DURING THE PAST MONTH, THE Registry staff has been busy with a different kind of task. When the Foundation was first formed in 1995, it drew upon its scientific, ethical, and legal experts to form a Registry. The confidentiality protections of Registry members included that their names would never be given to a researcher or pharmaceutical company. Furthermore, the Foundation itself would not be able to access the names of Registry members. Thus, the Registry would be centered in a University with expertise in Alpha-1 as an independent agent of the Foundation. The Medical University of South Carolina has held that distinction since 2000.

The Registry currently has three research coordinators who are trained in Registry policies and procedures. These individuals sign a non-disclosure statement that information learned through the Registry will never be passed to others. Although the main database resides in Charleston, copies of the database on laptop computers have been made available to the coordinators at offsite locations. You may have seen the Registry coordinators with a computer at Alpha-1 Education Days, allowing you to update your record in person. This month a Registry member questioned whether Registry confidentiality is jeopardized by having the database ever leave the Registry center in Charleston.

One of the wonderful aspects of working for the Alpha-1 Foundation is that problems and concerns have a thoughtfully conceived method for resolution. Most of you know that governance of the Foundation is by individuals with Alpha-1 who sit on every working group. From inception, the Registry has had an Oversight Working Group that was quickly made aware of the concerns. Problems that might touch on ethical concerns are also channeled to the Ethical, Legal and Social Implications (ELSI) Working Group.

As this edition of the Registry newsletter goes to press, laptops and all copies of the database have been pulled back to Charleston until deliberations concerning the confidentiality risks are complete. You will be informed about the outcome of these discussions.

Unfortunately, we live in an age where the privacy of medical information has few protective Federal laws. One purpose of this letter is to highlight what is done to protect your information in the Registry and allow those of you who did not know the confidentiality procedures in place to become familiar with our policies. We continue to feel that the Alpha-1 Research Registry excels as a model of patient education and research facilitation and are confident that no breach of confidentiality has occurred to date.

This edition of the newsletter highlights the Alpha-1 liver programs. We often get complaints that the liver disease community is never included with the same enthusiasm that the lung disease community enjoys. My spin is that none of us get the recognition we deserve in this rare disease that too few know about. We need to have a unified voice to advance rare disease research. Take time today to tell a friend about Alpha-1 and enjoy this edition of the newsletter.

Sincerely, Charlie Strange
Alpha-1 Foundation Update
by Silvana Rodriguez, Alpha-1 Foundation

Since the Registry Update was last issued in the spring, the Alpha-1 Foundation has continued its efforts to attract leading international investigators and clinicians to cutting edge Alpha-1 research efforts through increased sponsorship of research studies and clinical trials, organization of international scientific conferences, and innovative research initiatives.

This increased sponsorship of research has had a major impact on not only advancing our knowledge of Alpha-1, but in attracting the best scientific minds to resolving problems related to Alpha-1. Since 1995, more than $10 million has been funded in Alpha-1 research and programs, including grants and awards to over 31 institutions throughout the world. The level of sponsored research in Alpha-1 is at an all-time high and holds much hope for development of viable therapies and the future health of individuals diagnosed with Alpha-1.

Research & Funding
The Alpha-1 Foundation is profoundly grateful to the Fundación Leopoldo Fernandez Pujals for its ongoing dedication and commitment to research. The Fundación has provided annually renewed funding in the amount of $1 million. To date the Alpha-1 Foundation has received $3 million as core funding for liver related research of Alpha-1 Antitrypsin Deficiency. The Foundation, in turn, has fulfilled its commitment to the Fernández by securing matching funds including ALF, AASLD, NIDDK, and other sources.

Meetings, Conferences and Workshops
Critical Issues Workshop Series named after Gordon L. Snider

The Alpha-1 Foundation Board of Directors has named its Critical Issues Workshop Series after Gordon L. Snider, M.D. in recognition of his distinguished service to the Foundation and his many contributions to the field of pulmonary medicine.

- Recent and upcoming meetings organized by the Foundation:
  Epidemiological Aspects of Alpha-1 Antitrypsin Deficiency, November 14 – 15, 2002, Charleston, SC.


- Gordon L. Snider Critical Issues Workshop No. 6, Environmental, Occupational and Genetic Risk Factors for Alpha-1 Antitrypsin Deficiency, August 19, 2002, Research Triangle Park, NC.
In addition, the Foundation has provided support for the following meeting:
Management of COPD in the Pacific Rim: A Bridge to Tomorrow, January 10-12, 2003 in Waikoloa, Hawaii. This international conference seeks to improve understanding of COPD in the Pacific Rim and the disease burden impact of COPD. The scientific program includes presentations on the societal, economic and familial impact of lung disease, and reviews existing resources such as disease management programs for COPD patients in Pacific Rim countries. The conference brings together international investigators and draws upon the expertise of both local and global experts in the management of COPD. For more information about the conference visit http://www.thoracic.org/copdbrochure.html

Advocacy & Public Policy
Miriam O'Day continues to work diligently in the Washington area to promote and highlight Alpha-1 awareness among legislators and to ensure that relevant issues are evaluated for their impact on the Alpha Community. She actively participates in a number of advisory committees; some of her recent activities on behalf of the Foundation are detailed below:
A unanimous resolution by the Department of Health and Human Services, Advisory Committee on Blood Safety and Availability was recently passed that highlights the need for special attention for the reimbursement of plasma-based therapies. The Advisory Committee recommended to Secretary Thompson that plasma derived therapies such as Prolastin® receive adequate reimbursement in the hospital outpatient setting.
The Alpha-1 Foundation provided testimony to the Committee requesting action in the form of a resolution and illustrating the impact on Alpha-1 patients, including a detailed cost analysis. The resolution is aimed at ensuring patient access to care. Testimony was also heard from numerous individuals receiving plasma-based therapies. The Foundation commends the Advisory Committee and its members for taking action on behalf of all plasma consumers. The Foundation is pleased that John W. Walsh was reappointed to serve a second term on this important committee. The Secretary’s response to the Advisory Committee recommendation and the impact on CMS rule making are eagerly awaited.

Initiatives
COPD Initiative
Alpha-1 Foundation has joined the U.S. COPD Coalition in its effort to build a network of organizations to increase awareness of Chronic Obstructive Pulmonary Disease (COPD) and improve prevention, diagnosis, and care.

Last November, President Bush reaffirmed the importance of COPD awareness by proclaiming November National COPD Awareness Month. This effort has enabled the union of organizations to raise the profile of COPD and work to designate November as National COPD Awareness Month each year.
The Alpha-1 Foundation has also teamed up with the American Lung Association, American Association of Respiratory Care and Bayer Corporation to create awareness of COPD and Alpha-1 among physicians and the general public. For more information on the efforts of the U.S. COPD Coalition, visit: www.uscoped.com.

Florida Detection Campaign
The Alpha-1 Foundation is now embarking on the third year of the Florida Awareness and Detection Campaign with additional funding from the State of Florida. It is the Foundation’s goal to reach as many individuals at risk for Alpha-1 as possible. Free test kits are therefore made available through this campaign for the general public and the healthcare community.

Carol Motsinger, the newly appointed Campaign Coordinator, encourages Alphas and supporters of the Foundation to bring Alpha-1 test kits to their physicians. The goal of the Campaign is to test 3,000 individuals with COPD by the end of 2002.

For more information about the Campaign, confidential Alpha-1 testing or to receive a free test kit, please contact Carol Motsinger, Campaign Coordinator, 1 (888) 825-7421, ext. 246, or cmotsinger@alphaone.org.
Announcements
FDA Special Citation

John Walsh, Founder, President and CEO of Alpha-1 Foundation, was recently presented with the Food and Drug Administration (FDA) Commissioner's Special Citation for pioneering collaboration between drug sponsors, patient groups, and FDA review divisions in order to facilitate patient contribution to the FDA regulatory process in drug development. FDA Deputy Commissioner Lester M. Crawford and Dr. Marlene Haffner, Director Office of Orphan Drug Products Development, presented the Special Citation to Walsh, citing Walsh's outstanding personal commitment and contribution to improving the quality and accessibility of healthcare to his fellowmen.

Appointments

The Alpha-1 Foundation is pleased to announce the appointment of Bruce C. Trappell, M.D., as Scientific Director. In this newly created position, Dr. Trappell will provide scientific leadership for the Foundation's research program, and will help in the organization of national and international scientific meetings, as well as provide advice and scientific input relating to public policy issues. He will also continue as Chair of the Foundation's Grant Program Advisory Committee and Grant Review Working Group.

Robert (Sandy) Sandhaus, M.D., Ph.D., F.C.C.P., has been appointed Clinical Director and Executive Vice President. Dr. Sandhaus will coordinate clinical activities with clinical sites and serve as liaison to clinical investigators and the Foundation's Working Groups.

Alpha-1 DNA & Tissue Bank.

The Alpha-1 Foundation DNA & Tissue Bank, housed at the University of Florida (UF) College of Medicine, is now ready to move into phase 2 of its operations. The Tissue Bank Director, Mark L. Brantly, M.D. and his research staff have completed their application to the University of Florida Institutional Review Board for approval to acquire tissue samples for the Bank. Institutional oversight is required for all human subjects research, so approval of tissue acquisition activities means that tissue removed during surgery or transplantation can be donated to the Tissue Bank (with the patient's permission). This phase of the Tissue Bank program at the UF will serve as the template for establishing collaborations with other transplant centers in the U.S. to obtain tissue from Alpha-1 Antitrypsin Deficient individuals. The goal is to collect 1,000 DNA and tissue samples from AAT Deficient individuals. To date, over 200 samples of DNA have already been collected and are stored in the Tissue Bank.

This Bank also serves as a model for other organizations where ownership of tissue and DNA is retained by a not-for-profit foundation on behalf of a patient community, and managed by a university-based research program. This arrangement ensures that patient rights to privacy are respected and that use of the tissue will only be for valid scientific purposes. The Bank is operated under a management contract with UF and, according to the rules of the IRB and oversight from the Foundation's Tissue Bank Advisory Committee, samples will be made available to investigators throughout the world. The establishment of this Bank is a significant milestone for the Alpha Community and removes a critical impediment to research on the pathology of AAT Deficiency.
The Alpha-1 Foundation has provided $10.4 million in sponsorship for over 34 projects and programs since 1998. The Foundation is currently funding 20 research projects at 18 institutions. These include projects in the areas of basic, clinical, and translational research and include studies on the epidemiology of liver and lung disease, social and ethical aspects related to AAT Deficiency, and various therapeutic approaches for the treatment of the clinical manifestations of AAT Deficiency. The Foundation’s Research Portfolio now includes studies on every possible aspect of Alpha-1 Antitrypsin Deficiency, giving us ever greater hope that together these studies will lead to new therapies and a cure.

Projects funded in the Spring of 2002 include research investigating the impact of Alpha-1 on families, the use of stem cell therapy for Alpha-1, and studies examining the underlying causes of cell transport in the liver and cell death and its impact on lung inflammation. In addition, a clinical study has begun to examine the impact of heterozygosity for Alpha-1 and liver disease. Brief descriptions of each of these projects follows:

Dr. Eugene Schiff, University of Miami School of Medicine, is conducting a clinical study to determine what percentage of individuals with liver disease has abnormal AAT alleles. The study will also seek to determine if the severity of a liver disease from various causes is made worse by being a carrier for only one abnormal AAT allele.

Dr. Richard Sifers, Baylor College of Medicine, is conducting a laboratory study exploring the basic mechanisms of PI Z AAT disposal in the liver. His study examines an early biochemical process that is necessary to break down and dispose of mistranslated AAT protein. When the disposal mechanism doesn’t work properly, the accumulation of the undegraded protein is thought to lead to toxicity and liver injury. Pinpointing the precise mechanism of disposal may lead to an understanding of how to prevent or treat liver injury at a much earlier stage in its development.

Dr. Welsh, Louisiana State University, is conducting a laboratory study on the potential of pluripotent cells from adult bone marrow as a therapy for individuals with AAT Deficiency. He hypothesizes that use of marrow stromal cells may lead to tissue regeneration in the lungs as well as serve as a delivery system for the prolonged delivery of AAT. The long term aim of such studies is to identify a therapy for emphysema due to AAT Deficiency.

Dr. Joanne Fanos, California Pacific Medical Center, will be conducting a survey among Registry enrollees to assess the psychological impact on families of having a sibling affected by Alpha-1 and the implication for brothers and sisters of diagnosed Alphas about their own genetic status. The survey will help establish whether siblings understand test results and the genetics of AAT Deficiency, if they want to be tested themselves and how it is affecting them psychologically.

Dr. Jung Hwa Lee, Postdoctoral Fellow in Dr. Mark Brantly’s laboratory at the University of Florida College of Medicine, is comparing the processes leading to inflammation in the lower respiratory tract to see if Alpha-1 lowers immunity. This would explain why those individuals with Alpha-1 get lung disease more often than those with usual (not inherited) COPD. Her study will examine several related cellular processes and compare these processes between normal individuals, those with COPD and those with COPD from Alpha-1.

Dr. Rubin Tuder, the Johns Hopkins University School of Medicine, is investigating whether disruption of normal cellular maintenance processes in the lung leads to cell death and emphysema. He is also examining whether AAT can protect against oxidative stress, such as is caused by cigarette smoke. If successful, it is felt these studies may have a tremendous impact on our understanding of the basic mechanism of emphysema and may lead to the identification of precise targets of therapy for the disease.
The Alpha-1 Foundation Liver Task Force
by Mark Zern, M.D., and Charlie Strange, M.D.

A new physician/scientist collaborative has been developed within the Alpha-1 Foundation to better serve the liver disease community with targeted research on Alpha-1 Antitrypsin Deficiency. The first goal of the liver task force is to facilitate an increase in the number of liver disease research proposals that are developed. A second initiative is to review the balance of liver disease research between basic science initiatives and clinical studies.

Basic science initiatives include studies investigating the fate of non-secreted Alpha-1 Antitrypsin (AAT) protein within the liver cell where it is made, and the subsequent mechanisms of liver cell damage caused by AAT build up. By understanding the response of the liver cell to non-secreted AAT, ways to prevent or repair damage to the liver cell can be developed.

The perfect solution lies in clinical studies seeking to improve the transport of abnormal Alpha-1 Antitrypsin protein from the liver cell into the bloodstream. The first ‘chemical chaperone’ clinical trial is underway at the University of Florida in Gainesville to investigate the effectiveness of 4-Phenyl Butyrate or 4-PBA in aiding the exportation of AAT from the liver cell. Results on this study have not been reported. However, aside from the drug’s effectiveness, most of the liver disease community feels that the information gained from liver biopsies about the rate of liver disease progression will be an enlightening outcome of this study.

Very few human research studies in Alpha-1 liver disease, such as the 4-PBA trial, have been performed to date. An important goal of the Task Force is to determine which studies in liver disease will be likely to yield meaningful results. Future candidate studies seek to determine what makes some Alphas develop severe liver disease, while other individuals seemingly maintain normal liver function. Comparing groups of individuals with severe liver disease to age matched Alphas without liver disease is the best way to perform these studies. The range of comparisons can include other genes, other liver diseases, and/or intensity of environmental exposures. Critical to such studies are an accurate assessment of all possible causes of liver damage. Just because there is some liver damage and you have Alpha-1, does not mean the Alpha-1 is the only cause of disease. Only after screening for all the other liver diseases, can the effect of differences in alcohol, diet, or environmental exposures be assessed. An analysis of the liver-affected Alpha-1 Research Registry participants is being planned to begin to understand the natural history of Alpha-1 liver disease. If you get a phone call in the next few months from the Registry, please give of your time to help understand liver disease in our community.

Another set of studies is being planned to determine the natural history of the liver cells in Alphas without clinical liver disease. At the present time, nobody knows what intermittent elevations of blood tests of liver enzymes means in some Alphas and whether liver damage accumulates gradually or suddenly after stress. These studies will require liver biopsies, where a needle is passed into the liver to obtain a tissue sample to investigate liver cell function.

Also in the planning stage is an initiative to team with liver transplant centers in the United States to obtain liver tissue from the diseased livers of Alpha-1 trans-
point. Also, it is small, a limiting factor in some situations. Other viral vectors are being developed and studied in the laboratory. Non-viral vectors are also being developed as vehicles for gene transfer. Lipids (fat molecules) and proteins containing the DNA have also been engineered and are being studied. Different vectors have unique characteristics and different diseases have varying target properties. The problem is to get the right vector to safely and efficiently transfer the normal gene to the desired target. The development of a growing number of and variety of vectors is encouraging and necessary for the advancement of gene therapy.

**Place of Transfer**

The characteristics of the target-cell and the specific goal of therapy determine the place of delivery. Gene transfer may take place outside or in the patient's body. In ex vivo gene therapy, cells are removed from the patient's body and the normal or healthy gene is introduced into the cells. Once the transfer has taken place, the cells are then returned to the body. This can only occur when the target cell is capable of being reintegrated into the body. An example of this is removal of bone marrow, infecting the stem cells of the bone marrow with the vector, and then injecting into the blood stream as was done in patients with SCID. In contrast, gene transfer for cells of the bronchial epithelium of the airways of patients with cystic fibrosis must occur in vivo, that is within the body. A vector under study for this disease is being administered by inhalation. In diseases where the missing protein is normally secreted into the bloodstream, a vector with the necessary gene may be injected into muscle cells stimulating the cells to make the protein and secreting it into the bloodstream.

**Ultimate Goal of Gene Transfer**

The ultimate goal of the transfer is for the replacement gene's coded (DNA) information to be incorporated into the targeted cell and to function as it is supposed to function to ameliorate or cure disease. The focus of clinical trials in gene transfer to date is on making corrections, replacing or manipulating the somatic (non-reproductive) cells, correcting the disorder within the individual. The genetic information of somatic cells is not passed on to offspring. Thus the genetic disorder may still be passed on to the offspring.

**Application of Gene Therapy**

Our knowledge of genetics has increased rapidly with the Human Genome Project and many different disease-causing genes have been found. Researchers have encountered many problems. Scientists are working hard to understand the processes of the diseases and the viral and non-viral vectors in order to develop vectors that will provide safe and efficient gene transfer. Researchers, agencies and federal regulatory agencies are working to provide the optimal clinical design for gene transfer carried out in a responsible manner.

More than 500 clinical gene-therapy trials involving about 3,500 patients have been identified worldwide (June 2001; 78% in the United States and 18% in Europe²).

The vast majority of trials are for cancer. French researchers and more recently English researchers report having successfully treated young boys with a disease called severe combined immune deficiency (SCID). Most of the human clinical trials involving gene transfer, however, are still in the early stages of research.

**Development of Gene Therapy for AAT Deficiency**

Investigators at the Powell Gene Therapy Center at the University of Florida have developed a new Alpha-1 Antitrypsin (AAT) gene therapy vector, utilizing a gene vector adeno-associated virus (AAV) that appears to be effective when injected directly into the muscle. Previous studies of this vector in animals have been very encouraging, in that a single injection of the vector into the muscle appears to lead to very prolonged production of the normal AAT protein. The regulatory review process governing human trials is long and complex, but all animal studies performed to date have been reassuring with regard to the potential safety of this agent, indicating that it may be suitable for use in future trials.


For additional information on these programs, please contact: Terence R. Flotte, M.D. Nemours Eminent Scholar Professor and Chair of Pediatrics, U of FL College of Medicine Margaret Humphries, R.N. Coordinator, Clinical Programs, U of FL Powell Gene Therapy Center
plant patients. Tissue in the Alpha-1 Foundation DNA & Tissue Bank in Gainesville would then be available for researchers to study with a variety of tools to understand the disease process better.

Although the majority of affected Alphas have lung disease, the importance of studying the liver should be understood by all of us since long-term cures for the disease might best occur by treating the liver. Although all of us want a cure now, the best way to get there is a comprehensive understanding of both the clinical and molecular bases of this disease. At the Alpha-1 Foundation we know the liver is important.

Scan of a liver

**RESEARCH UPDATE**

**New Developments in Gene Therapy**

by Margaret Humphries, R.N., UF Powell Gene Therapy Center

Gene therapy is the transfer or delivery of normal or healthy genes to replace, manipulate or supplement non-functional or malfunctioning genes\(^1\). Genes are located along chromosomes in the nucleus of the cells of our body. Genes are composed of deoxyribonucleic acid (DNA) carrying the code or instructions needed to make the proteins in our body. It is estimated that we have 30,000 to 60,000 genes. Nonfunctional or malfunctioning genes contain damaged DNA, lacking the instructions to produce the proteins needed and, depending on the seriousness of the damage, may cause disease. Some diseases have been identified as being caused by the deficiency of a protein controlled by a single gene; examples are cystic fibrosis, severe combined immune deficiency (SCID), sickle cell anemia, hemophilia, and Alpha-1 Antitrypsin Deficiency. Most diseases, such as diabetes and asthma, however, are caused by a complex interaction of more than one gene along with environmental factors. Even the diseases identified as being caused by one particular gene may be influenced by other genes and environmental factors varying severity or symptoms from one individual to another. Gene therapy at its essence is relatively simple. By supplying a good copy of the gene that encodes for the protein to the cell, the problem in theory is solved. This is often easy to do to cells in the Petri plate in culture in the laboratory. It is, however, more difficult to reproduce that gene transfer in an intact living person.

**Vehicles of Transfer**

In order to do that we need a carrier or "vector" to insert the normal gene into the cell. Usually viruses are used as the vehicle to carry the gene as they are very efficient in obtaining entrance into our body cells. They have evolved mechanisms for efficient gene transfer. The virus is altered to carry the good gene and to hopefully retain fewer of the potentially pathogenic or undesirable properties of the virus. The viruses do though retain important properties of the virus from which they were made. Many of the earliest gene transfer experiments were done with retroviruses and required cells to be actively dividing to work and so the vectors still required the cells to be actively dividing to work, limiting their use. The adenovirus vector, although altered to retain fewer properties of the virus, can cause inflammation. Another virus, the adeno-associated virus (AAV), is a common virus that infects people but does not make them sick. It does insert its genes into cells in a way that last for a very long time. These characteristics make it very useful in gene transfer. The AAV vector does not appear to cause inflammation or other immediate side effects, but the use of this vector system in humans has been very limited up to this
From the Patient Perspective
by Bob James

When the Registry Staff comes across someone who the Foundation has touched in a personal way we occasionally ask them to write an article for the Registry Newsletter. — C. Strange

We've Come a Long Way

In 1995 the doctor said, "You've got Alpha-1 Antitrypsin Deficiency, a very rare genetic disorder. You have lost approximately 60% of your lungs to emphysema and you are in end-stage liver failure. You need to have a liver transplant within six months to live." Here I am seven years later, a survivor of a liver transplant and witness to exciting progress in the focus on research and awareness for this disease.

When I was diagnosed, I was phenotyped MZ with an AAT protein level of 20 micro-molar. A liver biopsy confirmed that Alpha-1 Antitrypsin Deficiency (Alpha-1 or AAT Deficiency) had caused me to develop liver disease and emphysema. The question was, "How could that be?" All the research to date said only individuals with phenotype ZZ develop Alpha-1 related liver and/or lung disease. Over the last seven years, I have attended numerous educational conferences about Alpha-1 and have carefully watched as the opinions of experts in Alpha-1 have changed and evolved.

In the early days I sat in total amazement hearing experts proclaim that MZs were only carriers (Alpha-1 Carriers) of one abnormal AAT gene and were never affected. Never is a very strong word and here I was as living proof of the disorder.

Recently, things have changed. As our knowledge advances, it turns out that Alpha-1 liver disease can affect Alphas at any age and in rare cases, like mine, Alpha-1 Carriers can develop liver and/or lung disease. Most importantly, experts realize we don't yet know the whole story of Alpha-1 Antitrypsin Deficiency. Why do some people develop liver disease, but have normal lungs and others lung disease with seemingly normal livers? Why do Alpha-1 Carriers sometimes experience disease while some individuals with severe AAT Deficiency never show symptoms? Why do some people develop symptoms in childhood and others late in life?

The good news is that what we do know about AAT Deficiency is enough to work towards the cure. The source of the problem is the inability of abnormal AAT protein to exit the liver cell where it is made. Build-up of abnormal AAT protein in the liver cell causes liver damage and lack of AAT protein in the blood stream deprives tissues such as the lungs from AAT protection. It is now becoming clear that even though the majority of those affected by this devastating disorder have lung disease, the greatest potential for a cure for lung and liver disease alike lies in fixing the problem that originates in the liver.

Recently, the Alpha-1 Foundation has targeted more research dollars toward Alpha-1 liver disease. Notably the Alpha-1 Foundation is funding research by Peter Arvan, M.D., investigating the implications of accumulated AAT and Z-AAT protein in the liver. Mark Zern, M.D., is working to develop a human cell line to produce normal liver proteins including AAT. Jeff Teckman, M.D., is exploring how build-up of Z-AAT protein damages liver cells and the liver's response to such damage. Equally as exciting is a gene therapy study by Terry Flotte, M.D., and Sihong Song, Ph.D., to reprogram muscle cells to make normal AAT protein. We've come a long way.

It is also exciting for me that the Alpha-1 Foundation has implemented two very important targeted screening programs, the Florida Alpha-1 Screening and Detection Program and the Alpha-1 Coded Testing (ACT) Trial. The programs are designed to offer free testing for those at risk and confirm findings of gene frequency studies suggesting there are over 100,000 ZZ affected Alphas and 20 to 25 million of Alpha-1 Carriers in the U.S. I feel confirming these statistics will motivate more investigators to dedicate more time and resources to Alpha-1 research realizing the presence of Alpha-1 in the population is significant and that early detection, better treatments and the eventual cure will save lives.
What really hits home for me is the personal tragedy of Carol, Margaret, Larry, Bill and many other MZ and ZZ liver and/or lung Alphas that I have personally known, and interacted with while being an Alpha-1 Association Peer Guide. All these people have died of complications of Alpha-1. This terrible disease originates in the liver, but thanks to research fostered by the Alpha-1 Foundation we continue to learn more and Carol, Margaret, Larry and Bill’s children have hope for a cure in the future.

My personal mission is to spread awareness of Alpha-1 liver disease. Scientists are recently finding this complication of Alpha-1 Antitrypsin Deficiency is more prevalent than previously thought and unfortunately often overlooked. I challenge all of you, especially lung affected Alphas, to talk with your physicians about Alpha-1 liver disease and monitoring your liver carefully. Unfortunately, to date the only real cure for AAT Deficiency is a liver transplant, which restores normal liver function and AAT protein levels to the body. I look forward to the day an individual with Alpha-1 Antitrypsin Deficiency no longer must face a liver or lung transplant. Progress is being made. I believe that day is coming.

Genetic Discrimination Study
by Connie Ray Stockham, J.D.

Genetic discrimination in the workplace and health insurance coverage has been talked about and studied, federal legislation and state laws have been suggested yet evidence that genetic discrimination is actually occurring remains anecdotal. Until there is conclusive data, skeptics will not acknowledge it and without a clarification of the problem, risks of genetic discrimination will continue.

Terri Sergeant’s case publicized the fact that discrimination based on genetic information can occur. Recent studies by a variety of scholars suggest that such discrimination is occurring more frequently than the public realizes. These studies indicate that up to 23% of individuals affected by a genetic condition believe they have been discriminated against by being refused jobs or hired from current jobs because of their genes. Some believe they were denied health insurance or lost their health insurance for the same reasons. This striking figure is even more startling when you know that only three charges of genetic discrimination have been filed with the EEOC, ever. Terri Sergeant filed one of the EEOC charges. The other major charge that has received national attention is the Burlington-Northern Santa Fe (BNSF) case. BNSF chose to test their employees who had developed carpal tunnel syndrome in an effort to prove that their condition was pre-existing due to their genes and thus not covered by insurance. When the employees learned that they were being tested, they were outraged and filed charges with the EEOC. The EEOC granted a temporary injunction to stop the testing and BNSF eventually compensated the employees for this violation by paying a total of $2.2 million dollars.

Up to 23% of individuals affected by a genetic condition believe they have been discriminated against in the workplace.
One thing that is not clear is the reason that many individuals believe they have experienced discrimination while the number of charges filed is practically non-existent. Some scholars claim that the low number of complaints indicates that genetic discrimination is not happening. These two cases are viewed as mere accidents and the problem is not widespread. Our position differs. Absence of formal legal claims may be unrelated to the extent of genetic discrimination. In order to assess the frequency of the experience of genetic discrimination, documentation of the events is needed. Identification of the factors associated with the lack of formal complaints about perceived genetic discrimination is important in order to address the problem.

Regardless of the legal merits of these cases, the impact of the perception of discrimination is also an important social issue. Therefore, an important research question is to understand how discriminatory employment and insurance decisions affect the views and actions of individuals with genetic conditions. Many individuals attempt to protect their genetic information by requesting aliases at treatment centers and asking to be coded when they enroll in databases. Discrimination is not the only concern these individuals possess about revealing their conditions to others, but it is important to determine whether this concern is driving secretive behavior and what experiences the concern rests on.

We have submitted a grant application for funding to the Alpha-1 Foundation and will be soliciting enrollment in this study through the Alpha-1 Foundation Research Registry. The first area of study is a survey of the members of the National Employment Lawyers Association (NELA) concerning their experiences with genetic discrimination in the workplace. NELA members represent individuals with all manner of discrimination claims. Ours is the first study to specifically find out from the lawyers about what their experience with genetic discrimination cases is. We are interested to discover whether they have been approached with cases of genetic discrimination, what their perceptions of the merits of the case were, how they have counseled clients about these cases, and what remedies they have pursued, if any. The second area of inquiry will be to collect documentation of genetic discrimination events and explore the personal consequences of these experiences. We hope to determine the reason for the discrepancy in reported experiences of genetic discrimination and numbers of formal complaints. This information will help to demonstrate the magnitude of genetic discrimination that is occurring and suggest mechanisms to provide relief to those affected by it.
The Alpha-1 Foundation is pleased to announce the appointment of Bruce C. Trapnell, M.D., as Scientific Director on July 1, 2002. In this newly created position, Dr. Trapnell will provide scientific leadership for the Foundation’s research program, and will provide expert scientific advice on international scientific meetings, and public policy issues. He will also continue as Chair of the Foundation’s Grant Program Advisory Committee and Grant Review Working Group and participate in other Foundation Working Groups and Advisory Committees.

Alpha-1 Foundation President and CEO, John W. Walsh, says, “Dr. Trapnell has the experience, leadership skills and vision needed to help the Foundation achieve its goal of finding a cure for Alpha-1. These qualities will help him strengthen our research program and shape our agenda for the 21st century. Under his guidance the Foundation’s Research Portfolio has grown to become a productive and relevant program of basic and clinical research related to improving the health of individuals living with Alpha-1 Antitrypsin Deficiency.”

Deeply interested in genetic lung diseases, Dr. Trapnell has worked throughout his career to define the molecular mechanisms of lung inflammation and lung disorders and has published more than 75 original articles and 90 abstracts in the scientific and medical literature.

An internationally recognized expert in gene therapy, he was involved in the initial efforts at the NIH to develop in vivo human gene therapy for cystic fibrosis lung disease and was co-investigator on a human gene therapy clinical trial conducted at Cincinnati Children’s Hospital. He currently maintains an active, NIH-funded research program focused to mechanisms of lung host defense and lung gene therapy.

Dr. Trapnell first became involved with the Alpha-1 Foundation through his expertise in the scientific peer review process.

Previously, he served on scientific peer-review groups and as a site visitor for a number of organizations including NHLBI, NIDDK, General Clinical Research Centers, Cystic Fibrosis Foundation, Texas Advanced Research & Technology Program, and the Veteran’s Administration Merit Program.

He has been a member of the Cystic Fibrosis Foundation’s Research and Training Grant Review Group for more than ten years and is a current member of the their Data Safety Monitoring Board. Dr. Trapnell first represented the Alpha-1 Foundation by leading an international research review group for the Fundación.

Leopoldo Fernández Pujals. Subsequently, he was recruited to join the Foundation’s Medical and Scientific Advisory Committee where he helped form and now chairs the Foundation’s Grant Award Advisory Committee. He drafted the guidelines for the grant review program and then assembled an international team of scientists and clinicians into the Foundation’s first Grant Review Working Group of which he is the Chair. He has assisted in planning and the execution of various other scientific activities of the Foundation including national and international scientific meetings, preparation of progress reports and development of the Alpha-1 Foundation’s internal and public policies.

Dr. Trapnell may be contacted by electronic mail at Bruce.Trapnell@chmcc.org or by phone at (513) 636-6361.
Q: Why do some people have "S" Alpha-1 genes and what do they mean?

A: The alpha-1 antitrypsin (AAT) gene codes for the "normal" alpha-1 antitrypsin protein in approximately 96% of persons in the United States. The normal or "M" protein does many things in the body, the most important being to protect the lungs from the effects of proteins called elastases. Scientists are still trying to figure out many of the other effects of "M" alpha-1 antitrypsin.

At some time in the distant past, one piece of the DNA that makes up the AAT gene was changed. This single difference in the DNA gave the AAT protein a different shape. The two most common different AAT proteins are the "Z" protein, that is often the subject of discussion in the newsletter and the "S" protein.

"S" alpha-1 antitrypsin protein has one major problem. Just like the "Z" protein, it cannot get out of the liver as well as the normal "M" protein. Therefore blood levels are lower than normal (although not as low as in persons with the Z protein) and are determined by how many copies of the S gene are present.

Remember that we get one AAT gene from our mother and one from our father so the phenotype possibilities that include the "S" gene are Pi MS, Pi SZ, and Pi SS. I will talk about each of these combinations separately, although all of these share the common theme that one or more of the "S" genes can be passed to our children.

Pi MS individuals have nearly normal levels of AAT protein. No increase in risk for health problems has been proven in this population although some studies have suggested an increased risk for asthma. These studies that would prove an increased risk for asthma are difficult to do since asthma is very common in the U.S. with about 6% of the entire population affected. Asthma patients often cough and wheeze when lung irritants are inhaled. The good news about asthma is that symptoms are controllable and the disease does not lead to a shortened lifespan.

Pi SS individuals are very rare. Since the "S" gene is even less common than the "Z" gene, there is very little information available about the health effects of the condition. What is clear is that the levels of alpha-1 antitrypsin protein in the bloodstream are higher in individuals with Pi SZ suggesting the frequency of lung or liver disease should be much less.

Pi SZ individuals can have severe deficiency of alpha-1 antitrypsin. They are at increased risk for emphysema with cigarette smoking, although individuals with a smoking history may have normal lungs. Very little is known about the risk for liver disease although an occasional case of cirrhosis (liver scarring) is seen. Since emphysema can be progressive in SZ disease, some individuals have decided, with their physicians, to begin augmentation therapy with Prolastin®, particularly if their AAT levels are at the lower end of the range of most Pi SZ individuals. As always, we welcome individuals with deficient phenotypes or carriers of the S gene to become members of the Alpha-1 Foundation Registry.
Advocacy Victory
Alphas are Heard on Capitol Hill
by Miriam O'Day

Over 150 people attended the first Alpha-1 Advocacy Day in Washington, DC, on June 6, 2002. They powerfully advocated for access to care for individuals with Alpha-1. On November 1, 2002 the Centers for Medicare and Medicaid Services (CMS) ruled that outpatient payments for Alpha-1 will be based on a "reasonable cost basis" ensuring patient access to care. This ruling restores the cuts which were implemented in April and guarantees adequate reimbursement in the outpatient setting for Alphas beginning January 1, 2003.

The CMS regulation indicates that the Alpha-1 message was delivered and received. A hard fought battle has been won.

Both Rare Disease bills which were the focus of Advocacy Day have passed the House and the Senate and are expected to be signed by the President in early November.

Advocacy Day participants included Alphas, family members, health care providers, industry guests, volunteers, and staff, who called on Congress to ensure that individuals living with Alpha-1 have access to their sole therapy, hope for the development of new therapeutics, and increased Federal investment in rare disease research. At individual meetings with members of both the U.S. Senate and House of Representatives, Alpha-1 advocates told their story and stressed the importance of supporting policies that improve the lives of those living with chronic disease.

The Reserve Officers' Association overlooking the U.S. Capitol served as the prestigious headquarters for Advocacy Day. Attendees participated in a morning education and training program with guest speakers, Paul Billings, American Lung Association, Diane Dorman, National Organization for Rare Disorders (NORD), and The Honorable John S. Reid, State Delegate from Virginia. Fellow Alphas Fred Walsh and Cathy Valenti gave a presentation on Alpha-1 Medicare reimbursement and headed up a question and answer period improving knowledge of the issues for afternoon Congressional meetings.

Special awards were presented to members of Congress who have made contributions to improving the health care needs of individuals suffering with lung disease. Congressman Jim Ramstad (R-MN) was honored for his leadership in healthcare legislation and deep commitment to individuals with Alpha-1. Congressman Ramstad was the first to sponsor a letter stressing the urgent need for adequate Medicare reimbursement for plasma-based therapies.

Congressman Joe Pitts (R-PA) quickly joined Mr. Ramstad as a co-sponsor of the letter that was sent to all Members of Congress for support. Following Advocacy Day the Ramstad/Pitts letter received 36 signatures from republican and democratic Members of the House of Representatives and was sent to Tom Scully, Administrator, Centers for Medicare and Medicaid Services (CMS). The signatures on the letter signify the commitment obtained by our advocates while visiting Capitol Hill and in subsequent communications with Congressional offices.

Accepting the award for Congressman Ramstad, Michelle Mackey stated from the podium that individuals suffering from rare diseases such as Alpha-1 do not suffer any less then individuals with well known disorders such as Parkinson's or Cancer, in fact they probably suffer more, as a result of delayed diagnosis and limited
therapies. The award was presented by the Minnesota delegation and constituents Judy and Ed Schuck, Board of Directors, Alpha-1 Foundation.

Congressional awards were also presented to: Michael Bilirakis (R-Fl) for health policy leadership; Cliff Stearns (R-Fl) and John Lewis (D-GA) were recognized for their co-sponsorship of the Chronic Obstructive Pulmonary Disease (COPD) Proclamation. Additional awards were presented to Diane Dorman, NORD, for excellence in public policy, and Julie Birkofe, Plasma Protein Therapeutics Association, for fostering consumer and industry collaborations.

A full-page ad was taken out in the June 6 issue of Roll Call, the newspaper of Capitol Hill, which raised awareness and educated Members of Congress about Alpha-1. The struggles faced by Alphas as a result of recent cuts in Medicare reimbursement was described in the ad: “She knows why it’s so hard to breathe. Now explain why her life-line is being squeezed.” The accompanying photo had significant impact featuring an Alpha who is a Medicare recipient and using oxygen. Readers were made aware that Medicare sets the national trend for all private insurers eventually impacting all Alphas. The Roll Call ad accompanied our Advocates into their Congressional appointments.

Comments from attendees were overwhelmingly positive with many noting the empowerment they felt through addressing the issues they face with people who can positively impact health policy.

Advocacy Day was co-sponsored by the Alpha-1 Foundation and Alpha-1 Association. Bayer Corporation, AlphaNet, and Aventis Behring provided generous corporate sponsorship.

**What did we ask for on Capitol Hill?**

Why did over 100 Alphas and their families travel to Washington, DC to highlight “Access to Care” in Congressional meetings? In April 2002 Medicare reduced benefits for the treatment of Alpha-1 and proposed additional cost containment for 2003. Advocacy Day provided an opportunity to request that members of Congress take action on behalf of the Alpha-1 Community as CMS reclassifies the sole therapy for the treatment of Alpha-1.

**Medicare Reimbursement:**

- Advocates requested Congressional support for the Ramstad/Pitts letter to CMS Administrator Scully.
- Advocates requested Senate support for a “Dear Colleague Letter.” Following Advocacy Day many members of the Senate wrote to Administrator Scully. Senator Santorum (R-PA) initiated a letter and asked all members of the Senate to join him.
- Advocates asked for an Alpha-1 specific cost study that would provide government sponsored data and protect Alpha-1 treatment from extreme cost reductions. Because Alpha-1 is a rare disorder, CMS review of hospital claims data does not represent the true cost of treatment for Alpha-1. The cost study was also designed to explore a home health care benefit for Medicare beneficiaries.

**Rare Disease Funding:**

- Advocates requested support for HR 4014, which doubles the budget for the FDA, Office of Orphan Product Development (OOPD) over the next four years. The OOPD will use the majority of this increase to fund clinical research grants. New treatments for Alpha-1, including gene therapy, may result from the doubling of the OOPD budget.
- Advocates requested support for HR 4013, which doubles the NIH, Office of Rare Diseases (ORD) funding over the next four years. The ORD was established in the early 1990s to meet the neglected needs of 25 million Americans suffering with 6,000 rare “orphan” diseases in order to stimulate and coordinate research in rare diseases.
National Education Conference in Washington, DC
by Silvia Moore

I was blessed this year by having the opportunity to attend, for the first time, the 2002 Alpha-1 Association National Education Conference at the Hilton McLean in Tyson's Corner, VA. I want to share the growth in community and informative sessions I experienced while being there. On Friday, June the 7th, 2002, I attended two receptions: The first one for Support Group Leaders and the second reception for Peer Guides. At the end of the day myself and other Alphas willing to help their newly diagnosed peers on a one-on-one basis were granted a Peer Guide Diploma. Both receptions were very emotional and masterfully guided by Sue Landers, who is in charge of both programs with the Alpha-1 Association. Just a humble suggestion, get involved! It gives you a new perspective and helps you realize you are not alone. It allows you to divert your attention from yourself to other Alphas, and you become part of a team, fighting for the same ideals and goals. This was a very special day for me.

That same night, Alphas who felt the need to honor one or more of our fellow Alpha Angels, attended the Memorial Service. Mrs. Sue Landers and Mr. Fred Walsh delicately and very tastefully hosted this event. Many people were remembered with a smile and beautiful anecdotes. We didn't mourn our Alphas that are gone; we honored them by recognizing the positive impact that they left in our lives.

Saturday, June 8th began with a session on healthcare rights presented by Richard McKeon, Ph.D., followed by break out sessions with a lung, liver and caregiver track. In the afternoon Mark Brantly, M.D.; Jeff Teckman, M.D.; and Edwin K. Silverman, M.D. chaired a panel on Alpha-1 clinical research. Topics of discussion included future studies designed to investigate the efficiency of chemical chaperones that may aid in the exportation of alpha-1 antitrypsin protein from liver cells, and the Harvard Sib Pair study directed by Dr. Silverman. The afternoon sessions were followed by a special awards banquet where Alphas, researchers and doctors were recognized for their important work. To name a few, Robert A. (Sandy) Sandhaus, M.D., Ph.D., was presented with the Physician Special Appreciation Award, and Symma Finn from the Alpha-1 Foundation was recognized with the Advancement of Research Award. Joe Reidy was given the Peter Smith Award and Len Geiger received the Claude Baril Communication Award. Much of the dinner was dedicated to a warm farewell to outgoing Alpha-1 Association, CEO. Sandy Brandley. Her 13 years of dedication to this community continue to have a great impact and we continue to miss her dearly.

Sunday, June 9th began with a very informative session titled, Dying Well, Reclaiming the Last Chapter of Life. Ira Byock, M.D., sensitively addressed this very difficult topic and expressed the importance of dealing with the issue we all must confront. The morning and mid- afternoon break out sessions included tracks geared toward liver disease, lung disease and Alpha-1 caregivers. Topics included nutrition for liver disease, pulmonary rehabilitation, transplantation, meditation and exercise. The Sunday conferences concluded with a session on disease management by Sandy Sandhaus, M.D., and Bonnie Boyd, B.S.N. A patient’s panel and closing remarks by Dennis Barbour, CEO of the Alpha-1 Association concluded conference events.

This meeting was fulfilling for me in many ways. I caught up with old friends and made new ones. I was reminded how important it is for us to gather together for support and to work towards common goals. I was delighted by the relevance of the speaker sessions and the applicability of topics, not only to my life, but also my peers. More details about next year’s conference in Chicago, IL are coming. Scholarships to attend may be available through the Alpha-1 Association, please contact them for more information 1-800-521-3025. God Bless.