Letter from the Director
by Charlie Strange, MD

Dear Registry Members,

In this issue of the Registry Newsletter you will find a glimpse of new projects that are nearing completion. We are honored to have the Alpha-1 Center at National Jewish Hospital in Denver give us a glimpse of their clinic. Here in Charleston, we are busy entering the >1000 responses to the asthma questionnaire that went out with the fall newsletter. We really like it when you write as small as you can between all the lines to tell us as much as possible about your disease. Seriously, the responses have been tremendous, and yes, we asked you to list everything to which you were allergic.

The Registry enrollment is rapidly closing in on 2500 members (see attached graph). Many of you may have participated in a survey last year that was sponsored by the Alpha-1 Foundation, Alpha-1 Association, and AlphaNet through a research organization called SRBI. By anonymously combining the mailing list of these organizations in the spring of 2003, the Alpha-1 community learned that the mailing list of all Alpha-1 patients known in the United States numbers 5222 persons. This means that about half of all known Alphas in America are members of the Registry, a remarkable achievement in my mind.

The responses to that survey have been transferred to the Registry (without any identifying information attached) so that we can do statistics on your responses. The picture of Alpha-1 in the United States is marked by severe lung and liver disease at a relatively young age. We will share our findings with you as the data is published.

What would we do if suddenly another 1000 persons were diagnosed with Alpha-1? The prospect of this occurring is more likely due to a national detection program that is rolling out soon from the Alpha-1 Foundation. Some of you remember the fears and misinformation that can accompany a new diagnosis with a rare disease. The goals of the Registry include both advancing the science in Alpha-1 and helping new Alphas gain the essential knowledge to understand this difficult disease. Please welcome these new Alphas into the community and encourage Registry enrollment.

Some of the projects discussed in the fall Newsletter continue to advance. The response to the Brigham and Women’s Hospital sibling pair study was good. One hundred seventeen “Opt in” cards were received from Registry participants demonstrating the power we have in numbers to get needed research completed in this rare disease. For those who meant to talk to your PIIZZ brother or sister but still haven’t, it is not too late to pick up the telephone. Remember that instead of you going to the doctor, the study will come to your house with breathing tests. In addition we want to thank you for the close to 100 calls the DNA and Tissue Bank at the University of Florida received concerning participation following the fall mailing.

"...about half of all known Alphas in America are members of the Registry”

The Registry will have a presence at some of the education days that are coming up this summer and fall. We hope you introduce yourself to us at these events. Thank you for taking time to read the newsletter. We know of some large trials in the works that will be ready by fall. Best of health to all of you.

Sincerely, Charlie Strange, MD

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Registry Members</td>
<td>0</td>
<td>119</td>
<td>485</td>
<td>110</td>
<td>149</td>
<td>631</td>
<td>661</td>
<td>287</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Registry ENROLLMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>------</td>
</tr>
<tr>
<td>Registry Members</td>
</tr>
</tbody>
</table>
Spring 2004
Registry Update Contents

△ Letter from the Director, Dr. Strange . . Page 1

△ Alpha-1 Foundation
Foundation Update/Research Agenda . . Page 3

△ Research Update
Rare Lung Disease Consortium Project . . Page 4
△ SRBI Survey Results . . . . . . . . . . . . . . Pages 6-7

△ Targeted Detection Programs
Florida Detection Update . . . . . Page 9
△ National Targeted Detection Program . . Page 10

△ Feature CRC
Ask the Alpha Doc, Dr. Sandhaus . . . Page 11
△ Alpha-1 Center National Jewish . . . Pages 12-13

△ Education Days, Events, and Meetings
Summary of the American Association for the Study of Liver Diseases (AASLD) Annual Meeting in Boston . . . . . . . . . . . . . . . . . Page 14
△ Other Meetings . . . . . . . . . . . . . . . . . . . . . Page 15-16
PATIENT ADVOCATES MOVE CLINICAL CARE FORWARD

One of the priorities for the 2002 Alpha-1 Advocacy Day was gaining support for HR 4013 the Rare Diseases Act. This legislation succeeded and provides important provisions for the National Institutes of Health (NIH) Office of Rare Diseases, including doubling its budget over a five year period and requesting the establishment of rare disease clinical centers. In November 2003 NIH announced $5.1 million had been awarded to fund 7 Rare Diseases Clinical Research Centers. The center that we are most excited about is the Rare Lung Disease Clinical Research Consortium which includes Alpha-1.

ON THE HILL

The Foundation’s public policy program gains congressional support to enhance the federal Alpha-1 research portfolio and improve access to care for individuals. In the current year Alpha-1 priorities are moving forward as a result of Congressional intent being expressed in legislative report language. Of specific interest to Alpha-1:

- The U.S. Centers for Disease Control and Prevention has been encouraged to promote Alpha-1 Screening and Detection utilizing public and professional education regarding lung disease, both genetic and tobacco related.
- NIH was encouraged to conduct an Alpha-1 State of the Science Meeting leading towards the development of a five-year research agenda.
- Federal agencies with oversight of Federal Aviation Administration (FAA) regulations have been asked to address the need for the development of a consistent policy regarding supplemental oxygen usage on airlines.
- FDA has been asked to expedite review of new therapies for Alpha-1 and to report to Congress on their progress by March 31, 2004.

CONGRESSIONAL BRIEFING

The Foundation co-sponsored the first ever COPD and Alpha-1 congressional briefing, which was well attended by congressional staff, patients and health care providers.

Dr. Alan Barker made the trip to the Capitol from Portland, Oregon to give a clinical overview of COPD and Alpha-1. Several patient advocates spoke about the challenges they face living with COPD. Congressional staff engaged in a lively Q&A and many stayed after the program for an informal exchange with the participants. This was a very successful forum to discuss our health policy concerns and raise awareness.

REIMBURSEMENT

Augmentation Therapy; Medicare Victory for 2004

We analyzed the Centers for Medicaid and Medicare Services (CMS) claims data and proved it was flawed. These errors were among the arguments made to CMS by the Foundation, Association and hundreds of Alpha Advocates during another round of proposed cuts in reimbursement for augmentation therapy. Augmentation therapy won a very favorable reimbursement rate for 2004. This ruling was codified in the massive Medicare reform legislation signed into law in December 2003. This is a two year provision so be prepared for the future call to action.

ICD-9 Diagnostic Code: Based on the recommendations of the Foundation’s Medical and Scientific Advisory Committee, a petition to change the Alpha-1 International Classification of Diseases-ninth revision (ICD-9) Diagnostic was submitted to the National Center for Health Statistics Coordinating Committee who oversee all proposed changes for CMS. The Foundation defended this petition in December 2003 by providing expert testimony at a public hearing convened at CMS headquarters in Baltimore. We expect a favorable determination in October 2004. The ICD-9 is the number that is used by health care providers to classify the reason patients are treated. It is used on all medical and insurance forms. Currently the Alpha-1 ICD-9 is classified in a sub-heading and is often not properly captured on medical/insurance forms. Our petition requests that Alpha-1 be raised up in the classification scheme to have it’s own number instead of a sub-number. This will allow for better data collection and increased Alpha-1 awareness.
Rare Lung Disease Consortium Project

by Bruce Trapnell, M.D., Scientific Director, Alpha-1 Foundation and Bethany B. Barnett, M.S.P.H., Clinical Research Administrator, Alpha-1 Foundation

In November 2003, The National Institutes of Health (NIH) announced the establishment of the Rare Diseases Clinical Research Consortium. Funding for this Consortium has come from several NIH divisions and totals $5.1 million over five years. The Consortium consists of seven Rare Diseases Clinical Research Consortia (RDCRCs) and a Data Technology Coordinating Center.

Because patients affected with rare diseases are spread throughout the country, research of these diseases requires the collaboration of scientists and the ability to share resources and patient populations. The purpose of this Consortium is to facilitate this collaboration, building a strong foundation for continuing research and support for the rare disease community.

One of the seven grants awarded was to Dr. Bruce Trapnell, Scientific Director for the Alpha-1 Foundation and Associate Professor at Cincinnati’s Children’s Hospital Medical Center, to form the Rare Lung Disease Consortium (RLDC). The rare lung diseases that are the focus of this Consortium include: alpha-1 antitrypsin deficiency (Alpha-1), lymphangioleiomyomatosis (LAM), pulmonary alveolar proteinosis (PAP), and hereditary idiopathic lung disease (hILD).

The clinical centers and investigators involved in the effort include:

<table>
<thead>
<tr>
<th>Children's Hospital Medical Center</th>
<th>Cincinnati, OH</th>
<th>Bruce Trapnell, M.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleveland Clinic Foundation</td>
<td>Cleveland, OH</td>
<td>James Stoller, M.D.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mani Kavuru, M.D.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Jeffrey Chapman, M.D.</td>
</tr>
<tr>
<td>Harvard/B Brigham &amp; Women’s Hospital</td>
<td>Boston, MA</td>
<td>Ed Silverman, M.D., Ph.D.</td>
</tr>
<tr>
<td>International Medical Center of Japan</td>
<td>Tokyo, Japan</td>
<td>Koh Nakata, M.D., Ph.D.</td>
</tr>
<tr>
<td>Medical University of South Carolina</td>
<td>Charleston, SC</td>
<td>Charlie Strange, M.D.</td>
</tr>
<tr>
<td>National Heart, Lung, and Blood Institute/NIH</td>
<td>Bethesda, MD</td>
<td>Joel Moss, M.D.</td>
</tr>
<tr>
<td>National Jewish Medical &amp; Research Center</td>
<td>Denver, CO</td>
<td>Robert Sandhaus, M.D., Ph.D.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kevin Brown, M.D.</td>
</tr>
<tr>
<td>Oregon Health &amp; Sciences University</td>
<td>Portland, OR</td>
<td>Alan Barker, M.D.</td>
</tr>
<tr>
<td>Royal Melbourne Hospital</td>
<td>Melbourne, Australia</td>
<td>John Seymour, M.D.</td>
</tr>
<tr>
<td>University of Cincinnati Medical Center</td>
<td>Cincinnati, OH</td>
<td>Frank McCormack, M.D.</td>
</tr>
<tr>
<td>University of Florida Medical Center</td>
<td>Gainesville, FL</td>
<td>Mark Brantly, M.D.</td>
</tr>
<tr>
<td>University of Texas Health Center</td>
<td>Tyler, TX</td>
<td>James Stocks, M.D.</td>
</tr>
</tbody>
</table>
The consortium also depends on the active involvement of patient organizations. Active patient groups therefore established a Rare Lung Disease Foundation Consortium, in order to provide support for patients with disorders for which no such organizations currently exist, such as PAP and hiLD. The active foundations assisting in this endeavor are the Alpha-1 Foundation, LAM Foundation, and the Pulmonary Fibrosis Foundation. The Alpha-1 Foundation has hired Bethany Barnett, MSPH in the position of Clinical Research Administrator. She will be the central administrative person for all the clinical centers and patient foundations.

The purpose of the Consortium is to 1) promote collaboration among centers already focused on clinical research in rare lung diseases, 2) attract and train highly qualified investigators, 3) collect clinical data from patients worldwide into a large, centralized database, and 4) make clinical data available to those affected by a rare lung disease, their clinicians, and the general public. In order to obtain all these goals, 4 Specific Aims have been established.

1. Conduct longitudinal studies of individuals with Alpha-1, LAM, and PAP.

Currently, a clinical protocol is being finalized for the Alpha-1 longitudinal study. This study is a 5-year study that will utilize advances in the field of radiology to assess lung health and changes over time. Similar protocols for the LAM and PAP longitudinal studies are in the works.

2. Conduct a pilot and demonstration project program.

Grant applications will be accepted from the participating clinical centers and up to three awards will be made each year. These projects will investigate causes or test new methods to diagnosis or treat the rare lung diseases under study in the Consortium.

3. Expand and enhance training programs in clinical research for rare lung diseases.

This program will provide specialized training in rare lung disease clinical research for outstanding pulmonary medicine trainees. The fellows will participate in the clinics, in clinical research projects and will publish the results of their research in medical journals.

4. Expand and enhance educational resources in rare lung disorders for investigators, clinicians, and the general public.

Each of the participating patient foundations currently provides educational materials to patients, caregivers and researchers. Additional educational resources will be developed by the Consortium and will include a rare lung disease website, a lecture series, and annual scientific meetings.

The first annual meeting of the Rare Lung Clinical Research Consortium took place on March 26-28, 2004 in Cincinnati, Ohio. It consisted of scientific sessions for PAP, LAM and hiLD, joint scientific sessions for all these rare lung diseases, and an Alpha-1 patient education day on Saturday the 27th.
The National Survey of Patients with Alpha-1 Antitrypsin Deficiency

To better define issues affecting the Alpha-1 community, the Alpha-1 Association, the Alpha-1 Foundation, and AlphaNet commissioned a joint national survey in the spring of 2003 to focus on patient perspectives concerning healthcare and Alpha-1 community issues. The survey was conducted through Schulman, Ronca, and Bucuvalas, Inc. (SRBI), an international research organization in Washington, DC. SRBI signed a confidentiality agreement with each of the three sponsoring organizations so that they could construct a single sampling population from the mailing list of all three organizations omitting duplicates. From these lists there were a total of 5,222 unique potential participants representing the best estimate of the number of diagnosed persons with Alpha-1 Antitrypsin Deficiency in the US. Questionnaires were sent to the participants beginning in April 2003. By June 11, 2003, 1,953 (37%) questionnaires had been returned to SRBI.

Results showed severe deficiency of AATD (PSZ, PIZZ, Pi Znull) was present in 92.7% of the survey participants. Another 2.0% were caregivers answering on behalf of a deficient individual and 4.8% were PiMZ carriers. Carriers were excluded from the remainder of the analysis unless specifically reported. The mean age of participants was 53.1 years. We compared the percent of Alpha-1 respondents in each age category to the general population based on the 2000 US census. As expected, results show the majority of Alpha-1 patients are middle-aged as symptoms most often present after the third decade. Sixty two percent of known Alpha-1 patients are age 45-64, while only 22% of the general population falls into that age range. Ninety percent of the survey population falls within the age range 35-75, while 45% of the US population falls in that age range. Few children and young adults are known in the Alpha-1 community since the majority of symptoms present later in life.

The mean age at first diagnosis of AATD was 43.9 years. The majority of participants (58%) were diagnosed between ages 40-59, 9% were diagnosed between ages 60-79 and less than 1% were diagnosed after age 80. More than a third (40%) of respondents report being diagnosed within a year after seeking treatment for symptoms. Overall the mean time between seeking treatment for symptoms and diagnosis was 5.6 years. It seems that physician knowledge of Alpha-1 in the US may be improving as time to diagnosis decreased as decade of birth increased. This suggests the awareness and Alpha-1 education efforts of national patient organizations have been effective. For those born before 1950 the mean time between seeking treatment for symptoms and diagnosis was 70 years. The mean time to diagnosis decreased to 4.5 years for those born in the 1950s and 4.0 years for those born in the 1960s.

Participants were able to self-report any combination of diagnoses associated with Alpha-1. The prevalence of emphysema, asthma, chronic bronchitis, and liver disease in the survey population was 53%, 45%, 38% and 8% respectively. Sixteen percent of respondents do not report any pulmonary or hepatic symptoms. Among Alpha-1 carriers, 46% did not report any symptoms, 33% report asthma, 29% report chronic bronchitis, 15% report emphysema, 14% report COPD and 8% report liver disease. Although Alpha-1 is classically characterized as a cause of genetic emphysema, this survey highlights the high prevalence of wheezing, cough, and bronchitis in this population. The clinical message is that an Alpha-1 test should be ordered for every patient with COPD as suggested in the recent ATS/ERS statement.
Sixteen percent of severely deficient Alphas report having had a transplant or being on a transplant list. Those participants report age at first diagnosis to be significantly younger (group mean 39.7 years versus 45.2 years) than Alphas who do not report a transplant or being on a transplant list. This suggests that persons diagnosed in the third decade of life, presumably due to symptoms, may be more likely to need a transplant in the future than persons diagnosed in the fourth decade of life or later.

Nearly three quarters (74%) of the severely deficient Alphas report that they are currently infusing augmentation therapy. Participants infuse less frequently than scheduled often (3%), sometimes (25%), rarely (50%) and never (22%) in the respective percentages. Overall, the majority (62%) of non-carriers say they would be willing to try another FDA approved IV therapy at the same cost. When compared to participants not on augmentation therapy, those reporting augmentation therapy use are older, diagnosed at an older age, report longer time to diagnosis after onset of first symptom, are more likely to report symptoms of lung disease, more frequently use oxygen therapy, and report better quality of life.

Survey responses show that most participants were familiar with and satisfied with the three main national Alpha-1 patient organizations; the Alpha-1 Association, the Alpha-1 Foundation and AlphaNet. In particular the respondents look to these organizations to promote development of new therapies, research funding, physician education, screening and detection, and public awareness. Notably over 90% of respondents rate their AlphaNet Coordinator as excellent or good in providing service, information and support. Respondents felt that COPD education is an appropriate topic for Alpha-1 Education Days.

In conclusion, this survey tells us that less than half of the known Alphas in the United States are members of the Alpha-1 Research Registry as there 2,500 Registry members and there were 5,222 individuals eligible to receive the SRBI survey. Overall, participants are familiar with the national patient organizations and support their activities. This survey provides some evidence that early diagnosis provides benefits to the population and suggests that screening for this disorder in all patients with COPD should be routinely performed.
Productive Year for Florida Detection

by Carol Motsinger, Detection Coordinator
Alpha-1 Foundation

The Florida Detection Program, sponsored by the Alpha-1 Foundation and the State of Florida, Department of Health, is midway in its fourth year and continues to make significant strides in creating awareness about Alpha-1 and facilitating the testing of individuals at risk for Alpha-1 throughout the state.

In addition to reaching and educating many physicians in Florida, the Foundation has developed testing programs at four clinical centers: University of Miami Pulmonology, University of Miami Center for Liver Disease, University of Florida Pulmonology at Gainesville and University of Florida at Jacksonville. Due in great part to the efforts of our clinical partners, and the Alpha-1 Coded Testing (ACT) Program managed by the Medical University of South Carolina, more than 4,000 individuals in the state of Florida have been tested since the inception of this program in 2000. Of this number, 161 individuals were identified with Alpha-1 (ZZ & SZ) and 291 Alpha-1 carriers (MZ) were identified. The ACT program, which facilitates confidential testing for Alpha-1 has processed a total of 220 tests in Florida, identifying 6 individuals with Alpha-1 (ZZ & SZ) and 54 “carriers” thought to be in the carrier category most at risk for developing the disease. One of program goals is to establish more partnerships with new pulmonary and hepatology clinics along with specialty practices to facilitate testing.

The recent American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus document has helped to create awareness of Alpha-1 testing guidelines within the medical community. That document was published in the American Journal of Respiratory and Critical Care Medicine Journal on October 1, 2003. The Alpha-1 Foundation is dedicated to informing healthcare providers about this compelling, evidence-based data. It has developed and disseminated over 1000 Continuing Medical Education (CME) CD ROMS to physicians and respiratory therapists providing 3 credit hours. This interactive CME provides educational data about Alpha-1 and includes information about the aforementioned ATS/ERS document.

This year’s goal is to test 2,788 individuals and expand the Foundation’s outreach programs to the medical community, the at-risk patient community and the general public. The Foundation’s detection staff regularly attends medical related meetings and conferences, coordinates CME courses, CEU presentations and grand rounds throughout the state as well as develops and initiates programs to Alphas and their families through education days and special events.

Each day, the Alpha-1 Foundation receives calls from concerned patients who have been diagnosed with various pulmonary conditions. These callers are either referred to the Medical University of South Carolina to obtain confidential testing or provided with a free test kit to be taken to their physician for testing. Both methods of testing are free of charge and are processed in the Alpha-1 Genetics Laboratory at the University of Florida in Gainesville. Much care is taken to evaluate the individual needs of our callers and to give them the best guidance within a framework of strict confidentiality.

The groundwork established in the Florida Targeted Testing Program is helping the Foundation propel to the next level, which is The National Targeted Detection Program. The month of May has been declared Alpha-1 Awareness Month in Florida. Please contact Carol Motsinger at (305) 567-9888 ext 211 or by email: cmotsinger@alpahone.org if you would like to help spread the word in Florida.
National Targeted Detection Program

by Marcia Ritchie, Vice President and Chief Operating Officer, Alpha-1 Foundation

The Alpha-1 Foundation has commenced the largest awareness and detection campaign in its nine-year history — the National Targeted Detection Program (NTDP). The Foundation’s mission is to provide leadership and resources that will result in increased research, improved health, worldwide detection and a cure for Alpha-1. The NTDP touches all aspects of this mission.

The goals of the program are twofold — educate the medical community and individuals with certain types of Chronic Obstructive Pulmonary Disease (COPD), liver disease, and/or pancreatitis for whom Alpha-1 may be an underlying factor in their disease and promote testing for Alpha-1 in symptomatic populations. The Foundation believes that this effort could uncover a significant number of people who are Alpha-1 deficient and who would benefit from early diagnosis. For example, it is estimated that there are currently 16 million people being treated for COPD in the United States and of that number between 1 and 3% may have Alpha-1.

Alpha-1 Antitrypsin Deficiency is often misdiagnosed or undiagnosed, resulting in sub-optimal medical care. The earlier Alpha-1 is detected, the earlier proper treatment regimens can be applied resulting in a better quality of life for the patient. Recognizing a need to treat people early in their illness, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) issued new “Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency” in October 2003. These esteemed international organizations recommended Alpha-1 testing for the following individuals:

- adults with emphysema
- chronic bronchitis
- COPD
- asthma with airflow obstruction that is incompletely reversible after bronchodilator treatment
- persistent obstruction on pulmonary function tests with identifiable risk factors
- unexplained liver disease
- necrotizing pancreatitis
- family members of an individual with Alpha-1.

Initiated in the fall of 2003, the NTDP is being implemented in two phases. Phase I, which has just concluded involved the distribution of the ATS/ERS document to physicians, nurses and respiratory therapists along with a continuing medical education (CME/CEU) program on CD ROM. Additionally, a strong message about the need for testing was targeted to health care practitioners and the COPD community through press releases, newsletter articles and various website postings.

“It is estimated that there are currently 16 million people being treated for COPD in the United States and of that number between 1 and 3% may have Alpha-1.”

Phase II will continue with an intensified education campaign targeted to the medical teams of the 7 Clinical Resource Network Centers of the National Heart, Lung, Blood Institute of the National Institutes of Health; 51 Foundation-designated Clinical Resource Centers; large pulmonary practices and various teaching hospitals and universities. Phase II also includes a direct to consumer message approach aimed at people with COPD encouraging them to be tested for Alpha-1. The goal is to test 25,000 people nationwide by the end of 2004 in hopes of finding some of the nearly 95% of undiagnosed Alphas.
Q: I am a carrier with an MZ phenotype. I have emphysema. Shouldn’t I be put on augmentation therapy?

A: This is a difficult question and one with no absolute answer. The simplest response is to point out that the package inserts approved by the Food and Drug Administration for every one of the current augmentation therapies including Prolastin, Aralast, and Zemara require that an individual have emphysema and be deficient in alpha-1 antitrypsin to receive such therapy. The Prolastin package insert even specifically states that it is not indicated in individuals with the MZ phenotype.

But the question could still be asked, “Does having the MZ phenotype contribute to the development of emphysema and, if so, wouldn’t augmentation therapy be expected to be helpful?” It appears that there is some consensus developing that individuals with the MZ phenotype have an increased risk of developing emphysema than the general population when exposed to risk factors such as cigarette smoking. That increased risk appears to be small. However, it is important to remember that the goal of augmentation therapy in individuals with Alpha-1 is to maintain the blood level of alpha-1 antitrypsin above 11 μM (or about 57 mg/dl). Virtually every individual with an MZ phenotype has naturally occurring alpha-1 antitrypsin blood levels that exceed 11 μM.

There are some individuals with emphysema and an MZ phenotype who have been prescribed augmentation therapy by their physician. In most cases, the insurance company has turned these prescriptions down and said it would not pay for this therapy. Some of these patients have paid for the therapy out of their own pockets. There has been no scientific study that has evaluated whether these patients do better once this augmentation therapy has been started.

Probably the best advice for an individual with the MZ phenotype and emphysema is to make sure that they keep the alpha-1 antitrypsin in their body as “healthy” as possible. We know that environmental exposures such as cigarette smoking, second hand smoke, dust, organic fumes, and infections can impair the function of alpha-1 antitrypsin and some of these agents can also recruit damaging white blood cells into the lungs. By avoiding these agents, we can allow the alpha-1 antitrypsin that is present to perform its function as the major protector of normal lung tissue.
The new Alpha-1 program at National Jewish Center in Denver

by Robert (Sandy) Sandhaus, M.D., Ph.D., Clinical Director, Alpha-1 Foundation

It seems strange to present the “new” Alpha-1 Program at National Jewish Medical and Research Center (NJIC) in Denver, Colorado. Why? Because this new center has been in existence since 1981! It is probably more appropriate to describe the NJIC Alpha-1 Program as “new and improved,” much like a laundry detergent or a breakfast cereal. Thanks to the foresight of the administration at NJIC and a commitment to focusing the institution on chronic obstructive pulmonary disease (COPD), additional resources have been applied to the Alpha-1 Program.

The important faces have remained the same. Dr. Sandy Sandhaus still heads the program as he has since 1981. Janis Berend has been the nurse practitioner for the Alpha-1 Program over the past 17 years and remains its primary driving force. As the picture shows, however, the team has grown recently. We now have a part-time data entry person (Cara Johnson), a scheduling expert (Judy Knight), two research coordinators (Katie Crawford and Amanda Sandhaus), and an administrative assistant (Marie Kindred).

In addition, the Alpha-1 Program now has expanded office space. Over the past five years, Janis and Dr. Sandhaus have shared a windowless closet that passed for an office, so any change would be an improvement. In fact, the Alpha-1 Program now occupies two large offices. One is a corner room with windows on two sides and space for four desks. The other is a single office that was immediately appropriated by Dr. Sandhaus. Both of these rooms are on the first floor of the Southside Building, the oldest facility at NJIC. It’s a beautiful, newly remodeled three story building with tall white columns and a leaded glass entry. At the turn of the century, this building was the nursing residence at NJIC and there is some talk of it being haunted by young ladies with small white hats bobby-pinned to their hair.

In addition, NJIC has a full floor of its main building devoted to the Weinberg Clinical Research Unit. This Clinical Research Unit is where studies involving human subjects are performed at NJIC. Katie and Amanda work there on studies testing new drugs for Alpha-1 and on the NIH ‘Genetic Modifiers of Lung Disease in Alpha-1’ study.

Over more than two decades, the NJIC Alpha-1 Program has seen hundreds of individuals with Alpha-1 as well as their family members. We follow nearly two hundred families on a regular basis. This Program was the third highest enrolling site in the NIH Registry of Patients with Alpha-1 Antitrypsin Deficiency in the early 1990s and has been involved in the study of virtually every drug that has been tested in the treatment of Alpha-1.

We are very proud of the integration of the Alpha-1 Program into the philosophy that NJIC has applied to the study and treatment of all sorts of lung diseases. This philosophy holds that education, rehabilitation, psychological support, and nutrition stand on a par with traditional medical care and sophisticated testing in the effective treatment of lung disease. Every person coming to the Alpha-1 Program at NJIC is offered pulmonary rehabilitation evaluations, free education classes, dietary counseling, and access to psychology staff with a special interest in the mental health implications of having a chronic lung disease. Probably of greatest importance, every person coming to our center gets the personal attention of Janis Berend from then on … a truly priceless asset as all who have come in contact with her can attest.
There is a very active group of liver specialists at the University of Colorado medical center with a specific interest in the evaluation of pediatric and adult liver disease associated with Alpha-1. The medical center is located a couple of blocks down the street from NJC.

One of the biggest issues raised by patients with lung disease who are considering a visit to our beautiful Rocky Mountain facility is the altitude. Denver is, after all, the “mile high city.” Some individuals with lung problems find that the altitude makes their breathing more difficult. Some even require supplemental oxygen, even though they don’t need oxygen at lower elevations. On the other hand, the clear mountain air is invigorating to many individuals, even those with lung problems and this is a wonderful part of the country to visit.

Let me extend a warm welcome from the new and improved, old National Jewish Alpha-1 Program! The National Jewish Medical and Research Center has been rated as the #1 respiratory hospital in the United States by US News and World Report for the past 5 years. And we aim to do even better next year.

Brigham and Women’s Hospital is a Harvard Medical School-affiliated institution in Boston that has a major commitment to clinical care and research in respiratory disorders. In the past year, Drs. Ed Silverman, John Reilly, Dawn DeMeeo, and Steven Shapiro started the COPD Center at Brigham and Women’s Hospital to coordinate multidisciplinary clinical care of COPD patients. The Brigham and Women’s Hospital COPD Center is an Alpha-1 Foundation Clinical Resource Center and is one of the sites of the recently established National Institutes of Health COPD Clinical Research Network. By providing care by pulmonary physicians with a major focus on COPD along with support from Nutrition, Pulmonary Rehabilitation, and Smoking Cessation, the Brigham and Women’s Hospital COPD Center can address the needs of COPD patients with and without AAT Deficiency.

As one of the participating centers in the National Emphysema Treatment Trial (NETT), Brigham and Women’s Hospital has extensive experience in Lung Volume Reduction Surgery; Brigham and Women’s Hospital also has a long-standing and very active Lung Transplant Program. With additional support from liver specialists, Brigham and Women’s Hospital provides comprehensive care of Alpha-1 patients.
Hepatotoxicity in Alpha-1 Antitrypsin Deficiency: Molecular Pathogenesis and Therapeutic Approaches

by Symma Fun, Director, Research & Grants Program, Alpha-1 Foundation

A very successful Alpha-1 Symposium was held at the recent American Association for the Study of Liver Diseases (AASLD) Annual Meeting in Boston. This well attended session was chaired by Eugene Schiff, MD, Bill Balistreri, MD and Mark Zern, MD, who are all well known for their expertise relating to Alpha-1. Dr. Schiff and Dr. Balistreri have both served as President of the AASLD, and each of these doctors is currently an active member of the AASLD, the largest organization of hepatologists and gastroenterologists in the world.

Alpha-1 is commonly recognized in hepatology/gastroenterology practices and the Foundation’s booth at the AASLD is visited each year by hundreds of physicians and researchers from around the world seeking information about Alpha-1 and the latest in treatment options for their patients. But, with the heightened interest in Alpha-1 with the publication of the ATS/ERS Standards for the Diagnosis and Care of Alpha-1, it was felt that a session on Alpha-1 would be very beneficial this year. The session was organized by the AASLD and the Alpha-1 Foundation, and held on Sunday, October 26, 2003. Although the session was held in one of the largest meeting halls, tickets were sold out well in advance. There were more than 600 people attending and many more standing in the back waiting to squeeze into the meeting hall.

The meeting had several important goals:
- To identify the current hurdles to developing therapies for the liver disease associated with Alpha-1 Antitrypsin Deficiency
- To describe the recently identified biological mechanisms of protein folding relevant to alpha-1 antitrypsin present within liver cells
- To discuss the current theories regarding the development of toxicity and liver failure related to Alpha-1
- To describe the potential risk for heterozygous carriers, and
- To understand the current gene therapies being developed for treatment of Alpha-1 Antitrypsin Deficiency related liver disease

The leading experts in Alpha-1 liver research, the majority of whom are recipients of Fernandez Liver Research Initiative Grants, presented at the session. This included presentations on the basic molecular processes underlying liver disease associated with Alpha-1 by Rick Sifers, PhD, Jeff Brodky, PhD and Jeff Teckman, MD, and presentations on liver fibrosis by David Brenner, MD and the heterozygote state by Anie Regev, MD. The session concluded with two presentations on recent advances in gene therapies by Terence Flotte, MD and Mark Zern, MD.

The presentations by Drs. Sifers, Brodky and Teckman provided new information on the complex processes involved in the folding of protein, export of Alpha-1 from the liver and the impact when polymerized Alpha-1 is retained in the liver. Much progress has been made in recent years in defining each stage of these complex processes, and in defining at which stage abnormalities in degradation begin that can lead to toxicity and liver damage. Through this type of research, therapies can be developed that may be able to prevent early damage, or allow the misfolded protein to be exported, thus providing some protection to soft tissue such as the lungs.

The session also included presentations that touched upon another aspect of Alpha-1 – its interaction with other genes and/or other disease conditions. Dr. Brenner discussed gene-environment interactions and whether Alpha-1 had an effect on fibrotic liver diseases. Dr. Schiff’s colleague, Dr. Regev, presented data from their study among liver patients to determine the impact of the heterozygous state on other liver disease.

The session concluded with exciting talks by Drs. Flotte and Zern detailing their progress with a variety of gene therapies. Dr. Flotte reported on the use of adeno-associated virus (AAV) vectors to introduce Alpha-1 into the muscle. His animal studies have been successful at maintaining high levels of AAT over many months, and plans are in place for upcoming studies among humans. Dr. Zern discussed two types of therapy, immortalized fetal hepatocytes and differentiated human ES cells. This research has been successful in its early stages, and may lead to two ways of replicating human hepatocytes that may be employed in the treatment of Alpha-1 or other forms of liver disease.

The Alpha-1 Foundation is grateful to the AASLD for including this session on their program and to the speakers, and recipients of the Fernandez Liver Research Initiative Grants, for their dedication to research of Alpha-1 and the liver. It was exciting to see an increased interest about Alpha-1 among the liver doctors and researchers, and to participate in such a successful session on Alpha-1.

1 Since the time of this presentation, this trial has moved forward and is currently recruiting patients for this study.
2004 COPD & Alpha-1 Education Days Series

The 2004 Alpha-1 and COPD Education Days Series incorporates the successful Alpha-1 Education Days and includes outreach to the COPD community offering educational programming to individuals affected by Alpha-1 and COPD. Where possible, there is a separate track to provide CMEs for physicians and CEUs for respiratory therapists and nurses.

Co-sponsors of this series include the National Emphysema/COPD Association (NECA), the Alpha-1 Foundation, the Alpha-1 Association, and where noted, the National Institutes of Health Council (NIH), National Heart, Lung, and Blood Institute (NHLBI) Clinical Research Network (CRN) and the Alpha-1 Clinical Resource Centers (A1F CRC).

Unrestricted educational grants have been provided for the 2004 Alpha-1 and COPD Education Day Series by: AlphaNet, Baxter, Bayer HealthCare Biological Products Division, Dey, L.P., GlaxoSmithKline, and ZLB Behring.

Series exhibitors include: Accredro Therapeutics and Coram Health Care.

For more information on organizing an Education Day please contact Brenda Buenaventura, Alpha-1 Foundation, at (888) 825-7421, ext. 242, or email, brendab@alphaone.org.

For more information on exhibiting at or supporting an Alpha-1 Education Day please contact Marlene Erven, Alpha-1 Foundation, at (888) 825-7421, ext. 242, or email, mserven@alphaone.org.

---

Oregon Alpha-1 Education Day*
Oregon Health & Science University (A1F CRC)
Portland, Oregon
June 6, 2004

University of Alabama COPD & Alpha-1 Education Day (NIH, NHLBI CRN)
Birmingham, Alabama
July 24, 2004

National Jewish Medical & Research Center (A1F CRC) & Denver Health & Hospital (NIH, NHLBI CRN)
COPD & Alpha-1 Education Day
Denver, Colorado
August 7-8, 2004

5th Annual Jean Wall Bennett Alpha-1 Education Day
Cleveland Clinic Foundation (A1F CRC)
Cleveland, Ohio
September 18, 2004

Harbor UCLA Medical Center COPD & Alpha-1 Education Day (NIH, NHLBI CRN)
Los Angeles, California
October 2, 2004

University of Maryland COPD & Alpha-1 Education Day (NIH, NHLBI CRN)
Baltimore, Maryland
October 15, 2004

University of North Carolina COPD & Alpha-1 Education Day
(A1F Clinical Resource Center)
Chapel Hill, NC
Nov. 13, 2004

Brigham & Women’s Hospital COPD & Alpha-1 Education Day (NIH, NHLBI CRN)
Boston, MA
FALL

University of Minnesota COPD & Alpha-1 Education Day
Minneapolis, MN
FALL

University of California COPD & Alpha-1 Education Day (NIH, NHLBI CRN)
San Francisco, CA
FALL

University of Washington COPD & Alpha-1 Education Day (NIH, NHLBI CRN)
Seattle, WA
FALL

* Alpha-1 Education Day only
Meetings and Conferences

Alpha-1 Association 12th Annual Education Day Conference
Atlanta, Georgia
April 30 – May 1, 2004

Celebration of Life Golf Tournament and Dinner
Miami, Florida
May 7-8, 2004

American Thoracic Society International Conference 2004
Orlando, Florida
May 21-26, 2004
- AIF CRC Forum; May 22, 2004
- ATS/PAR Forum on COPD Survey; May 23, 2004
- Alpha-1 ATS/ERS Standards Symposium at ATS; May 26, 2004

AIF Medical and Scientific Advisory Committee Meeting
Orlando, Florida
May 26, 2004

AIF DNA & Tissue Bank Advisory Committee Meeting
Orlando, Florida
May 26, 2004

Florida Respiratory Care 2004
Orlando, Florida
May 27-28, 2004

Genetics & Ethics in the 21st Century: Gender, Race and Culture
Aspen, Colorado
July 23 – 25, 2004

European Respiratory Society Conference
Glasgow, Scotland
September 4-8, 2004

NIH State of the Science Conference on COPD and Alpha-1
Washington, DC
September

National Society of Genetic Counselors Annual Education Conference
Washington, DC
October 7-11, 2004

American Academy of Family Practitioners
Orlando, Florida
October 13-17, 2004

Alpha-1 Foundation

For information about the Alpha-1 Foundation activities and sponsored research please visit their web site, at www.alphaone.org or call their toll free number, 1-888-825-7421. You may also contact the Alpha-1 Foundation Research Registry staff by email, at registry@alphaone.org for additional assistance in locating resources related to AAT Deficiency research, to obtain information about current research activities, 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 patients, administers clinical trials involving Alpha-1 therapies, and has developed a comprehensive disease management program to enhance the quality of life for those affected by Alpha-1. AlphaNet supports Alpha-1 research and community programs.

Alpha-1 Association

Information and educational resources related to Alpha-1 Antitrypsin Deficiency can also be obtained from the Alpha-1 Association, 275 West Street, Suite 210, Annapolis, MD 21401; by calling their toll free number, 1-800-521-3025, or by visiting their web site, at www.alpha1.org.