, that interacts with merlin. Another protein that interacts with ERM proteins, designated EBP50, was described by Dr. David Reczek (Cornell University) and Dr. Stephan Pulst (UCLA/Cedars Sinai) reported that schwannomin (merlin) interacts with βII-spectrin. Dr. Brooke McCartney (Duke University) presented findings with Drosophila NF2 mutants. The phenotype is one of overproliferation of cells. Another gene, expanded, leads to enhancement of the NF2 mutant phenotype when both genes are mutated. Expanded encodes a product with a protein 4.1 domain that co-localizes with merlin. Dr. Gareth Evans (University of Manchester, UK) presented data on NF2 mutation analysis in individuals with unilateral vestibular schwannomas. About 10% of individuals with NF2 presented with unilateral VS and had a significant delay before their contralateral tumor presented, and about 5% of individuals with unilateral VS were found to have germline NF2 mutations.

Dr. Nancy Ratner (University of Cincinnati) moderated the next session, devoted to the cell biology of NF2. She reported that schwannoma cells in culture display increased proliferation and spreading on a matrix compared with normal Schwann cells. The tumor cells also have a disorganized actin cytoskeleton and aberrant membrane ruffling. She presented evidence that the Rho and Rac pathways are activated in schwannoma cells. Dr. Dennis LaJeunesse (Duke University) continued the discussion of Drosophila merlin, describing studies that have revealed a region in the protein that is critical for its subcellular localization. Several of the speakers described interactions of merlin with itself and other proteins. Dr. Wallace Ip (University of Cincinnati) pointed out that merlin isoform I interacts with the active form of ezrin, whereas isoform II interacts with either active or dormant forms of ezrin. Merlin-merlin interactions are strongest between the two isoforms in either head-tail or tail-tail configurations. Dr. Markku Sainio (University of Helsinki, Finland) mapped regions of merlin required for interaction with ezrin and pointed out that, unlike ezrin, merlin does not require activation to self-associate. Dr. David Gutmann (Washington University, St. Louis) presented evidence that merlin interacts with RhoA, CD44, and focal adhesion kinase, as well as with actin. Dr. Reuben Shaw (MIT) reported that the non-phosphorylated form of merlin may be the active form of the protein and that RhoA is critical for control of this phosphorylation.

The next session focused on animal models of NF1 and NF2, and was chaired by Dr. Tyler Jacks (MIT). Dr. Luis Parada (University of Texas, Southwest) has created a

mouse model in which inactivation of NF1 is controlled by Cre-mediated recombination. Sensory neurons with inactivated Nf1 become neurotrophin-independent, consistent with a postulated regulatory role of Nf1 in the response to neurotrophins. Dr. Kristine Vogel (Louisiana State University) has found that Nf1^{-/-} sensory neurons in culture innervate both normal targets and tissues that are not normal targets, in contrast with wild type neurons that only innervate normal targets. Dr. Alcino Silva (Cold Spring Harbor Laboratory) reported on learning in Nf1 mutant mice. Nf1 mutant animals that also harbor an N-Ras mutation show normal learning, and the Nf1 mutant learning phenotype can be rescued by treatment with farnesyl protein transferase inhibitors. These findings support a role of the Ras pathway in the learning deficit in Nf1 mutant mice. Dr. Camilynn Brannan (University of Florida, Gainesville) reported that mice lacking the alternatively spliced exon 23a develop apparently normally. Dr. Radhika Atit (University of Cincinnati) has shown that Nf1^{+/-} mice display abnormal wound healing, with abnormal collagen deposition. NF2 mouse models were described by Dr. Marco Giovannini (CEPH Fondation Jean Dausset, France) and Dr. Andrea McClatchey (Harvard/MGH). Giovannini has used the Cre-lox system to develop an Nf2 mutant that is expressed in developing Schwann cells. A non-frameshift N-terminal deletion produces peripheral nerve tumors and Schwann cell hyperplasia, whereas a C-terminal mutation does not. This has suggested a possible dominant negative role for Nf2 mutations in causing schwannomas. McClatchey reported that Nf2^{+/-} mice develop osteosarcomas, fibrosarcomas, and hepatocellular carcinomas, in contrast with the human disorder. Nf1 and p53 mutations are cooperative with Nf2 mutations in producing tumors. Malignant peripheral nerve sheath tumors have been seen in Nf2/Nf1 double mutants.

The final session, chaired by Dr. Jackson Gibbs (Merck & Co.) was dedicated to experimental therapeutics. Gibbs provided an update on progress in the development of farnesyl protein transferase inhibitors. He pointed out that these inhibitors are not specific for RAS; among RAS proteins, Ha-RAS is most sensitive, but may be of lesser relevance in malignancies. It is hoped that these drugs will act along with other chemotherapeutic agents. Phase I clinical trials have begun (although not in patients with NF1). Dr. Jon Holmlund (Isis Pharmaceuticals) described the use of antisense oligonucleotides against c-raf and Ha-RAS. Clinical trials have also begun for these agents. Dr. Patricia Molloy (University of Pennsylvania) reported on results of the clinical trial of interferon alpha 2a and cis-retinoic acid in the treatment of plexiform neurofibromas. No objective instances of tumor shrinkage were found, although there were some instances of subjective improvement or improvement in function. She stressed the need for more information on natural history and the need for a control group in assessing clinical outcomes. She also described a study of the use of PET scanning to evaluate astrocytomas in NF1, pointing out that levels of glucose uptake correlated with malignant behavior. Dr. Kevin Shannon (University of California, San Francisco) reported on his work with leukemias in Nf1^{+/-} mice. He presented evidence that GM-CSF stimulation of hemotopoeitic precursors acts via the Ras pathway. The rate of development of leukemia in mutant mice was increased by treatment with the alkylating agent cyclophosphamide.

Overall, a number of important themes emerged from the meeting. First, studies of the mutations responsible for NF1 and NF2 have been hampered by the wide diversity of mutation types seen. Progress has been made in identifying genotype-phenotype correlations in NF2, but this has been more difficult in NF1, perhaps due to the large size of the gene and the complexity of the NF1 phenotype. Several laboratories have demonstrated the need for a multimodal approach to mutation

detection in NF1, which will permit a larger proportion of mutations to be identified. It remains to be seen if this will result in any prediction of specific NF1 complications, and whether a clinically useful diagnostic test can be devised. A second theme concerns the interaction of NF1 and NF2 proteins with other proteins. Both are involved in complex signaling pathways, the components of which are being elucidated. In this instance complexity may be seen as an advantage, since it offers many potential points for pharmacological intervention. A third theme is the need to identify the physiological basis for the clinical phenotypes of NF1 and NF2. For years our knowledge of neurofibromatosis was based on observation of the disorder in people, which stimulated interest in studies in animals and cell culture systems. Now, as information is coming in from these experimental systems there is a need to return to the clinic and sharpen the observations to relate knowledge gained in the laboratory with the clinical behavior of the disorder. This meeting has brought together both clinical and laboratory scientists who are working synergistically to understand the basis for the features of neurofibromatosis and develop therapeutic approaches.

Clinical Trials In Neurofibromatosis: Questions And Answers

The following is the text of a recent conversation Neurofibromatosis Newsletter editor Fran Morris had with NNFF Medical Director Allan Rubenstein, MD, regarding upcoming clinical trials in neurofibromatosis.

FM: The Foundation and several researchers have recently made comments that "we are about to enter the era of clinical trials in neurofibromatosis". Can you explain what this means and what people with NF can look forward to?

AR: For many years the Foundation has supported basic research into the causes of NF1 and NF2, and this investment has paid off. The research is now moving from the laboratory into the clinic. In the next five years, we expect to see several drugs screened for their potential to prevent tumor growth.

FM: How do clinical trials work?

AR: Clinical trials provide a structure to test the safety and efficacy of a treatment. Before the Food and Drug Administration can consider a drug for approval, it must go through at least three phases of clinical trials. In Phase I, a small number of patients participate to study a drug's safety, including the safe dosage range. These studies also determine how a drug acts in the body and the duration of its action. In Phase II, more patients with the target disease participate to test the drug's effectiveness. In Phase III, large numbers of patients in clinics and hospitals participate and physicians monitor them closely to confirm efficacy and identify side effects.

FM: What will be the Foundation's role in clinical trials?

AR: We expect the Foundation to play a critical role in clinical trials. The Foundation will be organizing the consortium of clinics needed to screen drugs. We plan to recruit a physician on staff to coordinate these efforts.

FM: Several years ago, Dr. Francis Collins, the director of the Human Genome Project, made a presentation at the Foundation outlining a strategy for clinical trials. Dr. Collins recommended that the Foundation follow a dual track. One track would be dedicated to take chemical compounds with reasonable rationales for treating tumors and test their effectiveness for NF-related tumors. The second track would be to develop a systemic approach, such as genetic engineering. Is this dual strategy still appropriate?

AR: Yes. This is the strategy we intend to pursue.

FM: Haven't there already been clinical trials in neurofibromatosis, such as the one the U.S. Army was underwriting at Children's Hospital of Philadelphia and other allied institutions?

AR: These clinical trials had mixed results. A major hurdle for these trials was that the variable growth rates of neurofibromas made it difficult to determine whether the tumors stopped growing on their own, which is characteristic of NF, or if they were affected by the treatment. The U.S. Army is now funding a natural history study of NF1 and NF2 that will provide the normal growth rates of neurofibromas. This data is crucial to gather before trials of various chemical compounds can begin.

FM: Recently there was big news that two new cancer drugs, in a class of drugs known as antiangiogenesis drugs, could shrink malignant tumors. Do they have any relevance for NF?

AR: Although the news was about breakthroughs in treating mice with cancer, antiangiogenesis approaches are being considered for NF and have been discussed at NNFF-sponsored scientific meetings for several years. It is important to keep in mind, however, that many promising treatments tested on mice have not produced the same results in patients.

FM: We've heard that there is a thalidomide trial underway. Can you tell us about that?

AR: Like the cancer drugs that were recently in the news, thalidomide may possess anti-tumor properties. That makes it a logical candidate to test on neurofibromas. Clinical trials of thalidomide for neurofibromas are currently underway, but results of these trials are not in yet.

FM: Previously, we have mentioned farnesyl transferase agents in this newsletter. What are they and what is happening with them?

AR: Farnesyl transferase is a chemical compound that interacts with the Ras oncogene. It shows great promise in animal models for treating a number of tumors, including those in NF1. Clinical trials of these agents are just beginning.

FM: Have drugs already been tested in animal systems, such as the mouse or fruit fly?

AR: Several of the compounds we have just discussed have been used in animal models with promising initial results.

FM: On some of the chat boards there have been new questions about the European asthma medication ketotifen. Some suggest it holds promise for NF. Is the drug useful for NF?

AR: Ketotifen is an anti-histamine that was suggested years ago as a treatment for NF1. It can reduce itching some may experience from neurofibromas, but there is no evidence that it affects neurofibroma growth. At this time, ketotifen is not available in the U.S.

FM: Are we as close to clinical trials in NF2 as we appear to be in NF1?

AR: Yes.

FM: How can patients with NF get involved in clinical trials?

AR: Right now, the preparation for clinical trials is not complete, so, I can't give specific directions on how to enroll. However, as soon as this information is available, the Foundation will post it on the NNFF web site (www.nf.org) and publish the information in this newsletter.

NF Research:

Where Are We On The Road To Treatments And A Cure?

(Editor's Note: The following article is based upon the text of a talk given by David H. Gutmann, MD, PhD, at the Annual Meeting of the National Neurofibromatosis Foundation, held in May in New York City. Dr. Gutmann is an assistant professor in neurology at Washington University School of Medicine and director of the St. Louis Children's Hospital Neurofibromatosis Program, both in St. Louis, Missouri. He serves as co-chairman of the Foundation's Clinical Care Advisory Board. Dr. Gutmann is also the lead author of the landmark article "The Diagnostic Evaluation and Multidisciplinary Management of Neurofibromatosis 1 and Neurofibromatosis 2", published in the Journal of the American Medical Association.)

Dr. David Gutmann admits that he can be a bit impatient. But, in Dr. Gutmann's case, impatience is a virtue. In fact, the neurologist and NF researcher is motivated by his impatience to help find targeted therapies for NF.

"NF research has come further in the last five years than it has in the previous 100 years," Dr. Gutmann noted at the Annual Meeting of the National Neurofibromatosis Foundation. "Because research has moved so quickly in the last five years, we've all become even more anxious to forge ahead and find 'magic bullets' for NF."

Great strides having been made in the basic science laboratory to decipher the complexities of NF, and these discoveries are helping researchers apply the available knowledge to test potential treatments for NF. While effective treatments are pursued, molecular biologists continue to seek answers to the remaining questions about NF.

"This two track approach of basic science research and clinical trials enables us to attack NF from all angles," Dr. Gutmann said. "With such a concerted effort, every year research should provide new insights into NF."

Dr. Gutmann put this two-track approach in context by using the example of three aspects of NF1: neurofibromas, optic gliomas, and learning disabilities. With each example, he asked two vital questions:

What is known?

What needs to be understood in order to move closer to development of targeted therapies?

Neurofibromas

What is known about neurofibromas?

Researchers already know a lot about how neurofibromas behave but need more accurate information about their growth patterns, according to Dr. Gutmann.

NF researchers know several things about neurofibromas that are key for developing and testing treatments:

what types of cells are found in neurofibromas and which type of cell causes problems;

the function of the Ras protein (one of the most important molecules in the cell for stimulating growth) in cells, and its relationship to benign and malignant neurofibromas

what happens to cells when the NF1 protein is reduced or absent

What needs to be understood about neurofibromas?

More information is needed about the normal behavior of neurofibromas: what stimulates their growth, what sustains their growth, and what makes them stop growing. These studies will begin in September 1998 with a study of plexiform neurofibromas coordinated by Bruce Korf, MD, a pediatric neurologist and geneticist at Harvard University and Boston Children's Hospital, who also serves as the Chairman of the NNF Clinical Care Advisory Board (see related article on page). In addition, a natural history study of vestibular schwannomas in NF2 is expected to be announced shortly by the US Army's NF Research Program.

Understanding the control switches that underlie the unique ability of neurofibromas to begin to grow and then suddenly start or stop may provide researchers with an opportunity to devise strategies for stopping tumor growth. If scientists know what causes tumors to stop growing, an appropriate therapy could be developed and tested, according to Dr. Gutmann. In addition, other events required for neurofibroma growth must be explored. Studying why some plexiform neurofibromas can turn from benign to malignant will provide other insights into the behavior of tumors.

Optic glioma

What is known about optic gliomas?

Researchers have learned much about how optic gliomas (brain tumors on the nerves that connect the eyes to the brain) behave and how they differ in people with NF1 from optic gliomas found in the non-NF1 affected population. The composition of the cells that give rise to optic gliomas is also known.

What needs to be understood about optic gliomas?

Scientists still need to determine how the NF1 gene regulates the growth of the cells that give rise to optic gliomas. In addition, scientific data is needed to determine which people and which optic gliomas are most likely to respond to treatment. It also must be established which people are likely to develop vision loss from these tumors.

Learning Disabilities

What is known about LD?

Research into the biology of learning disabilities has shown that neurofibromin plays a critical role in the development of the nervous system in general, and in learning and memory in particular. Initial experiments in animals with the NF1 defect have shown that reduced amounts of neurofibromin in the brain are associated with learning disabilities. Some studies also have suggested there is a relationship between LD and the unidentified bright objects (UBOs) found in the brains of some people with NF1.

What needs to be understood about LD?

Nerve cells are likely culprits in causing LD, but scientists also want to see if astrocytes (the brain's star-shaped cells) are involved, according to Dr. Gutmann. Determining which cells play what role is important for the development of therapies for LD.

While some researchers have noted a possible relationship between LD and UBOs in the brains of people with NF1, they still need to determine the significance of UBOs. In addition, scientists do not know what precise function neurofibromin, the NF1 protein, has in brain cells.

"The presence of neurofibromin in brain cells raises the possibility NF1 is more than just a tumor suppressor gene," Dr. Gutmann said. "Perhaps it has other functions we have not identified."

And, as with neurofibromas and optic glioma, researchers would like to find a way to predict which children are likely to develop LD and which are not.

What other information about NF is needed?

Dr. Gutmann noted that finding the NF1 gene was just the beginning. "We were able to find that needle in the haystack to isolate the NF1 gene," Dr. Gutmann said. "Now we have to put that needle back into the haystack of the human body to see how it functions in the context of hundreds of thousands of other genes."

As for NF2 research, Dr. Gutmann noted that NF2 research is moving along at an exciting pace, only slightly behind NF1 research. "Remember that the NF2 gene was discovered three years after the NF1 gene, so we have a bit of catching up to do," Dr. Gutmann said.

Dr. Gutmann urged the audience to keep supporting NF research. "These are the best of times because in the next several years we will begin to take information from the labs and clinics and meld it together to develop effective ways to treat NF," Dr. Gutmann said. "I urge you to dig down deep and push us even harder."

New Chapter Established In South Carolina

The National Neurofibromatosis Foundation announced the creation of its 30th state chapter in South Carolina.

Hannah and Mark Ehrli of Surfside Beach, SC are the co-presidents. Prior to starting the Chapter the Ehrli's were actively engaged in a broad range of NF patient information and support activities, public awareness and fund raising for NF throughout the state. Last fall they hosted a successful Harvest Luncheon at Planet Hollywood in Myrtle Beach. Mark Ehrli also coordinated a number of activities at the Official All Star Café to raise funds for NF research.

Hannah Ehrli has been active in creating more support services for patients with NF in South Carolina and has lobbied in the Nation's capital regarding issues concerning children with disabilities.

The "kick-off" for the inauguration of the Chapter was held in June in Myrtle Beach. "The Official All Star Café Golf Tournament and Charity Auction", a combination golf tournament and sports auction, was hosted by NNFF celebrity spokesman, Mark Chmura, a member of the Super Bowl XXXI Champion Green Bay Packers.

New Board Chairman and Directors Announced

At the May meeting of the NNFF Board of Directors, Bruce Judson was installed as Chairman of the Board. Judson, an attorney, Internet expert and best-selling author, has been a member of the Board of Directors for 10 years. The New York City resident succeeds William Tarbart, who has served as Chairman since 1994. In addition, William A. Scott, PhD, was elected vice chairman.

Five new Directors were elected to the Board: Suzy Crisci of Caldwell, ID; David Cross of Maitland, FL; Sharon B. Parente of Larchmont, NY; John G. Roman of Bernardsville, NJ; and Nate Walker of Encino, CA.

"Our newest 'class' of Directors adds a stronger level of representation from our chapters and adds the talents of people from the worlds of finance, real estate, and education, " Peter Bellermann, president, said. "With Bruce Judson at the helm, the Foundation will continue to move aggressively towards effective treatments and a cure for NF."

Mr. Judson is the founder and Editor of Bruce Judson's Grow Your Profits and is one of the nation's leading experts on using the World Wide Web for business.

He is the author of the nationwide bestseller NetMarketing: How Your Business Can Profit From the Online Revolution. Judson is a graduate of Dartmouth College, and holds advanced degrees from both The Yale Law School and The Yale School of Management.

Dr. Scott is President and Chief Executive Officer of Physiome Sciences, Inc. in Princeton, NJ. He previously held a variety of senior research positions at the Bristol Myers Squibb Pharmaceutical Research Institute and served as Associate Dean at The Rockefeller University. Dr. Scott was graduated from the University of Illinois with a B.S. degree in chemistry and went on to earn a Ph.D. in biochemistry at the California Institute of Technology.

Ms. Crisci is the founder and President of the NNFF Idaho Chapter, which was established in 1989. She is the founding Director of Learning Hands Preschool in Caldwell. In addition, Crisci is a local 4-H Club livestock leader. She was graduated from the University of Idaho in Moscow with a B.S. degree in agriculture education

Mr. Cross is the President of the NNFF Florida Chapter, which was established in 1985. He is first Vice President and Manager of the Private Banking Group of SunTrust Bank, Orlando. Cross graduated from Rollins College, Winter Park, with a B.A. degree in liberal arts with a minor in business administration.

Ms. Parente is the Chairwoman of the NNFF Council of Fellows, an advisory group comprised of professionals pre-eminent in their fields. She is the Managing Director of the Private Client Group of Warburg Pincus Asset Management, New York City. Ms. Parente graduated from the University of Virginia with a B.S. degree.

Mr. Roman is President of Merrill Lynch Trust Company (NY and NJ) and business unit manager for the Northeast region. He was graduated from Idaho State University with a B.A. degree and is a graduate of the Financial Institute's Trust School at Boston University. Prior to his career in finance, Roman played for the New York Jets for eight years.

Mr. Walker is the President of the NNFF California Chapter. He is First Vice President and Managing Partner of Investors Management Company, Inc., Tarzana. Mr. Walker graduated from California State University, Northridge, with a B.A. degree in radio-TV broadcasting.

Priscilla Short, MD: A Physician Who Truly Understands

(Ed. Note: This is another in an continuing series about individuals with NF. Readers are encouraged to send their suggestions about others who have a compelling story to tell.)

Every patient with a chronic condition yearns for a doctor that can truly understand what he or she is going through. Because NF is a variable and unpredictable disorder, how someone with NF is approached by their physician is critical in allaying fears and putting medical issues into context.

When someone visits Dr. Priscilla Short's office at the University of Chicago Hospitals and Clinics, they find a doctor who knows exactly what it is like to deal with NF on a daily basis. Not just because she sees a large number of NF patients, but because she has NF2.

Like many people with NF2, Dr. Short did not discover she had the disorder until she was an adult. At age 40, she experienced a terrible headache one Thanksgiving and went to a nearby hospital emergency room and was given a CAT scan. The scan revealed several tumors that suggested a diagnosis of NF2.

Dr. Short found the diagnosis ironic as her job in the NF clinic at Massachusetts General Hospital involved working in a clinic with the highest density of NF2 patients in the country and looking at schwannomas (benign tumors made up of schwann cells) under the microscope every day.

Coming to terms with her diagnosis under such circumstances was both easier and harder. "Denial can happen if NF is not in your face all the time," Dr. Short said. "And nobody wants to think about a chronic condition every day. Due to my work, I could not get away from NF2. NF causes you to feel a lack of control over your life coupled with uncertainty, which can do people in. It's important to put those fears aside so they don't become paralyzing."

Currently, Dr. Short's tumors do not cause her any problems. Like many people with NF2, she has hearing loss in one ear. Her hearing loss is not the result of NF2, but stems from a surgery she underwent as a teenager to treat a defect in her eardrum that caused a chronic infection.

NF has shown Dr. Short that as a physician she must balance a health professional's "missionary zeal to help patients with what a patient is ready to handle and do. I've discovered that the factors that go into a practitioner's definition of wellness is often very different than a patient's sense of well-being. For example, while internal tumors can be problematic, patients may worry more about external bumps on their skin."

-As a patient, Dr. Short found the strength to cope by looking to positive role models in her own backyard -- her hearing impaired mother and father. Her mother did not let her hearing impairment, which Dr. Short suspects was due to undiagnosed NF2, interfere with her goal of being a high school English teacher in Bridgeville,

Delaware, where Dr. Short grew up. Her father, who lost hearing due to otosclerosis, a condition which damages the stapes bone in the middle ear, worked as an accountant.

"Because of my parents, it didn't even occur to me to be depressed that I was losing my hearing," Dr. Short noted. "That is why it is important to have a mentor figure that understands the challenges you face."

She also found inspiration to become a physician from her encounters with the medical community. Visits to her small town family doctor, a woman who Dr. Short remembers had a wonderful way with patients, was an excellent model for her own bedside manner. She also recalls as a child accompanying her mother to John Hopkins Medical Center in Baltimore and was impressed by the amazing care provided that saved her life.

These experiences, helped Dr. Short decide early on to pursue a career in medicine. After graduating high school, Dr. Short attended Bryn Mawr College in Pennsylvania, where she was graduated with a bachelor's degree in biology and music. She went on to earn a medical degree from the Medical College of Pennsylvania. Her postdoctoral education included training in internal medicine, neurology, neuropathology and genetics at institutions including Hahnemann Medical College Hospital, University of Pittsburgh Medical Center, Massachusetts General Hospital, and Mt. Sinai Medical Center, respectively.

Today, in addition to her position at University of Chicago, Dr. Short works at the American Medical Association. She is the AMA's director of the Office of Biomedical Science and Clinical Research, an area dedicated to helping America's physicians better understand genetics and its role in their day-to-day practice. In this capacity, Dr. Short coordinated an educational conference for 250 primary care physicians that gave NF high visibility due to presentations by NF experts Bruce Korf, MD of Harvard University and Boston Children's Hospital, and David Viskochil, MD of the University of Utah.

When not consumed with the demands of her two jobs, Dr. Short can be found spending quality time with her husband, Michael P. Klein, and their son, 5-year-old Asher; pattering around her garden, or enjoying the famed architecture of the Windy City.

Scientist Explores New NF Links to Learning Disabilities

(Ed. Note: The following is a report on a talk given to the NFFF Council of Fellows at its May meeting by Dr. Alcino Silva of the Cold Spring Harbor Laboratory. Dr. Silva's research will be detailed in this newsletter as more data becomes available when it is published in a scholarly journal.)

Dr. Alcino Silva's laboratory at Cold Spring Harbor Laboratories in New York's Long Island is buzzing with activities reminiscent of a day in high school – except all the students are laboratory mice.

Some of the mice are down at the pool paddling through the water in search of a platform where they can take a breather from their morning swim. Others are in home economics learning about the merits of a new mouse chow recipe. Meanwhile, another group of mice are cruising the halls checking out the new kids on the block.

These activities are ingeniously designed experiments testing the mice for various spatial and memory abilities. The experiments help Dr. Silva and his team evaluate how learning and memory in mice with NF1 differ from their unaffected kin – information that may benefit human students around the world.

Learning disabilities (LDs) are a crucial area of research since LDs occur five times more often among people with NF than the general population. Since the rate of LDs is unusually high among people with NF, Dr. Silva's project, funded by the NNFF, is exploring how the NF mutation might be linked to the cause of learning disabilities.

The results of his first year of research suggest that spatial-memory and social LDs are caused by a lack of neurofibromin. Neurofibromin is the protein produced by the normal NF gene, which is present in all unaffected people. People with NF have a mutated gene, which does not produce the usual amount of neurofibromin.

"Once we had data that indicated there was a link between this lack of neurofibromin in mice with NF1 and the occurrence of learning disabilities, we wanted to take the next natural step," Dr. Silva said. "We began to explore whether we could treat the NF1 mice with learning disabilities with a drug to try and reverse the affects."

To date, Dr. Silva's lab has run a series of experiments that give the NF1 mice a series of learning and memory, as well as social recognition, tests. The next step is to treat affected mice with a drug to see if improvements can be made in performing the same set of tasks. Initial research shows promise that drug therapy in NF1 mice can be effective in bringing their memory and learning skills back within normal levels.

"While the results are very promising, we must be cautious because these experiments have only been conducted on mice," Silva noted during a recent talk in New York City to the Foundation's Council of Fellows. "It is always a great challenge to translate these results into human patients."

Dr. Silva will be moving his lab to the University of California at Los Angeles, where he plans to conduct research on the human molecular biology of LDs. This basic science research is a necessary first step in applying his mouse model research to people.

"This is an exciting new direction in NF research that provides a ray of hope for people with NF and learning disabilities," Peter Bellermand, NNFF president, said. "And, if successful, a treatment could have benefits for the estimated 30 million people in the United States with LDs."

WebSite Brings NF Medical Expertise To All Areas Of The World

Physicians and other health care professionals anywhere in the world will now have access to a free internet service, the World Wide Neurofibromatosis Clinicians' Forum. The new service will enable them to benefit from the expertise of colleagues specializing in neurofibromatosis.

While NF is the most common neurological disorder caused by a single-gene, relatively few healthcare professionals anywhere are well-versed in the diagnosis and treatment of the two disorders, NF1 and NF2. The Forum, the first dedicated to NF-related medicine, is being made available at no charge to physicians and healthcare professionals via the National Neurofibromatosis Foundation (NNFF) web site (www.nf.org).

"Because very little attention has been paid to the neurofibromatoses and NF varies a great deal from one person to the next, health professionals find the two disorders difficult to recognize and manage," Peter Bellermann, NNFF President, said. "With the World Wide Neurofibromatosis Clinicians' Forum, healthcare providers from Bombay to Baltimore have easy, no cost access to world-class NF experts. More importantly, patients and families will benefit from care givers who are better informed about NF."

Healthcare professionals can access The Forum via special passwords, post their patients' profiles, and ask diagnostic and management questions about their patients. Patients' names will not be used on the site. The profiles and questions are then assigned by Bruce Korf, MD (Harvard Medical School/Chairman of the NNFF Clinical Care Advisory Board) to the appropriate Forum faculty members, each an internationally known expert in a particular aspect of NF.

The profiles and faculty responses will be archived by category on the Forum and will accumulate as a database for future reference by health care professionals around the world. According to Bellermann, the service is not a medical consultation and does not take the place of the local physician's medical examination.

"Conferring with the world's leading clinical experts in NF equips the local health care professional to provide better care to his or her patients," Bellermann said. "We believe this new affordable and accessible resource has the potential for greatly improving the quality of care for people around the world with NF1 and NF2."

The public can continue to access a wealth of NF information through the newly redesigned NNFF homepage at www.nf.org.

In Memoriam:
Sydney Staas

1921 - 1998

Vice Chairman, INFA

The National Neurofibromatosis Foundation mourns the passing of Sydney Staas who died in Sydney, Australia, on July 10, 1998, after a long illness.

Mr. Staas was one of the founders of the International Neurofibromatosis Association (INFA) and served the organization as Vice Chairman and head of its Nominating Committee. At the time of his death he was in the midst of managing the next election of the INFA Board of Directors, somehow managing this from his hospital bed.

Mr. Staas was also for many years the Secretary and driving force in the Neurofibromatosis Association of Australia.

INFA Chairman Peter Bellermann hailed Syd Staas, saying : "Syd was one of the great champions for people with NF throughout the world. We have lost in him a tireless fighter, who worked for us to the very end. He was a great and loyal friend, a person on whom we could always count when something had to be done. He will be missed, but his memory lives on. He inspired us to keep fighting for a cure, no matter what the obstacles."

In Memoriam:

Dr. Lester Weiss

The National Neurofibromatosis Foundation mourns the recent passing of Dr. Lester Weiss. Dr. Weiss was the Chairman of the Division of Genetics at the Henry Ford Hospital in Detroit, MI. He joined the staff of HFH in 1966 as a genetic consultant and became Chairman of Pediatrics in the early 1970's.

Dr. Weiss founded and led one of the first NF clinics in the World at Henry Ford Hospital.

YOUR TURN

Orthopedic Complications

I have a 6 year old boy who has scoliosis with a 230 curvature. The doctors are recommending a brace. But I am hesitant to put him through the trials of wearing a brace. Will it really help?M.F.; Bloomfield, NJ

Yes, it is worthwhile to undertake early aggressive treatment, since the curvature can worsen as the patient grows.

Another parent asked about bowing of the tibia:

The doctor says our 11-month old has bowing of the tibia and they want to put a brace on his leg. We have no knowledge of the process and won't be seeing the doctor for another month.-M.L.; New York, NY

Treatment of this type of bowing of the long bone in the leg should consist of early bracing to support the area, with the intention of preventing fractures and avoiding any surgical efforts to straighten intact bones. With careful orthotic fitting and good follow-up care, many NF patients now go safely through an at-risk period of relative bone weakness without fracture and subsequent surgery

In both of these cases the orthopedic problems can be treated successfully, if detected at an early stage. Prompt, appropriate treatment can usually prevent or reduce cosmetic deformity and functional impairment. The key to successful management of orthopedic complications in NF is early diagnosis of the condition.

Breast-Feeding

I have NF and am breast feeding my 7-month old who also has NF. I have noticed an increase in the number of my son's café-au-laits. Is it possible that the hormones I'm passing to him through my milk are increasing the spots? – O.T.; Marietta, GA

No. The increase in the CAL's are the normal progression of his NF. Their growth cannot be affected by in this manner. They can increase in number throughout childhood, but appear to stop increasing or even decrease in adulthood.

Organ Donation

I was happy to see in you last newsletter that it's OK to donate blood even if you have some form of NF. I there any known problems with organ donation? – K.K. Ladora, LA

No. It is the consensus of our researchers that the benefits far outweigh the risks to individuals who receive organ transplants from patients with NF1 or 1. While little clinical data is available, the group agreed that NF patients could donate organs.

Does recent cancer news have NF impact?

News coverage in May about two promising cancer drugs being tested, angiostatin and endostatin, raises the question whether these drugs could benefit people with NF-related tumors. The answer is that the research is relevant.

The results were reported by Dr. Judah Folkman, Children's Hospital in Boston, whose laboratory used the drugs to treat mice with cancerous tumors. The two drugs cut off tumors' blood supply by destroying new capillaries or preventing them from forming (a process known as angiogenesis). Without this nourishing blood supply, tumors stopped growing, shrank or disappeared. Scientists know of more than 300 substances that can halt angiogenesis. NNFF-funded researchers have been exploring the role of angiogenesis in NF for 3 years.

"While Dr. Folkman's results are indeed promising in looking at ways to stop or reverse tumor growth, the drugs have not yet been tested on people," Peter Bellermann, NNFF president, said. "Many drugs that inhibit angiogenesis have successfully treated tumors in mice, but have not been as helpful in treating tumors in people. However, this area of research is encouraging and worth continued examination for its potential benefits for people living with NF."

PEN PALS Wanted

I'm a 15 year old who would like to talk and become friends. Jonathan Armstrong@juno.com

I will write to anyone with NF1 or 2, I'm 52. Bobbie Keyes, 209E Broadway, Seminole, OK 74868

Thirty year old with NF is unsure about having children. Chris Farinella, 3619 Parkview Dr., Bensalem, PA 19020 or Cfirefly@aol.com

23 year old with NF2 & acoustic neuroma will reply to all. Theja Williams, POB 4731, Jackson, MS 39296.

I am 52 with NF1 and would like to hear from other adults. Winefred Montalvo, 252 56 St., Brooklyn, NY 11220.

I'd like a pen pal. Marc Nicholls, 2630 N. Pacific Hwy., Woodburn, OR 97071.

27 year old would like a penpal in Alabama. Scott Jarmon, 1050 Blue Bend Rd., Albertville, AL 35951-5514

I'd like a penpal who doesn't have NF, but has children who are affected. Luci Schiro, 1702 W. 6 St., Brooklyn, NY 11223

I would like to talk to young men, like me, and women in their 20's who have NF. Elijah Washington, 2611 W. Vineyard, Tempe, AZ 85282

Please write. Jennifer Dunlop, 2526 Bob White, Mesquite, TX 75149

My 15 month old has NF, would like to talk to other parents. Cincalme@aol.com

A father of 4 would like to talk to others. s.clawson@worldnet.att.net

Anyone who needs to talk write me. fourkons@juno.com

39 year old woman would love to hear from others. rgorski@epix.net

I'm 35 and would like some penpals. John Keith, 302 Stoney Brook, Fultondale, AL 35068

I'm a 30-something computer nut. Please write. Keith Keller; 1497 H Ave., Ladora,
IA 52251-7521