Letter from the Director

by Charlie Strange, MD

It has been a busy and productive year at the Alpha-1 Research Registry site in Charleston, SC. In search of new membership, staff has traveled to many patient meetings all over the country including the Alpha-1 Association’s National Patient Education Day in Oakbrook, IL and regional patient education days in Tampa, FL, Portland, OR, Denver, CO, Gainesville, FL, and Lebanon, NH. This exciting issue of the newsletter includes articles on preliminary data from the Alpha-1 Coded Testing Study, updates from the Alpha-1 Foundation, notes on the International Patient Meeting in Barcelona, Spain, and a summary of the Alpha-1 Foundation sponsored workshop, “Stem Cell Therapies in Reparative Medicine.” We hope you enjoy the fall issue.

I will take the next few paragraphs to fill you in on recent changes in Registry policies and procedures addressed this summer.

The Medical University of South Carolina (MUSC) Institutional Review Board has reviewed and approved the amended procedure for accessing Registry records at patient meetings. That means two traveling Research Coordinators, Ryan Dickson and Brian Holladay, will be able to access member records outside MUSC via an encrypted Internet connection. The purpose is to facilitate Registry enrollment by confirming membership and enabling better update of Registry records. The procedures in place were devised by the Alpha-1 Foundation’s Registry Working Group and approved by the Ethical, Legal, and Social Issues Working Group after lengthy debate. Specifically, a copy of the Registry database will be placed on a secure server at MUSC only on the weekends of patient meetings. This means a Registry laptop will not travel to meetings with a copy of the Registry Database. Members who would like to further discuss the security arrangements for the Registry are encouraged to call us toll-free at 877-886-2383 in Charleston. As always, members may cancel their enrollment at any time.

Also, many of you are aware of the Health Insurance Portability and Accountability Act (HIPAA). HIPAA is a federal law that requires the protection of information that can identify you. Protected Health Information includes information that pertains to your past, present or future physical and mental health conditions, or the provision of health care. Your Registry record falls under HIPAA guidelines since you have submitted Protected Health Information (PHI) in your Registry application. Since HIPAA went into effect 4/14/2003 any member enrolling on or after that date must sign a HIPAA consent form in addition to the Registry consent.

By signing the HIPAA form a member is agreeing to allow the Registry staff to use their PHI for the purposes set forth in the Registry application. Specifically, PHI submitted to the Registry is used in reports characterizing the Registry population and for mailing research invitations to subpopulations. Reports do not identify individuals. No member’s name or address is ever revealed to anyone outside of the Registry staff. If you enrolled on or after 4/14/2003 you should have received a request to complete a HIPAA consent form. Please be sure to review, sign and return the document to the Registry site in Charleston. New versions of the Registry application will include HIPAA authorization language.

Recent amendments also include web-based membership for members outside of the US and Canada. That means international members will access news about research studies and the newsletter on our website, www.alpha1registry.org. We will provide links to the latest information via the homepage. For our members outside of North America, this will be the last paper copy of the Registry newsletter you will receive.

Please stay tuned to our website for future updates. Since international members are often excluded from study participation due to geographic location and international mailings are expensive, the Registry Working Group decided these new procedures would result in the best allocation of resources.
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Alpha-1 Foundation Update

by Robert V. Callahan, VP of Development, Symma Finn, Director, Research and Grants Programs, Kurt Panton, Alpha-1 Foundation

The Alpha-1 Foundation continues to focus on its mission to provide the leadership and resources that will result in increased research, improved health, promote worldwide detection, and effect a cure for Alpha-1 Antitrypsin Deficiency.

Grants & Awards

The beginning of the 2004-2005 grant cycle commenced with the submission of 47 letters of intent. These new projects are being submitted to the Foundation for consideration of funding and include 10 pilot studies, 4 postdoctoral fellowships, 24 research studies and 6 liver research studies. The proposed projects include investigations of stem cell and gene therapy approaches, animal models of emphysema, studies on inflammatory factors and the impact of Alpha-1 in the airways, identification of biomarkers of disease, epidemiology and targeted detection programs, and studies on the use of High Resolution Computed Topography (CT scans) in Alpha-1. The 2004-2005 grant recipients will be announced in May 2004.

Meetings and Conferences

Several scientific meetings and workshops have been held throughout the fall of 2003. On October 11th the Foundation partnered with the University of Florida for the eighth workshop in the Gordon L. Snider Critical Issues Workshop Series. This workshop, The Impact of Genetic Testing: Ethical Legal and Social Issues, addressed the effects of the identification of a genetic condition on all aspects of a person’s life. This workshop was held in conjunction with the A1F Ethical Legal and Social Issues (ELS) Working Group meeting and resulted in a greater understanding of various types of genetic discrimination. It is hoped that the workshop will also stimulate the needed social research on the impacts of genetic testing as well as raise awareness in the Alpha and lay communities of these emerging ethical, legal and social issues. Faculty for the program was drawn from the University of Florida’s Colleges of Medicine, Law and Business, University of Miami, Case Western Reserve University, University of South Florida, Baylor College of Medicine, University of Colorado and the NIH National Human Genome Research Institute.

The final meetings in the 2003 Alpha-1 Education Days series, sponsored by the Alpha-1 Foundation and the Alpha-1 Association, were held this fall. The Alpha-1 Education Day in Arlington, Texas on October 18th and the New York COPD and Alpha-1 Educational Conference October 17th and the 18th were very successful events and the final opportunities, until the series begins again next year, for the Alpha community to gather and learn more about Alpha-1.

Other meetings this fall included the Alpha-1 symposium at the Annual Meeting of the American Association for the Study of Liver Diseases (AASLD) and the National COPD Conference. The AASLD symposium highlighted recent research on Alpha-1 and the liver, research made possible by the Fernandez Liver Research Initiative. A national COPD conference was held November 14-15 that brought together the pulmonary community to highlight advances in lung research and clinical care. This conference included over 30 US COPD coalition members who discussed issues that will shape COPD agenda in the US for years to come. John W. Walsh, President and CEO of the Alpha-1 Foundation addressed the conference on the role of patient groups and Alpha-1. The Foundation’s Medical and Scientific Advisory Committee (MASAC) members met in Washington, DC during this National COPD Conference.

Improving Patient Treatment

The ATS/ERS Standards for the Diagnosis and Management of Individuals with Alpha-1 Antitrypsin Deficiency was published this fall and has become a landmark document. The ATS/ERS Standards provide the benchmark for care for those being treated with Alpha-1. The document was printed in the American Journal of Respiratory and Critical Care and will be a must-read for much of the Alpha-1 community and physicians. It will directly address who should be tested and why. The standards, for the first time in the history of Alpha-1, will establish accountability for care and testing.

The past summer the Alpha-1 Foundation and the Alpha-1 International Registry (AIR) helped organize the first International Patient Congress. This meeting brought Alphas from all over the world to Barcelona, Spain to share information about Alpha-1. This meeting was a success and led to the formation of an international patient group. For more information, or to participate in this international patient group please contact Gayle Allison, at gallison@alphanet.org.

Funding Research Towards a Cure

The National Institutes of Health awarded $5.5 million over five years to Alpha-1 Foundation Scientific Director Bruce Trappell, M.D., as principal investigator on a study on rare lung disease. The award provides funding to a project that will use the Clinical Resource Centers the Foundation began establishing in 1998. Alan F. Barker, M.D., Mark L. Brantly, M.D., Kevin Brown, M.D., William A. Gahi, M.D., Mani Kavuru, M.D., Francis X. McCormack, Robert Sandhaus, M.D., Ph.D., Edwin K. Silverman, M.D., Ph.D., James M. Stocks, M.D., and James K. Stoller, M.D., collaborated on the grant and will also be part of the study. The multi-organizational grant was due to a concerted effort by the LAM Foundation, the Pulmonary Fibrosis Foundation and the Alpha-1 Foundation in forming the Rare Lung Disease Clinical Research Network. In the last seven years the Foundation has distributed $12 million for 26 peer-reviewed projects at 24 academic institutions worldwide through its Research Grants Program.
Notes on the International Patient Congress in Barcelona, Spain June 11-12
by Elaine Alfonzo

With the Port of Barcelona as background the 1st Alpha-1 International Patient Congress took place on the 11th of June. This meeting was held in conjunction with the AIR 2003 International Meeting on Alpha-1 Antitrypsin Deficiency, which was held on June 12-13.

The Alpha-1 Foundation sponsored the participation of delegates from Alpha-1 organizations in fifteen different countries—Argentina, Australia, Brazil, Canada, Denmark, England, Germany, Ireland, Netherlands, New Zealand, Norway, Puerto Rico, Spain, Switzerland, and United States. Each of these delegates was representing an Alpha-1 organization in their country. Patients, family members, and health professionals were also participants of this important activity.

The Patient Congress offered a wonderful opportunity to meet some of the experts in Alpha-1 care worldwide, hear about the latest research, and most importantly, interact with Alpha-1 leadership from around the world. It provided the chance to share information about the resources developed in each of the Alpha-1 communities represented, what patient support groups are achieving, and have an interactive exchange on how to work closer together in the future. Input gathered from delegates will help the Foundation identify needed areas of research and lead to new ways of approaching the issues surrounding the challenges of Alpha-1.

The goals and objectives achieved at this 1st Alpha-1 International Patient Congress were:
• To bring together representatives of patient support groups from around the world to increase our understanding of the impact of Alpha-1 on those the disease affects.
• To learn of each other’s experiences and identify similar problems, concerns, and important issues, and work toward coordinated solutions.
• To identify what resources are available to patients and their families and how to access them; show where resources are missing and help find solutions so that all Alphas worldwide can benefit from existing or anticipated resources and programs.
• To educate patients on what types of research is being done and how they can participate in a research study, survey, or clinical trial.

The Patient Congress was co-chaired by Shane Fitch, President of the Spanish Alpha-1 Association and Sally Everett, Alpha-1 Foundation Board of Directors. The morning session included discussion of the problems faced by Alpha-1 patients and their families, and a panel discussion of existing resources for Alpha-1 patients and their families. Oral presentations were offered by delegates of different countries and included presentations by:

Lesley Kimble, Canada
Joe Clinton, Ireland
Shane Fitch, Spain
Gayle Allison, United Estates
Carlos Cambón, Argentina
Elisabeth Takahashi, Germany
Pat Caughley, New Zealand
Pieter Dik, Holland
Janne Ellingsen, Norway
Steven Knowles, Australia

Robert A. Sandhaus, M.D., Ph.D., Clinical Director of the Alpha-1 Foundation and AlphaNet moderated the scientific session. The scientific presentations offered during the afternoon session included a discussion of the molecular basis for Alpha-1 by David A. Lomas, M.D., Cambridge University, England. Lung disease was discussed by Jan Stolk, M.D., Leiden University, Netherlands and liver disease by Jeffrey Teckman, M.D., Washington University, United States.

Other scientific presentations included the European and American view of current and future therapies by Dr. Sandhaus, and Bruce C. Trapnell, M.D., Scientific Director, Alpha-1 Foundation. Finally, the topic of the different Alpha-1 registries was discussed, starting with the role of the International Alpha One Registry by Marc Miravilles, M.D., Hospital Clinic de Barcelona, Spain, followed by a description of the Alpha-1 Research Registry by Charlie Strange, M.D., Director, Alpha-1 Research Registry, Medical University of South Carolina, US. In addition, a presentation was given describing the Alpha-1 Genetic Modifier Study led by Edwin K. Silverman, M.D., Harvard University, US, and Robert A. Stockley, M.D., Queen Elizabeth Hospital, England.

The congress closed with a summary by John W. Walsh, President and CEO, Alpha-1 Foundation, of the most important issues covered in the Congress and a discussion of future initiatives. Gaps in resources were identified in the areas of screening and detection, awareness, access to therapy, organizational development, collaborations, funding challenges, and communications. Emphasis was given to the need of increasing collaborations between the scientific community; related liver, lung, and orphan/rare diseases organizations; government; and health research, and educational coalitions. Topics were also identified in the area of public policy and advocacy, such as the need to increase research funding, government support for targeted detection, supplemental oxygen issues, access to therapy, and transplant issues.

John Walsh, Sandy Sandhaus, Shane Fitch and other Alpha delegates to the International Patient Congress.
The term COPD signifies chronic obstructive pulmonary disease, which encompasses three very important ailments of the lung: 1) chronic bronchitis, 2) emphysema and 3) chronic irreversible asthma. All three of these conditions include obstruction to airflow in the bronchial airways and the symptom of shortness of breath on exertion.

Chronic bronchitis is an inflammation of the walls of the bronchial tree with an increase in mucus production leading to persistent cough and sputum production. Emphysema is a destructive change of the alveoli, the capillary rich sites in the lung where O2/CO2 exchange takes place. This alveolar damage results in a loss of elastic recoil of the lung and increased collapsibility of bronchial airways upon exhaling. Chronic irreversible asthma may develop from episodes of asthma in early life when airways are hyper reactive to allergens and irritants in the atmosphere. This form of asthma may be the result of remodeling of airway structure from long standing allergic asthma.

The prevalence of COPD in the USA is estimated to be 25 million individuals with two to three million manifesting predominantly emphysematous destruction of the lung. However, in many patients the elements of chronic bronchitis, emphysema and asthma are all combined in the same individual. At present COPD is the fourth highest cause of death in the US and, remarkably, deaths among females are now exceeding deaths among males, which had not been true in past years.

The most significant risk factor for the development of COPD is tobacco smoking, although COPD does occur in the absence of smoke exposure. An important subset of COPD patients is those with an inherited predisposition to develop pulmonary emphysema as the result of a genetically transmitted deficiency of a serum protein called alpha-1 antitrypsin (AAT). Individuals with the most severe deficiency of the protein (i.e. 0-15% of normal) are susceptible to develop emphysema whether or not they smoke, although smoking greatly increases the risk of developing emphysema by young adulthood or middle age. Approximately 1-2% of the patients with COPD are estimated to suffer from AAT Deficiency. The development of lung destruction in both COPD and inherited AAT Deficiency are considered to result from the same pathogenic mechanisms, namely lung tissue injury and destruction from the action of proteases. Proteases are enzymes, which are emitted by white blood cells and are capable of chemically degrading structural lung tissue components such as elastin, collagen and even cell membranes.

Under normal circumstances the action of these enzymes is held in check by chemical inhibitors, of which the most effective is AAT, a protein molecule synthesized in the liver and normally capable of increases in concentration in blood and tissues when there is an acute infection. In smokers the oxidant constituents in cigarette smoke cause a chemical change in the structure of AAT, which severely diminishes the inhibitory capacity of the molecule for proteases. These proteases are increased during acute or chronic infection or inflammation and cause lung tissue breakdown if unchecked. In inherited deficiency of AAT the existing levels of AAT in the lung and blood are inadequate to provide effective inhibition of the prevalent proteases. This imbalance between proteases and the enzymes that inhibit them, such as AAT, has provided a conceptual basis for understanding the development of emphysema and has provided a working framework for the development of therapies. In fact the discovery of the mechanism of lung tissue damage in AAT Deficiency was instrumental in the understanding of lung tissue damage for all COPD patients.

Current therapies for the lung disease of COPD and AAT Deficiency are being directed to alleviating the airway obstruction by bronchodilator aerosols and corticosteroid aerosols to overcome bronchial inflammation. Also smoking cessation and treatment of infections causing exacerbations are critical to slow the progression of the disease. None of these therapies, however, are effective in reversing the existing lung injury or significantly altering progression of the disease in either usual COPD or Alpha-1 Antitrypsin Deficiency.

In Alpha-1 Antitrypsin Deficiency, however replacement of AAT protein by regular intravenous infusions weekly, bi-weekly or monthly has demonstrated therapeutic benefit.
The Alpha-1 Antitrypsin Genetic Modifier Study: Updates and Participating Clinical Resource Centers

by Edwin K. Silverman, M.D., Ph.D.

The Alpha-1 Foundation Research Registry was created to stimulate the performance of high quality research on a variety of Alpha-1 related issues. One of the long-standing mysteries about Alpha-1 Antitrypsin (AAT) Deficiency has been why some people with AAT Deficiency develop severe Chronic Obstructive Pulmonary Disease (COPD) at an early age, while others with the same inherited form of AAT Deficiency never develop lung disease. For the past two years, Dr. Ed Silverman and collaborators from many medical centers around the U.S. have been conducting the AAT Genetic Modifier Study to investigate this mystery.

COPD includes emphysema, chronic bronchitis and asthma. People who inherit AAT Deficiency are at increased risk for developing COPD, but some individuals with AAT Deficiency develop COPD in their twenties, while others never develop COPD. Cigarette smoking accounts for some of this variation in the development of COPD among AAT-deficient people. Differences in risk for lung disease, and it has been clearly proven that cigarette smoking is a major risk factor for lung disease in people with AAT Deficiency. However, there are likely other important factors as well. In preliminary research in the late 1980's, Dr. Silverman and his collaborators 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 AAT Deficiency was influenced by inherited factors.

Building on this work, a group of physician-scientists joined together to try to learn whether there are any additional inherited factors that modify the expression of or contribute to the development of lung disease in individuals who inherit severe AAT Deficiency. Dr. Silverman at 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 (CRC) around the country are currently collaborating on this study, including: Denver, Colorado (led by Dr. Robert Sandhaus); Tyler, Texas (led by Dr. James Stocks); Cleveland, Ohio (led by Dr. James Stoller); New York, New York (led by Drs. Gerard Turino and Ed Eden); and Gainesville, Florida (led by Dr. Alan Barker). An additional group of Alpha-1 Foundation CRC's is being established, including sites in South Carolina, North Carolina, Nebraska, Washington, California, Ireland, and Canada. There are also CRC's located at Brigham and Women's Hospital in Salt Lake City, Utah.

If this study leads to the identification of inherited factors that modify the expression of lung disease in AAT deficient individuals, improved understanding of COPD may result which could lead to the development of new treatments. In order to identify these inherited factors, these investigators are performing measurements of pulmonary function, assessing respiratory symptoms and environmental exposure 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. In order to make it as simple as possible to participate in this study, home visits can be arranged at a time of your convenience. Even if you do not live near one of the study CRC's, members of the Traveling Research Team can meet with you at your home to perform the study testing.

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.
old and who are 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. An individual’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 individuals that participate to assist in contacting their brothers and sisters who also have severe AAT Deficiency, as well as any available parents, to assess whether they would also like to participate in this study. At the beginning of the study, people who had undergone lung transplantation were not eligible for the study, but we have now learned that such individuals can provide very useful information for this study. The goal of this study is to include as many people with severe AAT Deficiency 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, and reimbursement for travel to the study site.

Over the past two years, more than 200 people have participated in the AAT Genetic Modifier Study. This enrollment is an excellent start, but many more families will need to be included if this study is to be successful. 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 CRC of your choice directly to arrange participation.

This research project is a multicenter collaborative study that will take approximately five years to complete. However, with the support of the Alpha-1 community, we are confident that this project will discover important new information about AAT Deficiency that may ultimately lead to improvements in diagnosis and treatment. We hope that you will consider participating in this important study.
The Alpha-1 Coded Testing Study: Results of a Study to Examine Participant Perceptions of Genetic Testing for Alpha-1 Antitrypsin Deficiency

by Ryan Dickson, Alpha-1 Coded Testing Study Coordinator

The Alpha-1 Coded Testing (ACT) Study investigated the risks, benefits and psychological impact of genetic testing for Alpha-1 Antitrypsin Deficiency (AATD or Alpha-1) in a cohort of individuals who requested a home administered, confidential, finger stick blood test. Between January 2002 and February 2003, 3,551 kits were requested. Of these, 1159 (33%) test packets were returned. The ACT Study utilized the infrastructure of the Alpha-1 Foundation including a patient registry, regional meetings and website to advertise the ACT Study. Individuals asking for a test kit were mailed a study packet which included a) informed consent, b) a pre-test questionnaire, c) a finger stick blood-spot test kit, d) a brochure discussing the testing procedure, and e) a postage-paid return envelope. Returned test kits were coded by the research team and mailed to the University of Florida’s Alpha-1 Genetics Laboratory. Results were returned to the research team at MUSC. Participants were then mailed a follow-up packet that consisted of a) a letter detailing the genotype results of the test b) a post-test questionnaire, and c) a postage-paid return envelope. In addition, all participants who tested either positive for AATD (genotype ZZ or SZ) or were a carrier (genotype MZ) received an informational support brochure addressing possible health concerns. All participants had access to toll free telephone support.

Pre-test questionnaires included items pertaining to demographics, smoking status, reasons for seeking testing, and referral source. Six specific potential risks (losing health insurance, higher insurance premiums, job loss, psychological risks, religious impact, and increased stress) were presented in a scaled format (1=not likely, 5=very likely).

A total of 991 persons age 18 or over were included in the pre-test questionnaire analysis. The 991 participants averaged 43 years old with a range of 18-82 years. In keeping with the known demographics of AATD, 93 % of participants were Caucasian. Sixty one percent of participants were female. A total of 84% of participants reported having health insurance and 89% of participants report believing testing will provide them with very important information about their genetic makeup. The primary referral source for testing was family (57%) with 11% of participants reporting symptoms as a reason for testing. The results of the genetic testing included:

- 515 (52%) negative diagnoses of genotype MM (462) or MS (53)
- 407 (41%) carrier diagnoses of genotype MZ and
- 69 (7%) positive diagnoses of SZ (27) or ZZ (41)
- Rare alleles requiring serum phenotyping were suspected and confirmed in 2 cases.

Study findings suggest that, prior to testing, individuals generally anticipated more benefits than they did risks (Table 1). The greatest benefits were anticipated for the helpful effect of genetic information for the family and for establishing a firm diagnosis. Despite less than 40% of participants viewing higher insurance costs as a significant risk at the pre-test questionnaire, confidentiality was a very important reason for testing through the ACT Study for 61% of participants.

Persons concerned about confidentiality were more likely to be concerned about risks associated with testing.

The 24.4% prevalence of smoking among study participants is consistent with the current national statistic of 23.5%. One of the most important outcomes of establishing a diagnosis is to effect smoking cessation since smoking is the number
one environmental factor associated with developing Alpha-1 related lung disease. More than 75% of ACT participants report a strong likelihood of smoking cessation if they are diagnosed with Alpha-1. Little is known about smoking cessation among a newly diagnosed adult population predisposed for Alpha-1 lung disease. Follow up of this cohort may provide insight to success in quit attempts. Results from the National Heart Lung and Blood Institute’s Registry of Patients with the Deficiency of Alpha-1 Antitrypsin suggest that the Alpha-1 population is amenable to smoking cessation since only 8.3% of that cohort reported current smoking (McElvaney 1997). Also, previous studies indicate that screening at birth leads to a lower incidence of smoking among ZZ individuals suggesting at risk populations may benefit from early detection. (Thelin 1996).

A total of 512 (52%) participants who returned the post-test questionnaire, were first time testers and were at least 18 years old. Responses to the post-test questionnaire were compared between participants with a positive, carrier and negative test result. The post-test questionnaire included multiple items used to assess willingness to divulge results of genetic testing to others (e.g., family, employer, life/health insurance). Additionally, participants were asked to rate anticipated effects from genetic testing on a 5-point scale (1=not likely, 5=very likely). These effects included both potential benefits (e.g., improved physical health) and potential harms (e.g., depression, anxiety).

Following testing, Alpha-1 deficient participants and carriers appeared to be quite forthcoming with family members about their genetic status (Table 1). Participants with a carrier diagnosis were more likely to tell siblings, children and parents about their test results than participants with a negative test result. Although it was not statistically significant, participants with a positive test result were more likely to tell their physician about their test result as compared to participants with a carrier or negative test result. Despite less than 40% of participants rating the likelihood of losing insurance or increased insurance premiums a high risk at the pre-test questionnaire, many participants reported to be unsure if they would tell their physician or insurance company about their test result. These findings may underscore the fact that concerns about insurance may increase after receiving a test result.
The expectation of improved health after receipt of test results increases with the severity of test results. Participants receiving a positive test result rate the expectation of improved health higher compared to participants with a carrier or negative test result. Also, participants with a carrier test result rate the expectation of improved health higher than persons with a negative test result. This finding suggests knowledge of genetic status may serve as a stimulus for healthy behavior change for these participants. There seems to be a general consensus among participants that the benefits of testing outweigh the risks, and a trend of relief and a feeling of control with knowledge of test results. Forty percent of participants reported, “The test will have a positive impact on my quality of life,” and, “I will feel more in control of my life,” as very likely.

The vast majority of ACT testers (75%) report depression and anxiety as “not likely”. However, there is more of a trend towards those feelings in persons with positive or carrier diagnosis. Among 31 participants with a first time positive diagnosis in the ACT Study 13% reported a strong likelihood of depression versus 2.5% of carriers and 2.2% of persons with a negative diagnosis. We found 25% of persons with a first time positive diagnosis reported depression to be moderately likely versus 12% of carriers and 7% of participants with a negative diagnosis. Results were almost identical between the two groups when asked a similar question about anxiety. Taken together with prior research, the findings from the present study indicate that knowledge of genetic status does result in moderate distress for some people.

In summary, prior to testing, participants anticipated few risks but several benefits of testing. Following testing, participants indicated that they would share the results with family and often with physicians, but were unlikely to share results with insurance companies. After testing, AAT deficient individuals with SZ and ZZ genotypes were more likely to expect depression and anxiety, as well as increased expenditures on healthcare compared to participants with normal phenotypes. Paradoxically, participants with AATD were more likely to expect improved health compared to participants with a normal or carrier phenotype suggesting that test takers may change their lifestyle and benefit from knowledge of genetic status. The ACT Study demonstrates that confidential home testing for genetic disorders can be successfully administered with a comprehensive program of participant support. Evident concerns for insurability drive participants to seek privacy of test results. We are pleased that the Alpha-1 Foundation is continuing this important study providing people with access to confidential testing. For more information please contact the ACT Study coordinator toll free at 1-877-886-2383 or email alphasite@musc.edu.

Table 1: Risks and benefits of genetic testing

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<td>Losing your job</td>
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<td>Psychological risks associated with genetic knowledge</td>
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<td>Increased stress knowing that I have normal genes while a family member has abnormal AAT genes</td>
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<tr>
<td>Establishing a diagnosis</td>
<td>882</td>
<td>4.34</td>
<td>1.11</td>
<td>82</td>
</tr>
<tr>
<td>Benefit of a drug treatment not available without a diagnosis</td>
<td>844</td>
<td>3.89</td>
<td>1.41</td>
<td>67</td>
</tr>
<tr>
<td>Genetic knowledge that may be helpful for family members</td>
<td>882</td>
<td>4.47</td>
<td>1.00</td>
<td>86</td>
</tr>
<tr>
<td>Peace of mind if the genetic test is normal</td>
<td>876</td>
<td>4.28</td>
<td>1.19</td>
<td>79</td>
</tr>
</tbody>
</table>

*Rated on a 5-point Likert scale (1 = low risk or benefit, 5 = high risk or benefit)
\% scored the highest score of 4 or 5 on the Likert scale
N = number of participants responding to the question
Table 2: Comparison of participant plans to tell others about their test result between participants with a positive (ZZ or SZ), carrier (MZ), or negative (MM or MS) test result.

<table>
<thead>
<tr>
<th></th>
<th>% Who will tell a Positive Test Result</th>
<th>% Who will tell a Carrier Test Result</th>
<th>% Who will tell a Negative Test Result</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Spouse</td>
<td>100.0</td>
<td>96.5</td>
<td>94.4</td>
<td>0.57</td>
</tr>
<tr>
<td>At Least One Sibling</td>
<td>92.0</td>
<td>94.9</td>
<td>77.3*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Children</td>
<td>100.0</td>
<td>95.4</td>
<td>84.9*</td>
<td>0.003</td>
</tr>
<tr>
<td>Parents</td>
<td>95.2</td>
<td>21</td>
<td>21</td>
<td>94.7</td>
</tr>
<tr>
<td>Employer</td>
<td>26.7</td>
<td>17.9</td>
<td>27.8</td>
<td>0.18</td>
</tr>
<tr>
<td>Personal Physician</td>
<td>82.6</td>
<td>59.9</td>
<td>61.6</td>
<td>0.11</td>
</tr>
<tr>
<td>Health Insurance Co.</td>
<td>10.5</td>
<td>17.3</td>
<td>27.3*</td>
<td>0.05</td>
</tr>
<tr>
<td>Life Insurance Co.</td>
<td>6.7</td>
<td>15.2</td>
<td>25.7*</td>
<td>0.037</td>
</tr>
</tbody>
</table>

*Different from carrier groups (p<0.05)

p-value < 0.05 is statistically significant
Ask the Alpha Doc:

by Edwin K. Silverman, M.D., Ph.D.

"All of the members of my family had Alpha-1 testing, and my teenage daughter was found to have type PI ZZ AAT Deficiency. What are the chances that she will develop lung disease?"

The short answer is that we really don’t know. Although Alpha-1 Antitrypsin (AAT) Deficiency has been known about for more than 40 years and is one of the most well-studied inherited conditions, we still have much to learn. While thousands of AAT deficient people have been identified over the past 40 years, most of these individuals have been tested for AAT Deficiency because they had a health problem, such as lung or liver disease. This understandable testing pattern for AAT Deficiency has made it difficult to know about the health status of the entire group of AAT deficient individuals. For instance, if you only test for AAT Deficiency in people with lung disease, it will look like everyone with AAT Deficiency has lung disease. The problem is that we don’t know how common AAT Deficiency is in people without lung disease. Based on the estimated frequency of AAT Deficiency in the United States, there are approximately 80,000 AAT deficient people in the U.S., but only about 5,000 of them have been identified. Among the approximately 75,000 AAT deficient individuals in the U.S. that have not been identified, we don’t know how common lung disease is in this group of people. In the early 1970’s, 200,000 newborns were screened for AAT Deficiency in Sweden, and 122 individuals with severe AAT Deficiency were identified. We know that by the age of 30, significant lung disease has not developed in any of these Swedish AAT deficient individuals. As these individuals get older, we will learn much more about the risk of lung and liver disease in AAT deficient people in the general population.

We do know that cigarette smoking is a major risk factor for lung disease in AAT Deficiency, and it is critically important for all AAT deficient people to be nonsmokers. Other health measures such as avoiding exposure to second-hand smoke, aggressive treatment of respiratory infections, and regular monitoring with breathing tests are reasonable to consider, but we don’t have clear evidence that these measures will reduce the chances of developing lung disease. If studies like the AAT Genetic Modifier Study succeed in identifying other inherited risk factors for severe lung disease in AAT deficient people, we may be able to provide aggressive treatment to people that are especially likely to develop lung disease before they develop breathing problems.
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.
Stem Cell Therapies In Reparative Medicine, A Critical Issue Workshop, Sponsored By The Alpha-1 Foundation, April 19-22, Miami, FL

Notes by Katherine Arnoldi

(First, A note of thanks from Katherine to John W. Walsh, President and CEO, Alpha-1 Foundation)

Dear John,

Well, I could make this longer. I cut out stories about meeting the researcher from Sweden on the beach and discussing Alpha-1 in our bathing suits in waist high crystal clear water, or being in the customs line with Tatiana Zorina and Suzanne Bertera from the University of Pittsburgh and discussing Alpha-1 and their research, or meeting a cruise passenger who told me her husband was on oxygen at age 50 and she was taking a vacation from being a caretaker, and who, when I told her about Alpha-1, told me God had arranged all of it: her going on the cruise, the Alpha-1 conference being on that particular cruise and me eating maui-mai at her table. I agreed. But thanks to you, too! Many, many thanks. — Katherine Arnoldi
My grandchild, Sarah, is the most beautiful thing in the world. She laughs and smiles and giggles, is wild about being thrown up in the air and twirled around and around. She is bursting with joy to be a part of the world. There's a chance she could also be a Pi SZ. I do not want Sarah to live as I have, with constant pneumonias that started in my teens, with a continual temperature of 101 that would not go away for years, with constantly taking antibiotics that cease to be effective, or with spending mornings trying to cough up that last little bit of, well, I'd rather not say. I, like every grandparent, want my Sarah to have a life free of disease, hardship and pain.

So, when I was asked to attend the Stem Cell Therapies in Reparative Medicine Workshop, sponsored by the Alpha-1 Foundation, I knew the implications that such research could have for my Sarah or for Sarah's children. Of course I would go. The conference would be held on a weekend cruise to the Bahamas. "A cruise?" I asked, "Why a cruise?"

My friend Scott, who has a Master's Degree in Travel Management and who has worked for ten years as a meeting planner told me that a cruise is the most economical venue for meetings. "It's a bargain," he said. I also realized that the presenters could not just give their talks and skip out. At dinners and in the evenings, researchers could meet, increasing the chances for the exchange of ideas and collaborations. It also improved my chances to meet the participants and tell them how grateful I was that their research may change my life and the life of my Sarah.

The purpose of the stem cell therapies workshop was to bring together researchers from all over the world who are dedicating their lives to the prospects of helping those that suffer from many diseases including Alpha-1. The conference created a positive environment for stimulating and important research collaboration. Many important technical hurdles were discussed and ideas to meet common goals were exchanged. Let me tell you a little about what I learned. What is a stem cell anyway?

Stem cells have two important characteristics that distinguish them from other types of cells. First, they are uncommitted cells that renew themselves for long periods through cell division. The second is that under certain physiological or experimental conditions, they can be induced to become cells with special functions such as the beating cells of the heart muscle or the insulin-producing cells of the pancreas (www.nih.gov).

Scientists primarily work with two kinds of stem cells from animals and humans: embryonic stem cells and adult stem cells, which have different functions and characteristics. Embryonic stem cells are found in the 3 to 5 day old embryo where a small group of about 30 cells called the inner cell mass gives rise to the hundreds of highly specialized cells needed to make up an adult organism. Adult stem cells are found in tissues, such as bone marrow, muscle, and brain where they generate replacements for cells that are lost through normal wear and tear, injury, or disease (www.nih.gov).

Studies of human embryonic stem cells may yield information about the complex events that occur during human development. A primary goal of this work is to identify how undifferentiated stem cells become differentiated. Scientists know that turning genes on and off is central to this process. Some of the most serious medical conditions, such as cancer and birth defects, are due to abnormal cell division and differentiation. A better understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapy (www.nih.gov).

Human stem cells could also be used to test new drugs. Other kinds of cell lines are already used in this way. Cancer cell lines, for example, are used to screen potential anti-tumor drugs. But, the availability of stem cells that are able to develop into many different cell types would allow drug testing in a wider range of cell types. However, to screen drugs effectively, cell conditions must be identical when comparing different drugs. Therefore, scientists will have to be able to precisely control the differentiation of stem cells into specific cell types and stages for testing (www.nih.gov).

Perhaps the most important potential application of human stem cells is the generation of cells and tissues that could be used for cell-based therapies. Today, donated organs and tissues are often used to replace ailing or destroyed tissue, but the need for transplantable tissues and organs far outweighs the available supply. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including Parkinson's and Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and Alpha-1.

To realize the promise of novel cell-based therapies for such pervasive and debilitating diseases, scientists must be able to easily and reproducibly manipulate stem cells so that they possess the necessary characteristics for successful differentiation, transplantation and engraftment. To meet these goals, stem cells must be reproducibly made to: proliferate extensively, differentiate into the desired cell type(s), survive in the recipient after transplant, integrate into tissues after transplant and avoid harming the recipient in any way.

Despite existing hurdles, progress has been reported. Stem cells harvested from the brain of a man with Parkinson's were grown into neurons and then transplanted into his brain at Cedars-Sinai Medical Center in Los Angeles. Most of his symptoms disappeared (Washington Post 5/9/02). Massachusetts scientists have grown kidneys from cloned cow embryos and successfully transplanted them (Boston Globe 1/30/02). To summarize, the promise of stem cell therapies is an exciting one, but significant technical obstacles remain that will only be overcome through years of intensive research and continued collaboration such as that fostered by the Alpha-1 Foundation's Gordon L. Snider Critical Issues Workshop on stem cell research.

As if our limited knowledge were not a big enough stumbling block, I also learned progress in stem cell research is further hampered currently by the unavailability of stem cells in the United States until a national policy is formulated. On August 9, 2001, President Bush prohibited federal funding on any but existing cell lines, most of which are inaccessible or compromised. Currently Great Britain has no restriction on stem cell research, Australia and Canada have liberal policies and India and China may even be exporting cell lines. In early May of 2002, Orrin G. Hatch (R-Utah) introduced a bill that would "outlaw the creation of cloned human babies but allow the cloning of human embryos for research" (Washington Post 5/1/02). While the debate wages on, research is continuing within the limitations allowed.

While medical ethicists, theologians, philosophers, politicians and sociologists contemplate the future of stem cell research, what can we Alphas do? One of the reasons that this research could help Alphas and others who need transplants is because the need for organs will always outweigh the supply.
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Dr. Arthur Caplan, an ethicist from the University of Pennsylvania suggests a policy of presumed consent for organ donation that Spain, France, Austria, Belgium and the Czech Republic have (your driver’s license would say you are not a donor, otherwise you are presumed to be one), until then we Alphas can make sure we, at least, are registered and our relatives will give consent. How many Alphas that die while getting transplants have made such provisions to donate their working organs?

We are a large, organized group. We can lobby now for stem cell research, or presumed consent legislation. We can raise awareness in our communities about Alpha-1 and organ donation. We can organize fund raisers, attend the Foundation and Association’s Advocacy Days to encourage the doubling of funding for the FDA’s Office of Orphan Product Development, and we can do what we can to assist the vision of brave people like John W. Walsh, an Alpha, who just up and formed the Alpha-1 Foundation from scratch with the hope that in the future there will be someone who will say, “I used to have Alpha-1.”

Perhaps someone like my grandchild Sarah, now all roly-poly and full of laughs and love, will be that person. Perhaps it will be someone like your child or grandchild, someone who is the most beautiful thing in the world to you. Or, and this may be a possibility, it will be you who says, “I used to have Alpha-1.”

Calendar of Events

**American Association for Respiratory Care (AARC)**
**International Respiratory Congress**
Las Vegas, NV
December 8-11, 2003

**Rare Lung Disease Consortium Meeting**
Cincinnati, OH
January 17, 2004

**GOLD Science Meeting in London**
London, England
January 29-30, 2004

Alpha-1 Foundation

For information about the Alpha-1 Foundation activities and sponsored research please visit their web site, at www.alfaone.org or call their toll free number, 888-825-7421. You may also contact the Alpha-1 Foundation Research Registry staff by email, at registry@alpaphone.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 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. Since its inception in 1995, AlphaNet has contributed over $10 million to support 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, 1225 Eye Street NW, Suite 1225, Washington, DC, 20005-5918; by calling their toll free number, 800-521-3025; or by visiting their web site, at www.alpha1.org.

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