LETTER FROM THE MEDICAL AND SCIENTIFIC ADVISORY COMMITTEE CO-CHAIRS

by Mark L. Brantly, M.D., and James K. Stoller, M.D.

The past six months have been a productive time in the field of Alpha-1-Antitrypsin (AAT) deficiency research. Clinical trials on aerosolized product have begun, new discoveries in genetics and liver research have been made, and a number of important scientific meetings have been held, such as the Haverford International Scientific Conference and the recently held Critical Issues Workshop on Screening and Detection.

The scientific meetings were well-attended gatherings that presented the status of current research on AAT genetics, molecular biology, relation to liver disease, economic and psycho-social impacts and epidemiology. These multidisciplinary meetings brought together the leading researchers, industry representatives and government leaders in the field of AAT deficiency to share their latest findings, to stimulate interaction and collaborative research efforts and to increase understanding of the complexity of the disorder. Although much remains to be discovered about AAT deficiency, the Haverford International Conference in particular highlighted the many advances that have been gained in the past few years in our understanding of the basic science and our ability to manage and treat alpha-1 antitrypsin deficient individuals.

It's also an exciting time to be a part of the Alpha community. Patients and community organizations have been well represented on Alpha One Foundation Working Groups, at many of the recent meetings and workshops, at Team Alpha rides and at the national organization meetings and events. Alphas have contributed a great deal to discussions at meetings and workshops with both personal and professional examples of the disorder's impact on their lives, as well as having the opportunity of learning from the experts in the field. We encourage and applaud such activism, and will continue to provide information and the opportunity for Alphas to participate in research and community outreach activities.

Although not everyone can attend national meetings or participate in workshops and forums, Alpha One Research Registry enrollees do have the opportunity to participate in the upcoming clinical trials on aerosolized augmentation therapy and the current research studies (see page 7 for more information on current studies). It is important to encourage all diagnosed Alphas and their family members to enroll in the Registry. The questionnaire they fill out to enroll becomes an important part of the data being gathered on the epidemiology of AAT deficiency. In addition, enrolling ensures that Alphas are eligible for participation in research studies or clinical trials, including current studies such as the Marital Coping study and the soon-to-be-distributed questionnaires for Phase 2 of the Cost of Illness Study. These studies have been carefully reviewed by the Medical and Scientific Advisory Committee of the Alpha One Foundation and represent rigorous scientific attempts to advance understanding of AAT deficiency.

Data collected in these studies is then used by other researchers in implementing screening programs, establishing public health policy, or during lobbying efforts to effect legislation on health care and insurance costs. We, as scientists, physicians and researchers, have found the active involvement of Alphas to be both motivation and very supportive of our work. We appreciate your continued interest in our work and your active participation in the research that will someday lead to a cure.
The Alpha One Foundation promotes a wide exchange of information and current research findings throughout the year at a series of Workshops, Conferences and Forums. Each of these meetings focuses on a specific topic or type of therapeutic approach within the field of AAT deficiency research. The following are descriptions of Foundation sponsored meetings held in 1999 and plans for upcoming conferences.

**International Scientific Conference On Therapies For Alpha_1-Antitrypsin Deficiency, Haverford, PA, June 17-20, 1999**

*by Symma Finn, Research Administrator, Alpha One Foundation*

The International Scientific Conference on Therapies for Alpha_1-Antitrypsin Deficiency was held this past summer at Haverford College, Haverford, Pennsylvania on June 17-20, 1999. The conference was sponsored by the Alpha One Foundation, with additional support from the National Institutes of Health, National Heart Lung and Blood Institute and Office of Rare Disorders, and the National Emphysema Foundation. The organizing committee (Gordon L. Snider, M.D., Mark L. Brantly, M.D., Robert J. Fallat, M.D., James K. Stoller, M.D., and Robert Sandhaus, M.D.) envisioned a relatively isolated conference setting, with a small, invited group of AATD experts as participants, and an ambitious agenda with a common theme of expanding on the knowledge base relating to new therapies.

The setting was specifically chosen to be easily accessible to European participants.

As hoped, the conference achieved its goals and was an unqualified success. The ‘Haverford’ conference will be the first of annual conferences sponsored by the Alpha One Foundation which focus exclusive-
ly on research in the field of alpha1-antitrypsin deficiency, and planning is already underway for next year's conference. This year's conference was the first such international conference dedicated solely to AAT deficiency research to be held since the pivotal WHO meeting in 1996. A primary goal of the conference was to shorten the time between the research bench and the receipt by patients of new therapies.

The conference covered a broad range of topics, with an emphasis on AAT deficiency in lung disease. Presentations included sessions on inflammatory processes, markers of inflammation and destruction in the lung. Other presentations updated the difference between asthma and COPD and the separate pathogenesis among the various lung disorders. Other topics included the mechanisms of gene transport, and the latest in gene therapy. Another exciting new topic was the use of retinoic acid to regrow alveolar in emphysematous lungs. Presentations also included the results of clinical trials on aerosol delivery of alpha1-antitrypsin to the lungs. Of particular interest was one of the final sessions, in which representatives of the FDA discussed study design and clinically meaningful endpoints. As with other topics presented at the conference, this talk generated lively and productive discussions, and may lead to either more focused research design geared to quicker drug approval and/or a reevaluation of the clinical endpoints required for drug development and approval.

Another highlight of the conference was the attendance and award presentation made to Professor Sten Eriksson, Lund University, Sweden. One of the discoverers of the disease, and early researcher in the field, the Alpha One Foundation was proud to present to Dr. Eriksson the Award for Scientific Achievement in Alpha1-Antitrypsin Deficiency Research. This award will be presented in perpetuity as the Eriksson Award, and will recognize the most important researchers in the field. The keynote speaker at the award dinner, Dr. Ron Crystal, another influential and early researcher in the field, gave an informative talk which enlivened our evening. The Alpha One Foundation also announced the recipients of the Young Investigator Fellowship Awards, and introduced the fellows, Sihong Song, Ph.D., and Alexei Guerrasimov, M.D.

As evidenced by the many wonderful comments received following the conference, the "informal" atmosphere on the Haverford College campus, although rather rustic, did provide a proper setting for focusing on the science and did indeed promote a casual, informal and interactive meeting. Despite rush hour traffic nightmares, unscheduled and clamorous fire alarms, shared bathrooms with abundant cold water in the showers, towels the size of wash cloths, I wouldn't have foregone the delights of seeing renowned scientists padding down the hall in their scivvies or struggling into bunk beds at "Camp Haverford". But despite the "shades of everyone's freshman dorm life" as one participated so aptly noted, many commented on their appreciation of the stimulating interaction and the many new friends and former colleagues encountered at this year's meeting. I found Haverford College to be a most beautiful and historic campus and enjoyed, as did many of the participants; the fine walking and jogging trails around campus, the beautiful foliage, and the unseasonably cool weather. I look forward to next year's conference, and the continuation of our exploration into the complex and interrelating biological processes relating to AAT deficiency.
Critical Issues Workshop Series: Screening and Detection for \( \text{alpha}_1 \)-Antitrypsin Deficiency

The Alpha One Foundation recently held a one-day workshop on issues relating to detection of \( \text{alpha}_1 \)-antitrypsin (AAT) deficiency. The meeting was co-chaired by R. A. Sandhaus, M.D., Ph.D., National Jewish Hospital, Denver and by Edward A. Silverman, M.D., Ph.D., Harvard, MA. Invited participants included members of both the Alpha One Foundation and the American Thoracic Society/European Respiratory Society (ATS/ERS) Working Groups on Screening and Detection, government representatives, academic and clinical researchers, educators, advocacy and support group representatives and members of the Alpha community. Presentations were given on previous screening programs, current efforts and plans for future screenings. Also discussed was the epidemiology of AAT deficiency, the prevalence of the various types of \( \text{alpha}_1 \)-antitrypsin deficiency and penetrance of the disorder among various populations, and the ethical, legal, and social issues relating to screening programs. There was an outstanding presentation by Congresswoman Louise Slaughter on the legislative issues relating to screening and detection of a genetic disease, and a review of a recent pilot study on screening within a targeted population. As discussed more fully in Dr. Falla’s article on the Screening & Detection Working Group (see page 5), the workshop provided a focus and recommendations on the most critical issues related to screening and detection. An anticipated outcome of the workshop is the promulgation of policies and legislation that support responsible screening efforts for both \( \text{alpha}_1 \)-antitrypsin deficiency, and by extension, other genetic diseases.

American Association for the Study of Liver Diseases (AASLD) Alpha One Satellite Meeting

The Foundation sponsored a meeting which focused on liver disease and AAT deficiency, and was held during the AASLD Annual Meeting in Dallas, TX, on November 8, 1999. The meeting was entitled, “\( \text{alpha}_1 \)-Antitrypsin Deficiency and Liver Disease: History and Ongoing Investigations”. Since it was the fiftieth anniversary of the AASLD, well-known liver experts were invited to speak on the history of liver disease and its connection to AAT deficiency, as well as give presentations on the most current findings in the field. The Alpha One Foundation also exhibited at the AASLD, with information about AAT deficiency related to liver disease.

American Thoracic Society Principal Investigator’s Forum and Poster Session

Next spring the Alpha One Foundation will sponsor its second annual PI Forum at the Annual American Thoracic Society (ATS) meeting in Toronto, Canada. This forum will highlight current research in AAT deficiency within the larger context of pulmonary medicine. The 1999 PI Forum was successful in sharing the latest research findings, and included discussion about studies not previously published or presented at other forums. There were fifteen posters from five countries representing the latest research in AAT deficiency on studies ranging from molecular lung biology to pharma-economics. The Alpha One Foundation presented $1,000 Travel Awards for the three best posters on Alpha One Antitrypsin Deficiency Research to Morten Dahl, Ph.D., Copenhagen, Denmark, to Cyril Rooney, Ph.D., Dublin, Ireland and to Peter Elliott, Ph.D., The Netherlands. Each poster was presented by the researchers with commentary on hypothesis, research design and an interpretation of the findings. The session also introduced several young investigators to the network of \( \text{alpha}_1 \)-antitrypsin researchers, and brought together both European and North American researchers for lively discussion about the latest research relating to AAT deficiency.
WORKING GROUPS & COMMITTEES

Alpha One Foundation Screening & Detection Working Group
by Robert Fallat, M.D., Frederick de Serres, Ph.D., Robert A. Sandhaus, M.D., Ph.D.

One of the major efforts for the alpha community is earlier diagnosis of alpha 1-antitrypsin (AAT) deficiency so that appropriate prevention and treatment can be started. For many years, screening and detection programs have been sponsored by Bayer and the Alpha 1 Association in conjunction with local chapters and home care companies. These previous screening and detection programs have been designed and implemented with variable success.

In the Fall of 1998, the Alpha One Foundation instituted a two-part program to focus on the issues and mechanisms of screening and detection. The initial program was a pilot screening and detection program conceived and implemented by Dr. Lora Fleming at the University of Miami. The second program was the development of a working group to identify issues and establish guidelines for future screening and detection programs.

The Working Group is co-chaired by Dr. Fred de Serres, a board member of the Alpha 1 Association, and Dr. Robert "Sandy" Sandhaus of the Alpha One Foundation Board of Directors. Other appointments to the Working Group included three ethicists, Drs. Evan De Renzo, Robert Wachbroit and Mark Yarborough, an economist, Dr. Daniel Mullins, two legal consultants, Sally Everett of the Alpha One Foundation Board of Directors, and Barbara Fuller of the NIH Office of Policy Coordination, and a pediatric pulmonologist, now with the NIH Human Genome Research Institute, and Dr. Ben Wilfond, who has brought a rich experience from similar programs with Cystic Fibrosis (CF).

Another Working Group member is Dr. Henry Silverman, who is the editor of the psychosocial, legal and ethical section of an upcoming Consensus Statement on AAT deficiency sponsored by the ATS and ERS. Dr. Ed Campbell from the Salt Lake City phenotyping center, John Walsh, President and CEO of the Alpha One Foundation, and Robert Fallat, M.D., round out the panel. The Alpha community is represented by Dr. de Serres, Sally Everett, and John Walsh, who bring a patient’s perspective to the group.

The Working Group met several weekends from December 1998 to June 1999. These Working Group meetings culminated in a full-day workshop on September 13, 1999 in Bethesda with presentations by industry, physicians, patients and the Alpha 1 Association on past screening and detection projects.

The critical issues discussed at the workshop were summarized by Dr. Sandhaus, as follows:

- "Screening" is defined as testing an asymptomatic individual. Since there are no significant interventions in asymptomatic infants, children or even young adults who are non-smokers, and since there are still many unresolved ethical, legal, insurance and psychosocial issues, it was felt that widespread screening is not recommended but rather should be focused in the following situations:
- Pre-marital, pre-natal or neonatal testing would be limited to families with known AAT deficiency, obstructive airway disease (OAD) or neonatal liver disease
- Adults with family members with AAT deficiency, OAD or liver disease
- Adolescents could be offered testing with permission of both the adolescent and one parent if AAT deficiency, OAD or liver disease exists within the family
- “Detection”, on the other hand, is defined as testing in someone who is symptomatic with lung or liver disease or who has spirometry indicating the presence of OAD. Encouraging a wider use of spirometry in family practice offices as well as in public screening programs was felt to be a more effective and efficient way of testing for AAT deficiency since the people at greatest risk and most likely to have AAT deficiency are cigarette smokers with OAD.
- Certain occupations such as coal and hard rock miners are areas where spirometry and AAT deficiency testing should be applied.
- Finally, it was concluded that heterozygotes, particularly SZ, MZ and SS need to be identified not only in patients with liver disease and OAD but also with other diseases such as panniculitis, and Wegener's granulomatosis, since intermediate levels of AAT deficiency may be a contributing factor to the development of these diseases. More needs to be learned about AAT deficiency and its role in the management of these diseases.

It is anticipated that more rigorous and focused screening and detection programs will be instituted in the coming years throughout the USA. We need the help of all of you to make this a success.

Education and Training Materials Review Working Group

by Charles Gregory, Ph.D.

The Education and Training Materials Review Working Group exists to assist the Medical And Scientific Advisory Committee and others within the Alpha One Foundation in identification, production and review of education and training materials.

The Working Group is currently in the process of reviewing the Detection, Education and Training Materials developed as part of the recently completed Pilot Study of a Targeted Population Screening Program. This particular group of materials focuses on educating health care professionals, persons recently diagnosed with alpha1-antitrypsin (AAT) deficiency and persons who are considering being tested for AAT deficiency. Initial review by the Working Group of the Detection, Education and Training Materials was initiated in mid-July. The entire process of review input was conducted and expedited by use of the Internet and other electronic means. Many constructive suggestions and technical corrections were received from the Working Group and incorporated in the reformating of the materials prior to submission to an educational review consultant, Westat, Inc., for a formal validation process. The end result was an improved product with broad based application as an educational instrument.

On Monday, September 13, 1999, as part of the Alpha One Foundation - Critical Issues Workshop Series on Alpha1 Antitrypsin Deficiency, the Westat validation report was made. Their comments reflected on the high quality, thoroughness and comprehensive nature of the materials. In addition, the Westat analysis showed a consistently positive response to the materials. The Detection, Education and Training Materials will now go through a process of final review by the Working Group prior to publication and distribution.

Members of the working group are: Elaine Alfonso, Janis Berend, R.N., M.S.N., C-ANP, Evan G. DeRenzo, Ph.D., Lora E. Fleming, M.D., Ph.D.; Charlie Gregory; Peggy O'Hara, Ph.D.; Lynn Overson, R.N., M.N., A.N.P.; Robert A. Sandhaus, M.D., Ph.D.; Denise Schoolmeester, RCP, CPHQ; Julie Swanson; Debbie Waldrop, R.N., B.S.N., C.C.R.C.; Fred C. Walsh; Shannon Whalen, Ph.D.; and Ben Wilford, M.D. The Education and Training Materials Review Working Group is co-chaired by Peggy O'Hara, Debbie Waldrop and Charlie Gregory.
Characteristics, Functioning and Well Being in Marriages Confronting AIAD

Principal Investigator: Christine A. Cannon RN, Ph.D. (Family Studies), Associate Professor, Department of Nursing, University of Delaware, Newark, DE

The purposes of this research study include the generation of new knowledge and validation of existing knowledge concerning (1) the psychological and social impact of alpha₁-antitrypsin (AAT) deficiency on marital partners and the relationship they share, and (2) the individual and marital functioning/coping patterns associated with psychosocial well-being. Within the marital “system”, the inter-relationships between individual and marital (1) characteristics, (2) functioning, (3) coping strategies, and (4) well-being outcomes will contribute to “painting a portrait” of marriages confronting the challenges of AAT deficiency.

This is the first systematic investigation of marriages in AAT deficiency (except for the pilot qualitative and quantitative research upon which this study was designed [Cannon, 1997]). This study is also unique in its design since it is an independent collection of matched data from both partners and includes multi-level analyses. The analyses to be conducted include 1) individual patient-well spouse levels, 2) interpersonal – within relationship level, and 3) dyadic level – comparisons of groups of couples.

The findings of this research should foster the identification of couples at risk for problems and the development of interventions to promote effective and collaborative functioning within families. This study is the outcome and continuation of work started in 1994 that included the use of individual and couple interviews, focus groups and written questionnaires to collect qualitative and quantitative data needed to describe the nature of stress in AAT deficiency.

At the present time, married couples in whom one spouse has AAT deficiency are being invited to consider study participation. Letters have been sent from the Data Management Center at the University of Miami School of Medicine to qualifying couples. Those interested in participating are asked to reply to the Principal Investigator (or to the Data Management Center, if they wish to remain completely anonymous to the P.I.) so the research questionnaires can be sent to them. Both spouses must be willing to complete the questionnaire for the couple to be enrolled in the study. Couples who enrolled in the 1996 study or who completed the marital coping questionnaires within the last year do not need to complete additional questionnaires. All data collected in the past will be analyzed with data collected this fall. Data analysis will span into 2000 with publications and presentations to follow. The initial mailing to Registry couples and the data analysis is being partially funded by the Alpha One Foundation. Please contact the Principal Investigator, Dr. Christine Cannon, at ccannon@udel.edu or (302) 931-4389 for further information or copies of reprints on these studies.

Cost Of Illness Study

Principal Investigator: C. Daniel Mullins, Ph.D., (Pharmacoeconomics), Associate Professor, University of Maryland School of Medicine, Baltimore M.D.

Dr. Mullins has been working with data from the Alpha One Registry to develop a cost-of-treatment model for people with alpha₁-antitrypsin (AAT) deficiency. By documenting the high costs associated with current treatment, the results will be used to encourage federal agencies to spend additional dollars financing the cost of care and supporting new research that will improve therapy or find a cure. This information will bring additional national attention to this disease, which should assist in getting insurance companies to expand their benefits for treatment of AAT deficiency. The current analysis is based on a few questions from the initial survey that Alpha One Registry participants filled out. The results have been used to develop a new questionnaire that is being mailed to a sample of Registry participants in October.

The preliminary results show large variations in treatment costs due to current age, age at diagnosis, and related pulmonary illnesses such as chronic lung disease. The preliminary analysis has raised some new questions about whether expensive treatments, and the underlying illness associated with them, has caused a reduction in the work status of Alphas. The second phase will address concerns about work loss. It will also examine the relationship between costs and gender, type of insurance, and frequency of treatment.

As with any survey conducted by the Alpha One Registry, the responses to this questionnaire will be separated from the patients names before analysis is conducted. If you are one of the individuals who receives this, please take a few minutes to respond. Your support for this project is greatly appreciated. The summary results of this research will be published in a national journal and shared with various federal health agencies, politicians, and policy makers.
Animal Model of Emphysema Associated with Alpha1-Antitrypsin
by Alexei Guerassimov, M.D., McGill University, Meakins Laboratory, Montreal, Canada

Background: There is little doubt that the PiZZ phenotype for a1-antiprotease (AAP) is accompanied by emphysema in most smokers. The proposed mechanism for the lung destruction in this condition is based on the findings of increased numbers of activated neutrophils in the bronchoalveolar lavage (BAL), increased production of elastase, and the inability of the AAP to inactivate the neutrophil elastase with consequent lung destruction.

The study of the pathogenesis of emphysema in AAP-deficient patients, however, has been hampered by the lack of an animal model that could closely mimic the disease in smokers. Recently, a mouse model with a genetic deficiency of AAP in which emphysema occurs spontaneously late in life was described. This animal model closely reproduces important features of the human AAP deficiency and may provide new insights into the pathogenesis of emphysema.

Research Protocol: A research study was therefore developed to study the effect of cigarette smoking on the lung inflammatory cells and emphysema development in pallid mice. Preliminary studies found that AAP-deficient mice show significant air-space enlargement compared with non-smokers after four months of smoking and that these mice had much larger increase in lymphocytes and neutrophils than control smoking mice with normal AAP levels. This suggests that the AAP deficiency is responsible for the burden of these cells into the lungs. The study also showed that human AAP (Prolastin) could down-regulate the activation of mouse lymphocytes. This latter finding suggests that besides the classic antiprotease properties, AAP may also modulate immune responses which, in the case of AAP deficiency, might favor cytotoxicity in the lung, and provoke progression of emphysema.

Objectives: By studying smoking AAP-deficient mice over time we will describe the development of emphysema, and the inflammatory and immune reaction occurring in their lungs. This immune reaction is the most probable cause for the breakdown of the lung parenchyma, the obvious first step towards an understanding of the mechanism of lung destruction. Once this is known, the model could then be used to investigate the triggering mechanisms for the inflammatory reaction, the possible role of elastase and other proteases, cytokines, the role of lymphocyte depletion, and the role of a1-AP in the defense of the lung. In addition, the model could potentially be used for the study of ways to modulate the inflammatory reactions in the lung, and thus open the way for different therapeutic modalities for treatment of a1-AP deficiency.
Adeno-Associated Virus (AAV) Vectors for Skeletal Muscle Mediated Gene Therapy for Alpha₁-Antitrypsin (AAT) Deficiency-Preclinical Study in Non-Human Primates
by Sibongi Song, Ph.D., Dept. of Pediatrics, University of Florida College of Medicine, Gainesville, FL

The Gene Therapy Group at the University of Florida College of Medicine has been working together to develop gene therapy for alpha₁-antitrypsin deficiency (AAT deficiency) that is based on using a harmless human virus called aden-associated virus (AAV) as a carrier or vector. AAV has certain specific advantages over other gene transfer vectors since it does not cause inflammation and since it tends to persist in cells permanently. The one limitation for this vector, in the context of AAT deficiency, has been to produce enough vector so that a sufficient dose could be administered to achieve the very high blood levels that are required.

In work that was published this past November in the Proceedings of the National Academy of Sciences, our research team showed that a single injection of AAV-AAT into the muscle of a mouse was sufficient to produce a high blood level for at least 4 months, with no evidence of side effects. Since that time we have followed the blood levels in these mice and they have remained high for almost 2 years, which is a life time for a mouse.

We have also determined that the supply of AAT can be even more effective if the vector is injected into the liver or the lungs.

We are currently working hard to get this therapy into trials in AAT deficiency patients. A person with AAT deficiency is about 2000 times heavier than a mouse, but we have made some changes to the carrier that we think will let us get away with a dose that is only about 10 times higher than the mouse. We plan to test this concept in baboons. Meanwhile, we are forging ahead with extended animal safety testing in mice in anticipation of clinical trials in the not too distant future.

FROM THE RESEARCH BENCH

Current Clinical Trial: Aerosolized Transgenic Human Alpha₁-Antitrypsin, Principal Investigator: Mark L. Brantly, M.D., University of Florida College of Medicine

Press release by Victoria White

GAINESVILLE, Fla.---In an early test of breakthrough technology, University of Florida researchers have begun the first pilot study to determine whether the milk of genetically modified sheep can help people prone to life threatening lung problems caused by a specific protein deficiency.

PPL Therapeutics of Edinburgh, Scotland, the lead company involved in the development of Dolly, the cloned sheep, uses recombinant DNA technology - in which a gene from one organism is inserted into the DNA of another - to create "transgenic sheep" that produce the human protein alpha₁-antitrypsin, or AAT. The protein is then extracted from the milk.

Dr. Mark L. Brantly and his research team - Gwen Moen, RN, Chris Tobias and D.J. Szalanski in the University of Florida Alpha One Antitrypsin Genetics Laboratory.
Within the past 10 days, six patients whose bodies manufacture inadequate amounts of AAT, leaving them vulnerable to emphysema, have begun receiving inhaled doses of it at Shands at UF teaching hospital.

If the technique proves successful in this and larger controlled trials, a vast new source of AAT, at a sharply reduced price, potentially would be available to treat the estimated 100,000 Americans who have a deficiency of the protective protein that helps to keep lung inflammation and damage in check.

Such a new supply is critical. Currently, only a limited amount is available through blood plasma donations, so many eligible candidates must do without the therapy, which is delivered intravenously at an estimated cost of $60,000 to $80,000 annually per patient.

“I have great hopes that this will be the cornerstone therapy for this disease,” said Dr. Brantly, lead investigator for the study and a professor at UF’s College of Medicine.

“It could be the major 'bridge' treatment before we advance to gene therapy for this disorder,” said Brantly, who also is affiliated with UF’s new Genetics Institute, which is exploring such possibilities with grant support from the NIH. “One of the primary reasons for creating the Genetics Institute was to translate new technologies like this into treatment for patients,” said Dr. Terry Flotte, interim director of the institute. “This protein therapy and anticipated gene therapy for this disorder are prime examples of what we are trying to do.”

AAT Deficiency Liver Research

The Alpha One Foundation is pleased to announce an Alpha₁ Liver Research Initiative to raise funds for targeted research in α₁-antitrypsin deficiency and associated liver disease. The American Liver Foundation will provide matching funds up to $50,000 for contributions raised by the Alpha One Foundation through this initiative. The funding award for this matching grant will be made by the American Liver Foundation through its Grant Review Committee which will include a scientific liaison from the Alpha One Foundation. This is the first such collaborative effort of its type between these two organizations and it is hoped that it will serve to advance understanding of this fatal genetic disorder and stimulate research in the field of liver disease associated with AAT deficiency.

CLINICAL RESOURCE CENTERS AND PATIENT ACTIVITIES

National Jewish Medical and Research Center, Denver, Colorado
by Janis Berend, R.N., C.N.P.

The National Jewish Medical & Research Center was established as one of the Clinical Resource Centers of the Alpha One Foundation Research Network because it had all the elements necessary to train physicians and other allied health professionals about AAT deficiency, as well as be able to give patients what they needed to live a quality life.

National Jewish has been very supportive of our work as an Alpha One Antitrypsin Deficiency clinic, and provides access to state-of-the-art clinical and research expertise in pulmonary and critical care medicine (we are known as the #1 Respiratory Hospital). We get referrals from the Lung Line, from our doctors here in the Medical Center, local doctors, doctors from across the U.S. and AlphaNet. We also get patients calling that have found us on the Internet or are referred by our former patients.

One reason we are considered one of the premier respiratory facilities can be credited to Dr. Sandhaus, who has quite the reputation in the medical community and AAT deficiency community. Patients come from far and wide to see him. The greatest thing we have going for us is the devotion of
Dr. Sandhaus who VOLUNTEERS his time here to see patients.

Our CRC offers a number of resources for alpha patients including:

- Written materials on AAT deficiency
- Free classes on topics such as Managing your Lung Disease, Respiratory Medications, Tools for Fitness, Nutrition for Alpha Patients, and Oxygen
- An outstanding pulmonary rehab program with occupational and physical therapists
- A very good Psychiatric Department with access to the services of psychiatrists, psychologists and social workers who have expertise in dealing with patients with chronic lung disease
- A sleep lab and several doctors that specialize in sleep disorders
- Assistance with insurance companies for drug approval
- Assistance with disability issues and general questions patients and families may have
- Testing for family members by self-administered kits or in-clinic testing
- An infusion suite where we give Prolastin (usually to Medicare Patients), and an indigent program that provides for infusions
- A smoking cessation program in our outpatient clinic
- A library and a web site that has information about AAT deficiency

As of this date the clinic has been contacted by 145 patients that are diagnosed alpha1 ZZ, and 74 who are other Phenotypes. We have seen approximately 75 of those at National Jewish.

The Clinic also deals with patients that have TB or Atypical Mycobacteria. The team here is testing all lung patients for AAT deficiency because of a seeming prevalence within this targeted population. National Jewish is also one of the centers doing The National Emphysema Treatment Trials, these patients are also being tested for AAT deficiency and, in fact, we have identified at least three SZ patients and three MZ patients from that study.

We also have a strong support group and just had our annual picnic at Dr. Sandhaus’ home where more than 60 people attended.

Patients from the support group (ALPHABEATERS) are starting to maintain their own Web site, and are also active in the Alpha 1 National Association.

THE ALPHA PERSPECTIVE – PARTICIPATING IN A CLINICAL TRIAL

by Monica Davenport

The following is excerpted from Monica Davenport’s nine-part story, about what it was like to participate in the recent aerosol clinical trial.

The Opportunity: “Just like everyone else on the Alpha One Registry I got the invitation to participate in the trial that is using human alpha1 -antitrypsin (AAT) derived from the milk of transgenic sheep. How easy, I thought. And I met the criteria “18 or over”, “FEV1 or 50-90%” - mine has soared to 63% as recently as last month, “not received Prolastin for at least three weeks” - well, with the shortage it had been two weeks, and if this was a good deal I was willing to give up my Prolastin. I am a firm believer in Prolastin, Prayer, Positive Thinking, and the Treadmill. But, I was willing to give it up for another therapy...maybe. So I contacted Dr. Brantly at University of Florida and discussed my eligibility to participate in this trial. The protocol requires that the six participants travel to the University of Florida five times over a 14 week period. That was a lot of travelling and I really wasn’t so sure I could work it around my career.

[Monica decided to participate, worked out insurance and family issues, traveled to Gainesville, met with the nurse coordinator, signed release forms, underwent tests and a bronchoscopy and then faced her first dose of the aerosolized product].

The Great White Hope: Well, here it is, my Alpha friends, September 3, 1999, the day I received my first dosing of the Great White Hope...the reason for the pilot...the hope of all of us ‘zz’ folks...the culmination of about 15 years of research!!!

Continued on page 12
What a week it had been... meeting other alphas, getting to know my "new best friend" Gwen Moen (Nurse Coordinator for the clinical trial), having the opportunity to learn so much about my disease from Dr. Mark Brantly, having THE BRONCHI, everything!!! leading to this moment my first dosing.

Receiving the aerosolized AAT, Gwen taught me how to assemble the nebulizer and showed me the AAT protein in its containers and gave me the directions on how to care for it. It looks like white powder... just as I had expected it to. Each container had information on it that indicated these doses were for me and only me. I found that interesting. She gave me the liquid I would need to reconstitute the protein and gave me HUGE warnings on what NOT to do to the materials. Sufice it to say... these precautions/rules/warnings are very easy to follow. ALL of you could do them if you get the opportunity to use this therapy.

Okay, I've got the rules down... let's DO IT!!! I reconstituted the AAT powder and I WAS SHAKEING!!! I couldn't believe how deeply nervous I was about this monumental moment for me. I was afraid I would drop it or spill it... but I KNEW the importance of ALL of us taking this therapy. I wasn't seeing it as the 'cure' and maybe it won't even make it to 'market' in this form, but the pilot, the research has GOT to advance the alpha 'cause!

The Dose: So I sat there, brought the nebulizer up to my mouth... and I took a deep, full breathe into my lungs of A1AT from the milk of cloned sheep that had human DNA attached to their embryos. CAN YOU BELIEVE IT!!!!!!!! Gwen marked the time and started asking questions. Bottomline... absolutely no problems. It felt GOOD, cool, moist, and it tasted good! Yes, I know how weird this sounds, but that first dose reminded me of Breyer's Vanilla Bean Ice Cream; maybe that was because I hadn't had any ice cream in a long time, or maybe it really DID taste like that! It took me 19 minutes to take the entire dose. While I was taking my replacement therapy, Gwen explained information she had in a folder for me to take home. She had included copies of my lab work for my local doc, copies of my signed informed consent, a copy of the permission to amass and retain my bodily fluids and tissues, a nice letter, and other information about the different doctors and about the sheep! I really appreciated getting this material.

So, the actual dosing was rather uneventful even though it was so very special to me. I now take my treatment once a day right at my kitchen island so that my husband Randy and I can converse. I have had absolutely NO side effects whatsoever due to this great med, although I do tend to cough a bit afterwards. After my Prolastin I felt groggy, usually cold, sometimes a headache, and I just want to go to bed... then I am fine come morning. But there is NOTHING whatsoever from this form of A1AT.

Last Thursday I flew back to Shands for my weekly check on Friday. I am having no adverse reactions whatsoever... in fact, I'm doing very well with it. I will return in a couple of weeks for my second bronch and then again in 4 weeks for the 3rd one. After that, except for checkups, I'll be through. So, friends, I hope that this story interested you and educated you on what is going on in the medical research field for you and your children's futures. Dr. Brantly is most optimistic that if this proves as successful throughout the trials, the world will soon be welcoming this product on the market for alphas and it might even lead to successful treatments for other maladies as well. The sheep are abundant and the company that owns them has been given permission to greatly increase the herd (i.e., this truly can be an unlimited product). Yes, I do believe it is THE GREAT WHITE HOPE.