LETTER FROM THE DIRECTOR by Charlie Steange, M.D.,
Medical University of South Carolina (MUSC)

WE ARE EXCITED TO REPORT THAT 2001 PROVED TO BE THE LARGEST ENROLLMENT
year in the history of the Alpha-1 Research Registry with 640 new members. In the last issue of
the Alpha-1 Research Registry Update we informed members of the Registry campaign "2002
By 2002" with a goal to reach total enrollment of 2002 members by the end of the year 2002.
I am proud to report we will meet the goal before the mid-year mark.

Much of the initiative to enroll members came from three sources. Many of you have had discussions
with your AlphaNet coordinators about the Registry and we extend our thanks to them for recognizing
the benefits of enrollment. The Alpha-1 Association sent invitation letters to the patient community
that generated large numbers of applications. Lastly, you may have seen a Registry representative at a
regional Alpha-1 Education Day where on site registration is very successful. To those of you who
have heard about the Registry from every one of these sources and are now tired of hearing the message
we apologize.

Registry growth means more recognition in the medical and scientific communities, which will
foster new and innovative research directed towards advancements in the knowledge and treatment of
Alpha-1. The achievement of our membership goal does not mean our efforts to enlarge Registry
enrollment will subside. We eventually hope to enroll 10,000 Alphas and Alpha-1 Carriers in the
Alpha-1 Research Registry. This means we still need your help to recruit family members to the
Registry. This Registry project will not only serve to enhance enrollment, but will broaden the potential of the
Registry to facilitate research by establishing groups of related Alphas willing to participate in cutting edge
genetic research. Genetic studies have the greatest potential to shed light on many unanswered questions
about Alpha-1.

Only the Registry Coordinator and myself will have access to test results. After test results are
received, participants are asked to fill out and return the two-page post-test questionnaire. Once the
Registry Center has received the

second questionnaire, identifying
information can be deleted from
ACT Trial records.

I hope you will encourage your
family to be tested for Alpha-1.
I feel the benefits of knowing
Alpha-1 phenotype outweigh the
risks and that an early diagnosis can
help your physicians recognize
early lung or liver disease symp-
toms. Family members, especially
young family members, are more
likely to become non-smokers.
This decision could be the single
most important health decision of
their life. Also, it is important for
parents to know their Alpha-1
status and be informed about the
chances of passing on deficient
genesis to their children. The advantage
of this opportunity for testing is
that your family members will
confidentially know their Alpha-1
status and be able to privately
handle important information about
their genes.

Continued on page 2
Please inform your family members about this unique opportunity for free and confidential testing. This research study is supported by the Alpha-1 Foundation and will be available for at least the next 18 months.

In this newsletter you will find the description of a new research opportunity from Edwin K. Silverman, M.D., Ph.D. at Harvard that is searching for brothers and sisters with ZZ phenotypes. Please take the time to read about this important study. Its goal is to identify other genes that influence COPD. If other factors are identified, it may explain why some family members have severe lung disease and others are seemingly immune from lung disease.

The Registry has responded to the initiative with an effort to link families in the Registry.

To be linked to other family members in the Registry you must return a Family Linkage application. The application asks you to make the initial contact with your family member(s) concerning Registry enrollment. If they agree to be contacted by the Registry through the mail we ask you to list their name and address on the Family Linkage application and return it to the Registry Coordinating Center in Charleston, SC. Recognizing that this process could create family pressure, no family member will be informed of another family members' enrollment status by the Registry Staff. For more information on this project or an application please contact the Registry Coordinator toll free, at 1-877-886-2383.

Since we enroll Alphas and Alpha-1 Carriers in the Registry you may have family members who want to participate in the Family Linkage project but don't know their Alpha status. We will again offer you the Alpha Coded Testing (ACT) Trial. This research project offers a free and confidential opportunity for coded finger stick testing through the Medical University of South Carolina. The ACT trial has proved to be a huge success over the past nine months. Over 1,500 test kits have been sent to people all over the U.S. Most people seeking testing have been family members of Alphas. We are pleased to serve this at risk group. For more information or a test kit please call the Registry Coordinator.

Another project we will embark on in 2002 is our data clean-up project. With some records dating back to 1997 we want to ensure that all records are accurate including an up-to-date mailing address and telephone number for each member. Please expect a call from Registry Recruiter Carol Deanes this summer to confirm contact information in your personal records.

We expect an increase in opportunities to participate in research as the Registry grows. I want to ask that you carefully consider all research invitations. In the past we have been notified that presentation of research projects to Registry members has greatly increased interest and participation in clinical studies. The Registry is only as good as the commitment of its members so let's keep up the good work. I will take this opportunity to thank you for your support of the Alpha Coded Testing Trial, the Family Linkage project and our enrollment goals. Your dedication is what makes our work a success!
Alpha-1 Foundation Update
by Symma Finn, M.A.

The Alpha-1 Foundation has made significant progress over the past six months in expanding major programs and creating new opportunities for progress towards a cure of Alpha-1. This includes increased support for research, organization of meetings, conferences and workshops on the most critical issues in the field; successful advocacy and public policy efforts; increased recruitment through targeted Alpha-1 testing programs; reorganization of its advisory committee structure; and solidification of its strategic alliances and collaborations with other consumer health agencies. Some significant achievements include:

Research Portfolio: The Alpha-1 Foundation currently funds over $8 million in research projects at more than 28 institutions in the United States, Canada, and Europe. This funding includes over $700,000 in matching grants with the American Liver Foundation, American Lung Association, as well as matching grants with the National Institutes of Health, National Heart Lung and Blood Institute, the American Thoracic Society and American Association for the Study of Liver Diseases. The Foundation's portfolio is comprehensive and includes research of both the lung and liver-related diseases associated with Alpha-1, genetic and gene therapy studies, economic and social impact studies, as well as basic science and translational studies (see page 5 for additional details of specific projects). The Foundation instituted a formal Grants Award Program in 2001 so that all funded research is scientifically peer-reviewed. The portfolio reflects the Foundation's research agenda and therefore includes significant funding for liver research, as well as funding for areas identified as "research gaps" or previously unexplored topics relating to Alpha-1.

Meetings, Conferences and Workshops: Recent and upcoming meetings organized by the Foundation include:

- Critical Issues Workshop #5 on Stem Cell Therapies in Reparative Medicine, April 19-22, 2002, Miami, FL that examined recent progress in this exciting new field and its potential as a therapy for Alpha-1
- American Thoracic Society (ATS) Clinical Symposium on Alpha-1, Genetics & Lung Disease Session (ATS-Public Advisory Roundtable), and the 5th Annual Research Forum on Alpha-1, May 18-22, 2002, Atlanta, GA
- Alpha-1 Advocacy Day, June 6, 2002, Washington, DC in conjunction with the Alpha-1 Association
- Ethical, Legal and Social Issues Working Group Meeting, July 2002, Denver, CO

In addition, the Foundation has provided support for the following meetings:

- 3rd International Symposium on Serpin Biology, Structure and Function, June 2-5, 2002, Chicago, IL
- Society of General Physiologists Symposium on Trafficking of Transporters, Sept. 4-8, 2002, Woods Hole, MA

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. Recent public policy priorities include:

- Research – insertion of appropriations language on Alpha-1; strengthening of the strategic alliances with National Institutes of Health and the Food & Drug Administration, and the Foundation’s participation as a member of genetic coalitions on specific issues
- New Therapeutics – ongoing interactions among the Foundation, FDA and NIH Liaison Group to fast track agency approvals and study design for CT scan research, ongoing participation on the Blood Products Advisory Committee
- Access to care, medical privacy, genetic discrimination – interaction with CMS on important social impacts relating to privacy, and various types of discrimina-
tion arising from a diagnosis of a genetic condition

- **Blood product safety (DHHS-ACBSA)** – ongoing participation on the Advisory Committee for Blood Safety and Availability and inclusion of issues relevant to Alpha-1 on the ACBSA agenda

**Alpha-1 Targeted Testing Program**: The State of Florida Department of Health and Human Services, the University of Florida College of Medicine, the University of Miami School of Medicine, and the Alpha-1 Foundation have been conducting a multi-year screening and detection program for Alpha-1 since 2001. Jointly sponsored between the State of Florida and the Alpha-1 Foundation, the Alpha-1 Detection Program is targeted to screen Florida residents who are at risk for Alpha-1 and to inform healthcare professionals about the necessity of testing for Alpha-1 as a standard of care. Please see the complete article in the newsletter on the Florida Screening Project for additional information.

**Reorganization of Advisory Committee and Working Groups**: The Foundation has recently instituted a reorganization of its scientific and medical advisory committee structure. Under the leadership of James K. Stoller, M.D., M.S.O.D.A., Chair, the new Medical And Scientific Advisory Committee (MASAC) is envisioned as a satellite structure with a central committee composed of the chairs of the Foundation’s advisory committees and working groups, and with the working groups as the spokes on the wheel. The reporting relationships remain the same, with the Advisory Committees reporting directly to the Board of Directors and the working groups reporting to the MASAC. This restructuring is designed to streamline the MASAC meetings as well as infuse the working groups with increased vitality and functionality by providing clear charges, deliverables and timelines. The advisory committees include the MASAC (Dr. Stoller, Chair), a Grants Award Program Advisory Committee (Bruce Trapnell, M.D., Chair) and the Alpha-1 DNA & Tissue Bank Advisory Committee (Jim Hogg, M.D., Chair).

Working Groups include Alpha-1 Research Registry Working Group (Jim Stocks, M.D., Chair), Clinical Resource Center WG (Alan Barker, M.D., Chair), Educational Materials WG (Robert Senior, M.D., Chair), Ethical Legal & Social Issues WG (Mark Yarborough, Ph.D., Chair), Grant Review WG (Bruce Trapnell, M.D., Chair) and the Screening & Detection WG (Edwin Silverman, M.D., Ph.D., Chair).

**Strategic Alliances**: The Foundation is proud of its progress in coordination with other health service agencies, organizations and foundations to create coalitions and strategic alliances that strengthen each individual organization’s voice in affecting public policy. In addition to participation in the Genetic Alliance, National Health Council, American Thoracic Society Public Advisory Roundtable and the ACBSA, the Foundation was recently appointed as representative of the Alpha Community to the US-COPD Coalition, under the leadership of Suzanne Hurd, M.D., World Health Organization, Global Obstructive Lung Disease program. To recognize the importance of these alliances, and the mutual goals of these organizations, the Foundation recently honored the Chief Executive Officers of the American Liver Foundation and the American Lung Association at a Recognition Dinner, held in conjunction with a Foundation Board of Directors meeting held in January 2002.

For more information, questions, or comments concerning the research programs and activities of the Alpha-1 Foundation contact Symma Finn toll free, at 1-888-825-7421.
Currently Funded Research Awards by Silvana Rodriguez

The Alpha-1 Foundation has funded more than $8 million in Alpha-1 related research since its inception in 1995 with programs at 28 institutions throughout North America and Europe. Funded projects include studies of Alpha-1 influenced lung and liver physiology, a new technique to measure lung function in Alpha-1 patients with emphysema, basic science studies investigating the likelihood of developing emphysema in genetically predisposed individuals, and a study seeking to create a bio-artificial liver to make normal AAT protein.

Principal investigators receiving grant awards in 2001 include Manuel Cosio, M.D., for a study investigating animal models of emphysema, and Alexei A. Guerassimov, M.D., Ph.D., for his study to identify genetic risk factors that impact progression of disease.

Other studies include projects by Sheng Song, Ph.D., to research large animal models using AAV vectors, a harmless virus which can insert normal genes into cells and reprogram those cells to produce normal AAT protein. This study will help determine the dosage and effectiveness of gene therapy. Robert Wachbroit, Ph.D., is investigating Alpha-1 Antitrypsin Deficiency and the Burden of Disease, a study to determine the applicability of the World Health Organization’s recently adopted approach to health assessment and the public health implications of health resource allocations for persons with Alpha-1.

Recent research grants for lung-related Alpha-1 investigations went to N. Gerry McElvaney, M.D., to study inflammatory processes in the lung and alternative anti-enzyme proteins that will protect lung tissue from cell damage. Patricia Mergo, M.D., will seek to develop a new CT scanning technique for determining loss in lung structure and function in Alpha-1 patients with emphysema. Funding was also awarded to Terry L. Spencer, M.D., for a study to better understand how the body’s defense mechanisms function in individuals with inflammatory lung disease related to Alpha-1.

Equally important to our total understanding of the impact of Alpha-1 are the projects being conducted by Peter Arvan, M.D., Ph.D., and Mark Zern, M.D., recipients of research grants for liver related Alpha-1 investigations. Dr. Arvan is investigating the implications of accumulated AAT and Z-AAT protein in the liver. Dr. Zern’s study is directed at developing a human cell line (referred to above as a bio-artificial liver) that will produce normal liver proteins including AAT. This investigation’s findings may be useful in treating both the lung and liver disease in Alpha-1. Other liver related Alpha-1 investigations that are being conducted include a study by Jeffrey H. Teckman, M.D. with a project that seeks to understand how AAT-Z damages liver cells and how the liver responds to this damage. Human liver tissue, animal model tissue, and other experimental tissues are being examined to investigate possible methods to reduce or block cellular damage.

A complete listing of funded research by the Alpha-1 Foundation and the National Institutes of Health can be viewed in the Research section on the Alpha-1 Foundation’s web site, at www.alphaone.org.

For questions related to this article call Silvana Rodriguez toll free, at the Alpha-1 Foundation, 1-888-825-7421.
Florida Alpha-1 Screening and Detection Program Update
by Blaise Hubta

The Alpha-1 Foundation is in the second year of a multi-year contract with the State of Florida to support the Florida Alpha-1 Screening and Detection Program. In the first year, the Alpha-1 Antitrypsin Deficiency Laboratory was established for mass screening by Mark L. Brantly, M.D. and staff of the University of Florida (UF) Alpha-1 Research Program. In Year Two, the screening and detection process was initiated. This program is designed as a pilot program that could be implemented on a national level. The Florida Alpha-1 Detection Program is one of the first large-scale, genetic single disorder screening programs of its kind in the United States. The successes and failures of this program will be used as a model to design a national Alpha-1 screening program and provide valuable information for other types of genetic testing. This program is also designed to inform Florida healthcare professionals about Alpha-1 Antitrypsin (AAT) Deficiency and the importance of screening at risk Florida residents for the disorder. Under this program, clinicians are asked to test every patient under their care with COPD, asthma and/or liver disease for Alpha-1. Finger stick test kits and educational materials are provided to physicians free of charge.

Since December 2001, more than 3,000 Alpha-1 Screening Kits (see picture) with five individual finger stick test kits have been disseminated to pulmonary specialists, respiratory therapists, internists, allergists, gastroenterologists and general practitioners throughout Florida. To kick off the Alpha-1 Detection effort, an "announcement" letter from the Secretary of Health from the State of Florida was sent out to Florida physicians and test kit boxes followed three to four days later. Thus far, the response from the mass mailing has been a success and as of March 2002, the number of samples returned is nearing 1,000. To date nine affected individuals and 39 carriers have been identified.

The following activities have been launched as a part of the Florida Alpha-1 Screening and Detection program to inform the public of this exciting new project and encourage participation:

Media Outreach

- Articles on the Detection Program have been placed in various newspapers throughout Florida. Public service announcements have been disseminated to and run on Florida radio stations. In addition, television stations in Tampa and Miami have run feature stories on Alpha-1. This outreach effort is being done as we work in collaboration with the communications departments of our partner medical organizations and colleges in Florida.

Physician Outreach

- The Foundation and UF personnel are actively attending meetings, conferences and conducting medical seminars to promote Alpha-1 education among the medical community. Since July 2001 Foundation representatives have attended and exhibited at numerous medical and scientific meetings throughout Florida. Response to the program at these meetings has been very good and we look forward to being able to attend more in the future.

Partnerships

- Collaborative partnerships with medical organizations, hospitals and community health centers in Florida have been formed. These partners are helping to disseminate the kits to promote the program. Partners include: American Lung Association of Florida, Florida Medical Association, Florida Academy of Physician Assistants, Florida Society for Respiratory Care, Florida Thoracic Society, American Liver Foundation, Orange Belt Pharmacy and the University of South Florida College of Medicine.
Local Programs

- The Foundation's Clinical Resource Center at the University of Miami (UM) School of Medicine under the direction of Adam Wanner, M.D. is participating in the Detection Program. Dr. Wanner appointed Christopher Carter, M.D. to head up Alpha-1 screening efforts in the UM/Jackson community clinics and hospitals. We are also working with UM's public relations department to internally and externally publicize the screening program in South Florida.

In addition to the physician campaign, the Foundation is enthusiastically recruiting the Florida Alpha Community to provide their support and help for this large-scale endeavor. Florida Alphas can ask their physicians if they are familiar with this campaign. Blaise Huhta at the Foundation is happy to send information and test kits if needed, 1-888-825-7421 ext. 246. As more physicians become aware of the Detection Program and start asking themselves, “Could my COPD, liver disease or asthma patient have Alpha-1,” we hope to create a gradual change in physician behavior and to reach our goal of having all at-risk individuals in Florida screened for Alpha-1.

RESEARCH UPDATE

The Alpha-1 Sibling Pair Genetic Study
by Edwin Silverman, M.D., Ph.D.

We are pleased to let you know about a new study that has been started to investigate the reasons why some people with Alpha-1 Antitrypsin (AAT) Deficiency develop chronic obstructive pulmonary disease (COPD) at an early age, while others never develop significant breathing problems.

COPD includes emphysema and chronic bronchitis. People who inherit Alpha-1 are at increased risk for developing COPD, but some individuals with Alpha-1 develop COPD in their twenties, while others never develop COPD at all. Cigarette smoking explains some of this difference in risk for lung disease, but there are likely other important factors as well. In preliminary research in the late 1980’s, we at Washington University in St. Louis found evidence to suggest that at least part of the variation in the development of lung disease in people with Alpha-1 was influenced by inherited factors.

Building on this work, a group of physician scientists has joined together to try to learn whether there are any genetic factors that contribute to the development of lung disease in people with Alpha-1.

Dr. Silverman, Brigham and Women's Hospital and Harvard Medical School in Boston, is the principal investigator of this study, which is funded by the National Institutes of Health. The Alpha-1 Foundation is a major partner in this research study, and six Alpha-1 Foundation Clinical Resource Centers around the country are collaborating on this study: Denver, Colorado (led by Robert A. Sandhaus, M.D., Ph.D.), Tyler, Texas (led by James Stocks, M.D.); Cleveland, Ohio (led by James K. Stoller, M.D., M.S.O.D.A.), New York, New York (led by Gerard Turino, M.D. and Edward Eden, M.D.); Portland, Oregon (led by Alan Barker, M.D.); and Gainesville, Florida (led by Mark L. Brantly,
M.D.). There are also clinical centers located in Boston, Massachusetts and Salt Lake City, Utah that will participate.

If this study leads to the identification of genetic factors that modify the expression of lung disease in AAT deficient individuals, improved understanding of COPD may result. In order to identify these factors, these investigators are performing measurements of pulmonary function, assessing respiratory symptoms and environmental exposures with a questionnaire, and obtaining a blood sample to extract DNA. The pulmonary function measurements are the standard spirometry tests that most of you have performed on many occasions. Following baseline spirometry, the breathing test is repeated after two puffs of a bronchodilator medication (albuterol) to see whether the albuterol improves pulmonary function. The questionnaire covers issues relating to cough, phlegm, shortness of breath, other pulmonary symptoms, smoking, occupational exposures, and medical and family history. There is one study visit, which takes one to two hours to complete.

To be eligible to participate in this study, a family must have at least two siblings with type PI ZZ AAT Deficiency who are at least 30 years old and willing to participate in this study. Siblings who are of unknown AAT type can be tested to determine whether their family is eligible to participate in this study. All of the information collected by pulmonary function tests, questionnaire, and blood tests will be treated with strict confidentiality and will not become part of the participant’s medical records. A subject’s participation in the study will have no influence on their regular treatment or medical care in any way. To determine if a family is eligible for the study, the investigators will ask the AAT deficient subjects that participate to assist in contacting their brothers and sisters with Alpha-1, as well as any available parents, to assess whether they would also like to participate in this study. The Alpha-1 Research Registry will also be assisting in recruitment for this study. Members who have linked their Registry record with family member Registry records will receive information on how their family can participate. People who have had a lung or liver transplant are not eligible to participate. The goal of this study is to include as many subjects with severe Alpha-1 as possible, and to include all of their available parents and AAT deficient siblings who are willing to participate. In appreciation for participating, each family member will receive a $50 payment.

Dr. Silverman can be contacted at (617) 525-0856 at any time with questions regarding this study. If you are interested in participating in this study, please contact the toll free number for Dr. Silverman’s research group, at 866-328-9494, and you will be placed in contact with the nearest Clinical Resource Center for this study. Alternatively, you can contact the clinical center of your choice directly to arrange participation.

This research project is a complicated study that will take approximately five years to complete. However, with the support of the Alpha Community, we are confident that this project will discover important new information about Alpha-1 that may ultimately lead to improvements in diagnosis and treatment. We hope that you will consider participating in this important study.
4-Phenyl Butyrate-Mediated Secretion Rescue in Alpha-1 Antitrypsin Deficient Individuals
by Susan Pendrak, A.R.N.P.

The 4-Phenyl Butyric Acid (4-PBA) trial is currently underway at the University of Florida (UF) in Gainesville. The study involves ten participants: five individuals with Alpha-1 related lung disease and five individuals with Alpha-1 related liver disease. The goal of this study is to determine if 4-PBA significantly increases blood levels of alpha-1 antitrypsin protein (AAT) in AAT deficient individuals with and without liver disease. The second goal is to determine if 4-PBA reduces the accumulation of AAT in liver cells, and to assess whether the reduction of AAT in liver cells leads to a decrease in liver damage.

In individuals with Alpha-1 the AAT protein folds incorrectly in the liver. When this occurs it is difficult for AAT to be released from the liver into the bloodstream. This results in lower blood levels of AAT as well as an accumulation of the misfolded protein in the liver. The hope is that the drug, 4-PBA, will act as a chaperone and help to carry AAT out of the liver cells. This would, in turn, result in higher blood levels of AAT and decrease the accumulation of misfolded AAT in the liver.

To date five patients have completed the screening and dosing phases of the study. Three additional individuals will complete screening in April and dosing in May of 2002.

4-PBA has been FDA approved for use in cancer patients, pediatric patients with urea cycle disorders and individuals with thalassemias. This is the first time it will be used in individuals with Alpha-1 Antitrypsin Deficiency. Some of the possible side effects from this medication include dizziness, confusion, fatigue, mild nausea, bad taste in the mouth, vivid dreams, offensive body odor, swelling of the legs or other parts of the body, and build-up of fluid in the lungs. To date the drug has generally been well tolerated by all study participants.

This study requires all subjects undergo a 3-day screening visit, which includes a complete history and physical examination, pulmonary function testing, a liver biopsy and blood work. Once the screening visit is completed, subjects return approximately 30 days later for what is referred to as the dose escalation phase.

During this phase of the study, subjects spend 13 days at the General Clinical Research Center (GCRC) at Shands Hospital at UF, where they undergo multiple blood draws for AAT and 4-PBA levels. They also receive the study medication, 4-PBA, in increasing dosages over a 13-day period of time.

The dose escalation phase will be followed by a long-term treatment phase. During the long-term treatment phase, subjects will be placed on what will be determined by the investigators as "the optimum dose." This refers to the lowest dose of 4-PBA that results in the highest blood concentration of AAT. Patients will be monitored on a monthly basis in an outpatient clinic during this phase. At the end of the 6-month study period, study participants will be admitted to the GCRC for a final 2-day visit that will include a post-treatment liver biopsy, safety labs and blood work for AAT and 4-PBA.

We hope to begin the long-term dosing phase for this study sometime in late June or early July of this year. It is possible that 4-PBA treatments may not lead to a significant increase in serum AAT levels. In this case only patients with liver disease could derive benefit from long-term therapy and would participate in the long-term treatment phase.

The completion date for the trial is expected to be December 2002. The enrollment response for this trial has been excellent and we would like to thank the entire Alpha Community for showing an interest in this trial. In particular we would like to thank those who volunteered to participate.
Update on the Infusion Trial for Aventis Alpha-1 Proteinase Inhibitor
by Friedrich Kueppers, M.D.

There is good news and bad news for Alpha-1 patients who were recently affected by delays in Prolastin® distribution and worry about the return of periodic shortages. The good news is that the clinical part of the Aventis study comparing Aventis Alpha-1 Proteinase Inhibitor to Prolastin has now been completed.

The bad news is that it is not yet available. The clinical data was submitted to the Food and Drug Administration (FDA) last year. The submission of the required technical and regulatory data, which is a formidable task, will not occur until this year. Prolastin and Aventis Alpha-1 Proteinase Inhibitor are both alpha-1 antitrypsin preparations made from blood plasma.

The Aventis sponsored study enrolled 44 patients at seven sites. The patients received either Prolastin or Aventis Alpha-1 Proteinase Inhibitor infusions each week for 10 weeks in a double-blinded fashion, so that neither the patient nor the physician knew which product was given. After the 10 weeks, the patients received weekly infusions of the Aventis product for 14 weeks.

There will be several advantages to Alphas, when the Aventis product comes to market:

1. There will be more alpha-1 antitrypsin augmentation therapy available for distribution so that shortages may be avoided.
2. The competition of two similar products will perhaps help to keep the price of the products down.

These are important issues since the demand for alpha-1 antitrypsin augmentation therapy will surely go up as more patients are diagnosed. Meanwhile information continues to appear in medical journals confirming that augmentation therapy with alpha-1 antitrypsin (Prolastin) is indeed beneficial to Alphas. Several recent reports show a noticeable decrease in the loss of lung function per year under Prolastin therapy. In addition, there appears to be a positive effect on the frequency and severity of lung infections under augmentation therapy. These reports are most welcome to the Alpha Community and make our expectations for a new product even more urgent.

General Clinical Research Update
by Sandy Sandhaus, M.D., Ph.D.

Clinical research in Alpha-1 Antitrypsin Deficiency (Alpha-1) is alive and well. In discussing clinical research it is helpful to divide clinical research into two broad areas:

1) studies designed to help us understand the natural history, demographics, genetics, and factors that affect disease in Alpha-1, and
2) studies designed to evaluate specific new drugs or other therapies for Alpha-1.

Alphas seem most interested in the second of these categories, but the first category may provide the most exciting and useful information for the future.

Clinical research that helps us understand Alpha-1 better.

There is a wide variety of research moving forward that is designed to unravel the mechanisms behind Alpha-1, help us diagnose it better, or describe the scope of Alpha-1 more completely. The Alpha-1 Foundation through its grants, awards, and fellowships funds much of the research moving forward entirely or in part. For a complete listing of current projects see the web site, at www.alphaone.org. Simply click on Research, then on Funded Research on the left side of the screen, and then on Research Portfolio in the text that appears. I think you'll be amazed at the scope of research that is currently being done. A couple of trends are apparent even with a rapid scan of the titles: there is a great deal of research being devoted to understanding mechanisms of liver injury in Alpha-1, and there is a wonderful balance among studies involving very basic science, more direct clinical science, and the social sciences.
I would like to point out a couple of important clinical studies that are currently ongoing. The renowned scientist, Fred de Serres, Ph.D. is compiling an analysis of the world’s literature on the distribution and prevalence of abnormal Alpha-1 phenotypes around the world. This understanding should enable resources to be applied where they are most needed and point out areas where additional information is needed. Another important project that is just getting under way is the Alpha-1 genomic study of Edwin Silverman, M.D., Ph.D. In this NIH and Foundation sponsored study, Dr. Silverman, and a group of investigators from around the country, are trying to evaluate whether there are genetic influences, in addition to the alpha-1 antitrypsin gene, that help to determine whether an individual Alpha gets lung disease or not. This study will be looking to enroll 400 families that have at least two siblings with PI*ZZ Alpha-1 (thus, the nickname of this study: the Sib Pair Study). More information on this study is in this issue of the Registry Update.

Clinical research to develop new therapies.
Research by the pharmaceutical and biotechnology industries tends to be kept very confidential. But there are aspects of this field that are common knowledge within the Alpha-1 Community. Let’s look at the various types of upcoming therapies.

IV Plasma-Derived Therapies
We’ve all been anxiously awaiting the imminent approval of the Alpha Therapeutics IV product... for years now. Rumor has it that it may be on the launching pad, but rumor has been wrong in the past with this company. Aventis has completed its studies on their IV plasma-derived product so, hopefully, approval is on the way. Sources predict that there may be other companies on the horizon as well, so IV therapy may remain a good therapeutic option.

Inhaled Plasma-Derived Therapies
Aventis, with its inhaled plasma-derived powder, seems to be all alone in the inhaled Alpha-1 arena right now. The Alpha-1 Community hopes for a large study to start with this drug sometime this year. Again, the possibility of other plasma suppliers stepping in here always exists.

Other Inhaled Therapies
Inhaled transgenic/recombinant Alpha-1 from genetically modified sheep was the big news over the past year. This product from the union of Bayer and PPL has undergone some testing in humans but, unfortunately, the companies have decided to put a hold on these studies until some safety concerns can be addressed.

We expect other recombinant products that can be delivered by inhalation, as well as more unusual drugs, such as inhaled hyaluronic acid, a drug designed to protect the connective tissues of the lung from destruction.

The Magic Pill?
Well, maybe magic, maybe not. There are a couple of synthetic inhibitors of the white blood cell enzymes that cause lung damage in Alpha-1 that are still moving forward. Most of these can be taken as a simple pill.

Gene Therapies
The University of Florida Alpha-1 gene therapy program is still on track to begin studies in humans this year. This therapy hopes to insert the normal alpha-1 antitrypsin (AAT) gene into muscle cells of Alpha-1 patients so that the blood levels of AAT normalize.

And here’s a bit of unexpected good news: the “gene repair” technology first reported at an Alpha-1 Association meeting several years ago, owned initially by Kymeragen, then sold to Valigen, and then seemingly lost, is now owned by NaPro and they actually seem interested in Alpha-1.

Liver Therapies
The studies of Mark Brantly, M.D. on 4-Phenylbutyric acid (4-PBA) are moving along well in Florida. This treatment is designed to help the liver release the AAT that builds up in the livers of individuals with Alpha-1. This has the potential to help reduce liver injury and also increase circulating levels of AAT.
Growing new lungs and livers

Studies looking at all-trans retinoic acid (ATRA) have been ongoing in patients with emphysema for over a year now. This drug is reputed to be able to stimulate the lungs to grow new air sacs (alveoli). Preliminary results were recently reported that were not very impressive, but some investigators are now wondering whether it would be more appropriate to concentrate on Alpha-1 patients. Look for this to move forward in the coming year.

Stem cells have now been prompted to differentiate into liver cells and lung cells. Perhaps the future of therapy will involve the growing of new livers and lungs for Alpha-1 patients.

As you can see, the pipeline for improvements and cures for AAT deficient individuals is robust. We at the Foundation feel that your enrollment in the Research Registry is one very important cause of this interest. Thank you for your participation.

FEATURED CLINICAL RESOURCE CENTER

Every newsletter we feature one of the 50 Alpha-1 Foundation Clinical Resource Centers. This month we are happy to highlight Michael J. Krouka, M.D. at the Mayo Clinic in Rochester.

Alpha-1 Center – Mayo Clinic, Rochester, Minnesota
by Michael Krouka, M.D.

Historically, the Mayo Clinic has made several contributions to the evolving story of Alpha-1 Antitrypsin (AAT) Deficiency. Following the landmark paper by Laurell and Eriksson in 1963, Mayo lung physicians addressed issues of screening (1969), the effects of emphysema on airways (1972) and the natural history of never smokers with Alpha-1 (1978). Drs. Leo Black, Norman G. Hepper, Robert E. Hyatt, and R. Drew Miller conducted benchmark studies.

These investigators made important early observations about Alpha-1 such as, Alpha-1 was far more frequent than expected in young patients with COPD, breathlessness due to Alpha-1 related emphysema was linked to loss of elastic recoil and collapse of the airways with expiration, and remarkably, never smokers with severe Alpha-1 could be asymptomatic from the lung perspective and live well into their 70's.
From 1989-1992, Mayo was an active participant in the NIH Registry of Patients with Severe Deficiency of Alpha-1 Antitrypsin, and one of the top four enrolling institutions. Three Mayo pulmonologists have particular interest in Alpha-1 (Bruce A. Staats, Udaya B S. Prakash, and Michael J. Krowka), and refer AAT deficient patients to several appropriate clinical programs at Mayo including programs in Pulmonary Rehabilitation, Medical Genetic Counseling and Nicotine Dependence. Mayo’s Pulmonary Function Laboratory remains one of the busiest in the world (over 70 PFTs conducted per day). These services allow for continued innovative approaches and experience in meeting the needs of Alpha-1 patients.

Currently, a major Alpha-1 emphasis from the Pulmonary Division focuses on educating the Mayo physicians-in-training about advances in the science and treatment of Alpha-1. These physicians will be the primary care MDs and sub specialists of tomorrow who will screen and offer “state of the art” treatment for a disorder that has been frequently underdiagnosed. Practicing physicians at Mayo have not been forgotten; most recently the Department of Medicine Newsletter (circulated to over 500 MDs within this institution), featured an Alpha-1 “Fact Sheet” describing clinical advances in the field of Alpha-1.

Finally, a unique relationship has evolved between the Divisions of Pulmonary Medicine, Gastroenterology/Hepatology (with the assistance of David J. Brandhagen, M.D.) and the Mayo Transplant Center. A database of patients with combined liver and lung clinical problems due to Alpha-1 now exists to help clinicians address the complicated issues that affect Alpha-1 patients. Current clinical research concerns include: What is the outcome of liver transplantation conducted in Alpha-1 patients with emphysema? Can lung volume reduction surgery or lung transplantation be conducted in a patient with asymptomatic liver cirrhosis due to Alpha-1? Why do some patients with liver disease due to severe Alpha-1 have essentially normal lung function?

We encourage Alpha-1 patients and families with questions and medical needs to seek additional information/opinion from the many Alpha-1 Clinical Resource Centers such as the Mayo Clinic. Continual education of physicians, paramedical professionals, and patients remains one of our highest priorities.
ASK THE ALPHA DOC

FOR ALPHA S F A Q s

by Michael Krowka, M.D.

Q: Can patients with severe Alpha-1 Antitrypsin Deficiency have both liver and lung problems at the same time?

A: Although it is uncommon, individuals with severe Alpha-1 Antitrypsin (AAT) Deficiency can have serious, clinical problems involving both the liver and lungs at the same time. Emphysema is the most common problem that pulmonary physicians would encounter in Alpha-1, and cirrhosis of the liver is the most common problem seen by liver specialists caring for AAT deficient patients.

At the Mayo Clinic, the most common scenario involves an adult patient referred for liver transplantation due to cirrhosis of the liver (associated with ZZ or SZ phenotype) who smoked and, thus, developed symptomatic emphysema due to the combination of cigarettes and low AAT levels. The clinical picture includes symptoms of breathlessness at rest (worse with exertion), wheezing, cough, weakness, fatigue, and weight loss. Data from the Mayo Clinic will be presented at the May 2002 meeting of the American Thoracic Society describing 27 adult patients (mean age of 50, ZZ or SZ phenotype) with end-stage liver disease due to Alpha-1 who were in need of a liver transplant. During routine pre-liver transplant pulmonary assessment, expiratory airflow obstruction was found in 30% of the population. Not surprisingly, patients with the heaviest smoking histories had the worst lung function, and the most significant respiratory symptoms. The lowest measurements obtained included FEV1/FVC = 34% in an ex-smoker and FEV1/FVC = 55% in a never smoker. We are currently studying the long-term outcome (especially in terms of lung function) in this cohort of patients.

In Sweden, where long-term data has been collected on a large number of AAT deficient individuals, Dr. Sten Eriksson has studied the cause of death and autopsy findings in patients with ZZ phenotype and an average age of 63 years. Based upon his study of 40 adult deaths, 23 smokers died primarily of respiratory insufficiency. However, in the group of 17 never smokers, 71% died from complications of cirrhosis. Based on this study and additional investigations and analysis of long-term data Dr. Eriksson stated that cirrhosis of the liver has been underestimated in the past, especially in elderly never smokers with severe Alpha-1.

When the combination of emphysema and cirrhosis due to Alpha-1 does occur, not only do very debilitating symptoms develop, but also there exists a higher risk of complications following surgery. For example, we have recognized and managed significant deteriorations in liver and lung function following major heart operations such as aortic valve replacement. Such complications can result in prolonged postoperative intensive care and hospitalization.

In summary, an individual with severe Alpha-1 can have the combination of clinically important emphysema and cirrhosis. I would echo the comment by Dr. Eriksson that this duo is probably more common than previously expected, especially in older patients. Careful evaluation is advised for any such AAT deficient patient who is being advised to have major surgery.
Cleveland Clinic, Alpha-1 Education Day, October 27
by Ryan Dickson

A special thanks goes out to Dan Laskowski for organizing a successful Alpha-1 Education Day at the Cleveland Clinic in Cleveland, Ohio on Saturday, October 27, 2001. Speakers included James K. Stoller, M.D., M.S.O.D.A., on Alpha-1, Dan Laskowski on Alpha-1 Research, Jeffery Chapman, M.D. on lung transplantation, Sarah Everett, Esq. on the Alpha-1 Foundation, Sandy Brandley on the importance of Alpha-1 Association membership and Scott Marlow, RT on coping with COPD.

Portland, Oregon Education Day
by Carol Deanes

On October 14, 2001, the Oregon Health Sciences Center, in conjunction with the Alpha-1 Alliance, co-sponsored the Alpha-1 Education Day. The meeting was well attended by Alpha-1 patients and family members. Lynn Oveson, R.N., M.N., A.N.P. assembled an excellent program. Alan Barker, M.D., Professor of Medicine, Pulmonary and Critical Care, Oregon Health and Sciences University, provided the group with the latest information regarding Alpha-1. James Stocks, M.D., Professor of Medicine, Dept. of Specialty Medicine, University of Texas Health Center, Tyler, presented an impressive overview of the Alpha-1 Foundation and its many programs. Many Registry Questionnaires were distributed and all shared the overall enthusiasm of the day.

There was an opportunity to participate in a breath condensate and exhaled gases study conducted by Dan Laskowski to determine differences between AAT deficient patients and other individuals, and develop a new test for diagnosing Alpha-1 and other lung disease. The day proved to be a success for Alpha-1 Research Registry recruitment with 25 new members enrolled and several Registry record updates. Thanks to all of you who attended and helped make the day a huge success.

Alpha-1 Advocacy Day Slated for June 6, 2002

The Alpha-1 Foundation and Alpha-1 Association join together for its first annual Alpha-1 Advocacy Day. This Day will provide an opportunity for members of the Alpha-1 Community and their families to come to Washington, DC, meet with members of Congress and advocate for better access to care, the development of more treatments and increased medical research for individuals afflicted with Alpha-1.

Alpha-1 Advocacy Day is scheduled as a pre-event to the Alpha-1 Association’s Education Conference in McLean, Virginia June 7-8. Shuttle transportation will be available to take Alphas, their families and friends to and from the House and Senate Congressional Office Buildings. Please contact one of the following individuals for more information:
Marlene Erven
Alpha-1 Foundation
Toll Free: 1-888-825-7421 Ext. 211
Email: mserven@alphaone.org

Michelle Tragner
Alpha-1 Association
Toll Free: 1-800-521-3025 Ext. 102
Email: tragner@alpha1.org
CALENDAR OF EVENTS

Alpha-1 Advocacy Day
Washington, DC
June 6, 2002
Contact Marlene Erven 1-888-825-7421 Ext. 211

Alpha-1 Association 11th Annual Education Conference
McLean Hilton
Tysons Corner, Virginia
June 7-9, 2002
Contact Michelle Tragner 1-800-521-3025 Ext. 102

Alpha-1 Education Day
Joliet, Illinois
June 23, 2002
Contact Liz Veronda 1-888-723-9487

Alpha-1 Education Day—National Jewish
Denver, Colorado
August 3-4, 2002
Contact Janis Berend, C.N.P.
(303) 398-1858, (303) 281-5602

Alpha-1 Education Day—2nd Annual Northeast Education Day
Lebanon, NH
Saturday, August 17, 2002
Contact Cathy Valenti 1-800-521-3025, or
Vicki Cameron 1-888-526-9077

Critical Issues Workshop on Models of Emphysema
September 24-26, 2002
Contact Symma Finn 1-888-825-7421 Ext. 241

Alpha-1 Education Day—Cleveland Clinic Foundation
Cleveland, Ohio
October 2002
Contact Lauren Shockley (216) 445-1202

International Scientific Conference,
Epidemiology of AATD
November 13-15
Contact Symma Finn 1-888-825-7421 Ext. 241

Alpha-1 Education Days are held in geographically diverse regions of the U.S. and include speakers on a variety of Alpha-1 related medical topics and research activities. There is no cost to the participants other than their personal expenses for travel and accommodations.

Alpha-1 Foundation:
For information about the Alpha-1 Foundation activities and sponsored research please check their web site at www.alphaone.org or their toll free number, at 888-825-7421. You may also contact the Alpha-1 Foundation Research staff by email at registry@alphaone.org for additional assistance in locating resources related to AAT Deficiency research, to obtain information about current research initiatives, to participate in the Research Network or Registry, or to receive Foundation publications.

AlphaNet
AlphaNet, a not-for-profit disease management company, currently employs more than 20 Alphas. AlphaNet provides a wide range of support services to Bayer Direct subscribers, administers clinical trials involving Alpha-1 therapies, and is developing a comprehensive disease management program to enhance the quality of life for those affected by Alpha-1. Since its inception in 1995, AlphaNet has contributed over $4 million to support Alpha-1 Antitrypsin Deficiency research and Alpha-1 Community programs.

Alpha-1 Association:
Information and educational resources related to Alpha-1 Antitrypsin Deficiency can also be obtained from the Alpha-1 Association, 8120 Penn Avenue South, Suite 549, Minneapolis, MN 55431-1326, by calling their toll free number, 800-521-3025, or by checking their web site, at www.alpha1.org.

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