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

IT HAS BEEN AN EVENTFUL SUMMER WITH THE OFFICIAL OPENING OF THE ALPHA-1
Coded Testing Trial (ACT Trial). The Alpha-1 Community now has access to confidential coded testing.
It uses the finger-stick blood test for Alpha-1 that was first developed in Europe and now is available
through Dr. Mark Brantley’s laboratory in Gainesville, Florida. The test uses a small mechanism that col-
clects blood with minimal pain. It is similar to devices used by diabetic patients to check blood glucose.

The ACT Trial is a research study designed to investigate the risks and benefits of
genetic testing from a patient’s perspective. It is being conducted as a research trial to collect data about
how people feel about testing for a genetic condition that does not
absolutely cause disease. Since
many people with Alpha-1 have no lung or liver disease, the result of a
diagnosis of AAT Deficiency might
range from anxiety or depression to
no significant concern. Furthermore
people’s feelings might differ
depending on the person who sug-
gests the test (physician vs. family
member) and on the results of the
test. The research will also allow
ACT Trial investigators to learn
about the information being given
to patients by their physician
before an Alpha-1 test is ordered.
The second reason to perform the
coded testing through a research
trial is to protect the confidentiality
of each participant’s test results.
The test results are research records,
which, unlike medical records, cannot
be readily obtained by insurance
companies. In addition, a
Certificate of Confidentiality has
been issued for the ACT Trial from
the National Institutes of Health,
this is the best means available to
protect ACT Trial test results from
subpoena by a court of law.
The test is designed for individuals
at risk for Alpha-1 Antitrypsin
(AAT) Deficiency (Alpha-1) who
are concerned about the privacy of
test results. This is an excellent
opportunity for family members of
Registry participants to be tested.
Individuals of all ages are eligible
and the test can be administered in
the comfort of your own home.
To participate in the ACT Trial is
simple:
➢ Contact Ryan Dickson, the
Registry Coordinator, by either
calling toll free at 1-877-886-2383
or by emailing to
alphaone@musc.edu.
➢ Provide your name, the number
of test kits needed and your
address. There is no limit to
the number of kits you can
request.
➢ Included in the test kit package
will be a consent form, research
questionnaire and directions.
Complete the questionnaire
and consent form, enclose with
the blood test kit, and mail
back to the Registry Center at
MUSC.
➢ Fill out and return a 2-page
post-test questionnaire.
Each blood sample will be coded
with a unique number, all the iden-
tifying information removed, and
mailed to the Alpha-1 Research Lab at
the University of Florida for testing.
The coded results will be mailed
back to MUSC where they will be
matched to the appropriate partici-
pant and the results mailed to them.

Continued on back cover
2002 By 2002!
By Ryan Dickson, Alpha-1 Research Registry

The Alpha-1 Research Registry is proud to report that this year's enrollment has already exceeded total enrollment for the year 2000. Currently, the Registry hosts over 1,150 members. We've come a long way since 1997, but there's more work to be done. It is estimated that there are over 5,000 individuals diagnosed with Alpha-1 in the United States and millions more are estimated to be Alpha-1 Carriers. The goal is to enroll more of these Alphas and Carriers in the Registry. To build momentum for this goal the Alpha-1 Foundation and Research Registry have established a 2002 By 2002 campaign to build enrollment to over 2,002 members by 2002.

We need your help. As Registry members, you are our most important recruiters. Many not-yet-enrolled Alphas and Carriers are your own family members or Alphas you come in contact with at community events and meetings. You can make a big difference, and help meet this goal of 2002 by 2002 by encouraging people you know to enroll.

There are several reasons why so many Alphas and Carriers aren't enrolled in the Research Registry. Some people eligible to participate may not know that a Registry for diagnosed Alphas and Carriers exists. We encourage you to make sure eligible family members, Alpha friends, and physicians are familiar with the Research Registry. We will send you enrollment applications to distribute or you can simply refer those interested to our toll free number, 1-877-886-2383, or email, alphaone@musc.edu.

Another reason is that individuals at risk for having Alpha-1 or for being a Carrier may not know their status. They may hesitate to be tested due to concerns about confidentiality. If you know someone who would like to be tested, but is concerned about the privacy of results, tell them about the ACT Trial. Please visit the Registry's website, www.alphaoneregistry.org, to learn more about the ACT Trial.

Another concern may be the confidentiality of Registry member records. The Registry employs strict procedures to protect each member's identity and is governed by the Medical University of South Carolina's Internal Review Board for Human Research. All records are securely stored in a locked file cabinet and password protected database inaccessible from the Internet. Finally, a family member or friend may be concerned about what signing up involves. Assure them that members are not required to participate in a study. The primary responsibility of Registry membership is to consider participation in research. Research opportunities come in many forms ranging from participation in clinical trials for new treatments or to filling out questionnaires in the comfort of their own home. Everyone can make a contribution even if they cannot travel to clinical trials or are unable to join a research study due to family or work responsibilities. Simply filling out the enrollment questionnaire provides the Registry with valuable information concerning the numbers of Alphas and their clinical symptoms of disease.
Family Linkage in the Alpha-1 Research Registry
By Ryan Dickson, MUSC

The Alpha-1 Foundation has asked the Research Registry to find family members of Registry participants willing to join the Registry for family linkage studies of Alpha-1 genetics. The study of families with a history of Alpha-1 Antitrypsin (AAT) Deficiency will allow researchers to study genes that influence, or modify the progression of disease. Since the privacy of genetic information is an important issue in today’s society, the Alpha-1 Foundation and Alpha-1 Research Registry have worked hard to develop a method to accomplish family linkage in the Registry while protecting member confidentiality.

How can genetic studies benefit the Alpha-1 community and lead to development of improved treatments and a cure? In the past, scientists have been very successful at isolating genes commonly found in people with similar disease states. Once genes of interest are recognized, further studies can unlock the biological processes causing disease and ultimately lead to the development of new treatments. This is precisely the plan for genetic studies in Alpha-1. It is known that the gene for the alpha1-antitrypsin (AAT) protein plays a major role in the occurrence of AAT Deficiency. However, there are many important unanswered questions that genetic studies can shed light on. Such as why do some individuals with an abnormal Alpha-1 genotype never develop lung or liver disease and why do individuals with the same Alpha-1 genotype often suffer different severity of disease? One explanation for such a question is a difference in environment such as cigarette smoking. However, it has been noticed that some people with similar Alpha-1 genotypes have differences in lung or liver disease severity despite a similar smoking and environmental history.

Another possibility for differences in the incidence and severity of Alpha-1 is the existence of other genes that affect the disease state. Such genes can become targets to develop new therapies and treatments for AAT Deficiency.

The reason family participation is vital in these genetic studies is that families have a high percentage of identical genes. Scientists can use small differences in a family’s genetic code to narrow the range of genes that could be responsible for differences in the incidence and severity of Alpha-1. This eliminates the process of sorting through thousands of genes that make each individual unique. The goal of the Alpha-1 Foundation and Alpha-1 Research Registry is to assist genetic investigators in the difficult task of finding study participants for these important family studies.

Due to the confidential nature of the Registry the Medical And Scientific Advisory Committee (MASAC) of the Alpha-1 Foundation has carefully considered how to link family members within the Registry. Although a complicated process, the benefit of this type of research for the Alpha-1 Community outweighs the difficulty of linking family records. To accomplish family linkage, the Registry is asking its members to speak with family members about joining the Registry as a “linked” family willing to participate in family studies. If you already are aware of other family members who participate in the Registry please speak with them about linking your records.
The method to be used includes the following steps:

▶ You will receive a letter about family linkage in the mail and fill out a form. If you and other family members are interested in participating, you will fill out a form with contact information for willing family members.

Note: The person who fills out the form for a family is known as the Family Index.

▶ The Registry will contact referenced family members requesting their participation and permission to be linked to other family members. The Index will not be informed of results of Registry contact with his/her family member(s). Even when families are linked in the Registry no family member will be able to request information concerning another family member's record or enrollment status. Thus, the Research Registry will only reveal the Index's enrollment status upon requesting other family member participation.

▶ Each family member will be presented with research studies separately and given the option to accept or decline the opportunity. Some research will be as simple as filling out questionnaires or donating a blood sample, other research will be more involved. Not all studies are appropriate for all families for many reasons. Whenever possible the Registry will not reveal other family members' participation decisions. There will be some cases where this will not be possible. Please note, any family members can add or remove themselves from family linkage at any time.

Please carefully consider this opportunity. The goal of this project is to facilitate cutting edge genetic research that could answer complicated questions about the disorder and may eventually benefit people with Alpha-1. The Registry has tried to devise a method of linkage that is sensitive to family dynamics and alleviates family pressure, however there is no perfect solution. The major point is that every family that participates is helping to increase our understanding of AAT Deficiency.

Please stress to family members the registry maintains strict procedures to maintain member confidentiality and no member is ever obligated to participate in any study. As always your support of Research Registry programs is greatly needed and appreciated.

Questions concerning Family Linkage will be answered at the Registry office from 8AM – 5PM, Monday-Friday at 877-886-2383 or by email at alphaone@musc.edu (password protected email of Registry coordinator).

FOUNDATION UPDATE

2nd Million Awarded for Alpha-1 Research

The Fundación Leopoldo Fernández Pujals of Madrid, Spain has become the single largest private-foundation contributor to Alpha-1 research with its second $1 million grant, awarded to the Foundation in July 2001. We are proud of our relationship with the Fundación and express our deepest gratitude to them for their unyielding commitment to advancing research toward a cure and raising awareness about Alpha-1. This award provides funding for the Fernández Liver Research Initiative created in 2000 to support basic science and clinical research in Alpha-1 and for investigator-initiated matching grant initiatives with the American Liver Foundation and the NIH National Institute of Diabetes & Digestive & Kidney Disease (NIDDK). The investment by the Fernández Family has enabled six research grants to be funded and has generated over $1 million through matching grant programs. Mr. and Mrs.

Fernández have expressed their satisfaction with progress and administration of their $1 million grant last year.
Currently Funded Research

The Alpha-1 Foundation is currently supporting 22 research projects in a wide range of topics related to AAT Deficiency, including investigations of phenotypic distribution of AAT in worldwide populations, standardization of CT Scan technologies for imaging of lung damage, improved gene therapy systems, the basic transport mechanisms of AAT out of the liver, and the social and economic impacts on families with a diagnosis of AAT Deficiency. The Foundation also continues to support research on animal models of emphysema as well as studies of the processes in the liver associated with AAT Deficiency.

The most recent grant awards include the 2001 Young Investigator Fellowships, awarded to Karen G. Anthony, Ph.D., Mount Sinai School of Medicine for research on an Improved Gene Therapy System for AAT Deficiency and to Clifford J. Luke, Ph.D., Children’s Hospital Boston for a study entitled, Analysis of the Airway Antiproteinase System Biotechnology Marketplace. In addition, the Foundation has recently awarded a Pilot and Feasibility Grant to Robert J. Buchanan, Texas A&M, for his research investigating Profiles of Nursing Home Residents with COPD.

The Foundation also awarded Investigator Initiated Grants to Marilyn Coors, Ph.D., University of Colorado, for a study entitled Evidence Based Approach to Informed Consent and to Richard Sharp, Ph.D., National Institutes of Environmental Health Sciences - NIH for research on Patient Perspectives on the Role of Consumer Advocacy Groups: A Study of Patients with AAT Deficiency.

2001 Young Investigator Fellowship Award (Aaron Janoff recipient)

Clifford J. Luke, Ph.D., Division of Newborn Medicine, Children’s Hospital Boston, Boston, MA

Dr. Luke will investigate squamous cell carcinoma antigens, which are serpins (serine proteinases inhibitors) like the alpha1-antitrypsin (AAT) protein. In laboratory experiments, these antigens inhibit proteinases associated with elastin and collagen degradation. This is relevant to the understanding of AAT Deficiency since emphysema can occur when AAT inadequately inhibits neutrophil elastase. However, since many patients with AAT Deficiency never develop emphysema, Dr. Luke will also seek to determine whether proteinases and their inhibitors may also be involved in protection of lung tissue from injury. He will do this by using cell culture techniques as well as by seeing how these processes function in mouse models. His fellowship study, under mentor Gary A. Silverman, M.D., Ph.D., Chief, Division of Newborn Medicine at Harvard Medical School, will identify mouse serpins that have similar properties as the squamous cell carcinoma antigens to improve understanding of the proteinase inhibition network in the lungs. The title of the project is "Analysis of the Airway Antiproteinase System."

2001 Young Investigator Fellowship Award

Karen G. Anthony, Ph.D., Institute for Gene Therapy and Molecular Medicine, Mount Sinai School of Medicine, New York, NY

Dr. Anthony will investigate an effective and safe gene expression system that yields stable and therapeutic levels of alpha1-antitrypsin (AAT) protein synthesis in vivo (within a living organism). The development of emphysema can be prevented or delayed by gene therapy through the administration of a functional copy of human AAT (hAAT) in vivo. The delivery will be accomplished by applying the most current methodology in gene therapy research along with a few modifications that will enhance the delivery method. This new approach also utilizes a different type of adeno-associated virus (rAAV) vectors, which may improve the safety of this type of therapy. Her fellowship study, under the mentoring of Savio L.C. Woo, Ph.D., Professor and Director of the Institute for Gene Therapy & Molecular Medicine, will evaluate long-term gene expression in an animal model using this safe and effective gene delivery vector for use in clinical trials. The title of the project is "Improved Gene Therapy System for AAT Deficiency."
"Profiles Of Nursing Home Residents With Chronic Obstructive Pulmonary Disease (COPD)"
Robert J. Buchanan, Ph.D., Department of Policy and Management, The Texas A&M University System, School of Rural Public Health, College Station, TX

The Alpha-1 Foundation is pleased to fund this project through grant support by the Peacock Foundation, Inc. in Miami, FL. Dr. Buchanan, Principle Investigator, will be working with co-Investigators Bonnie Chakravorty, Ph.D., M.S.W., Tufts University, Suojuin Wang, Ph.D., Professor, Department of Statistics, and David Hackethorn, M.D. who will serve as medical consultant from Scott & White Clinic. This pilot project will obtain findings from a cross-section of newly admitted nursing home residents with COPD. The data will then be used as the foundation for an ongoing, long-term research study that will be submitted to the National Institutes of Health for funding.

Through national in scope and impact, this project will enable data to be extracted and analyzed for patients from southeast Florida (Palm Beach, Broward, Miami-Dade, and Monroe counties) to report on the level of care locally. These local results will then be compared to findings for residents with COPD in nursing homes in other parts of the country.

The study will identify similarities or disparities in care and treatment for nursing home residents with COPD at admission from the general population of individuals in nursing homes. The project will analyze geographic information, demographics, such as age, gender, or payment source, and other factors such as the number of other health conditions. The project will also analyze disability status of residents in nursing homes with COPD through three separate assessments: activities of daily living, the presence or degree of cognitive impairment (i.e., memory, recall ability, decision making), and presence or degree of depression.

1 Scott & White Clinic is an association affiliated with Scott and White Memorial Hospital in the Scott, Sherwood and Brindley Foundation.

RESEARCH UPDATE

Immortal Liver Cells – A Bifunctional Approach for AAT Deficiency
Mark A. Zern, M.D., Director, Transplant Research Institute, University of California, Davis

A bifunctional approach to the treatment of Alpha-1 Antitrypsin (AAT) Deficiency, one that addresses both the liver and lung disease, would be advantageous. At the present time this can only be undertaken by the use of whole liver transplantation, which corrects both the processes in the liver and prevents the development of the lung diseases associated with AAT Deficiency. Because there are considerable risks associated with the process of transplantation, and because more than a thousand people die each year while on the liver transplantation list, it is evident that improved and safer liver transplantation would be valuable, as would approaches that provide for an increased number of transplantations in a timely manner. A technology that might address both of these issues is the development of immortalized human hepatocytes (liver cells) that can be employed in liver cell transplantation. These cells are also being developed for their potential to be used in a bioartificial assist device which, similar to a dialysis machine, can be hooked up externally to provide needed therapy for the liver without surgery or transplantation.

A major issue in the development of this strategy is the very limited ability of normal adult liver cells to divide and produce enough new cells to transplant. Other investigators have used other animal cells, e.g. pig cells. However, there are concerns about the production of non-human proteins and the possibility of harmful immune reactions. Of particular concern with using pig cells is the potential for transmission of pig viruses, such as hepatitis E. Another possibility...
is the use of liver cancer cell lines. These lines divide, but do not maintain the normal liver function. An additional concern is that tumors might develop.

Our approach to develop an immortal human liver cell line (one that will continue to divide and maintain normal liver function) is to use a gene therapy approach to put the telomerase gene into normal human liver cells. Cell division is thought to be limited by telomere loss. In sperm and egg cells, the telomerase gene is active, telomeres remain long, and the cells continue their ability to divide. In the remainder of human cells, there is no telomerase gene, and the telomeres shorten each time the cell divides. When the telomere shortens too much, the division stops. Our hypothesis is that by putting the telomerase gene back into the human liver cells, the telomere length would not shorten, and the liver cell would continue to divide, thus providing a safe and effective source of cells for liver cell transplantation and a bioartificial assist device.

Over the last few months, we have established the gene therapy system and have been successful in putting the telomerase gene in both lethal and infant human liver cells. This process seems to be working and the 'immortalized' cells continue to divide at a stable rate, well beyond the time that the cells without the gene have stopped growing. In addition, they continue to produce normal liver proteins. Thus, we have taken the first step in developing a human cell line that will be useful in treating both the lung and liver disease in AAT Deficiency, as well as correcting other types of liver failure. Many more studies need to be undertaken successfully to ensure that these cells are appropriate for use in humans.

The Pediatric Perspective of Lung Disease Associated with Alpha-1 Antitrypsin Deficiency

L. Terry Spencer, M.D., Department of Pediatrics, Division of Pulmonary Diseases, University of Florida College of Medicine, Gainesville, FL.

Alpha-1 Antitrypsin (AAT) Deficiency is the most common genetic cause of liver disease in infants and children and the most common cause of early-onset emphysema in adults. We know that liver disease associated with AAT Deficiency also occurs in adults, but what do we know about lung disease in children and younger adults? It is commonly recognized that emphysema occurs in adults as young as 55 years of age. In fact, there are reports of severe lung disease occurring in young children and teenagers with AAT Deficiency, but this appears to be exceptionally rare. Knowing that lung disease associated with AAT Deficiency occurs because of excess inflammation, some key unanswered questions are:

1) When does inflammation begin?
2) What triggers inflammation?
3) Why do some individuals with AAT Deficiency develop lung disease earlier than others, even without a history of smoking?

Further investigation into the course of lung disease from childhood through the young adult years will likely answer these important questions.

What we do know so far about lung disease in children is primarily a result of two impressive screening studies started in the early 1970s. From 1972-74, Dr. Tomas Sveger performed screening studies for AAT Deficiency in 200,000 newborn infants in Sweden, identifying 129 with severe deficiency [Sveger, T., 1976]. Dr. Sveger and his group have followed these patients clinically since that time. This study has provided valuable insights into the natural history of liver and lung disease in children.
It appears that the frequency and severity of liver disease in children is not as bad as previously thought, and the news with regard to lung disease appears good as well. Dr. Sveger recently evaluated about half of these patients at 26 years of age and found the vast majority have normal lung function (unpublished data, personal communication). Importantly, his group's efforts with regard to smoke cessation education have paid off, with 88% of these patients being lifetime non-smokers.

The second study was performed in Oregon, where the State Public Health Laboratory screened 107,000 newborns between 1971 and 1974 [O'Brien, 1978]. Patients evaluated from this group during adolescence were also found to have normal pulmonary function, and low smoking initiation rates [Wall, 1990]. Studies performed by other investigators have suggested a link between AAT Deficiency and childhood asthma, but this is not fully established.

Avoiding cigarette smoking and secondhand smoke exposure is likely the most important factor in maintaining good lung health in children with AAT Deficiency. Additional recommendations include avoidance of other lung irritants such as atmospheric pollution and noxious fumes, aggressive treatment of asthma if present, immunizations (including pneumococcal and yearly flu shots), and taking antibiotics at the onset of respiratory infections.

While most studies have shown normal pulmonary function through the adolescent and young adult years, we must keep in mind that studies using more sensitive measures of lung disease detection such as CT scans and bronchoscopy have not been performed in these patients. It is important to address these issues, particularly as we work to develop more non-invasive methods of delivering AAT augmentation therapy, such as by inhalation. As aerosolized therapy becomes available, a key question will arise: When is the ideal time to begin augmentation therapy? Only by identifying when the process of chronic lung inflammation begins can we begin to answer this important question.

Better understanding of AAT biology offers patients, families and physicians improved prospects for prevention and treatment of this hereditary cause of liver and lung disease. When infants and children are diagnosed with AAT Deficiency by family screening or by a history of liver disease, families are eager for information about their child's risk for lung disease. Plans are underway at the University of Florida to develop a Pediatric Lung Center for AAT Deficiency. Emphasis will be placed on screening and detection, providing relevant educational counseling for patients, parents and primary care physicians, and offering opportunities for participation in research designed to address the many unanswered questions regarding the natural history of lung disease in children and young adults.

References
Update on Clinical Studies in Alpha-1
By Robert A. (Sandy) Sandhaus, M.D., Ph.D., VP & Medical Director, Alpha-1 Foundation

The recent announcement of a study using inhaled human alpha1-antitrypsin (AAT) purified from the milk of genetically modified sheep (transgenic recombinant AAT) has sparked optimism that newer therapies for Alpha-1 may be on the horizon. Now that enrollment in this 'sheep juice' study has been completed, many Alphas are wondering what's next and how soon will they see the fruits of their participation in these studies.

The specifics of upcoming studies tend to be closely guarded secrets within the pharmaceutical industry. Still, from public announcements and some conjecture, there are likely to be exciting developments in the near future (of course, 'near' is a relative term). First, we know that at least two companies have completed the studies required to seek approval of new plasma-derived IV products. One company (we'll call it A) has indicated that they will have their paperwork to the U.S. Food and Drug Administration (FDA) by the end of 2001. If this happens, and if the FDA agrees that the paperwork is complete, and if the FDA completes its review on an accelerated timeline, then we could see this drug on the market in the second half of 2002. All indications are that another company (we'll call this one B) is operating on a somewhat similar timeline. Many companies consider performing studies while awaiting FDA approval in order to get the drug out into the hands of prospective 'customers' while at the same time answering appropriate scientific questions. We'll have to wait and see if A or B do this.

The inhaled products, on the other hand, require a lot more study before they will be ready for submission to agencies like the FDA. There will likely be large studies performed in both Europe and North America over the coming years, involving hundreds of Alpha-1 patients. These studies will likely take three to five years to enroll all the subjects, follow them for a long enough period to find out if the drug is effective, and then analyze the data. Following this is the preparation of all this information into a submission to the regulatory authorities (FDA in the U.S.) and the time it takes for agencies like the FDA to review and, potentially, approve such a new drug. The only way to ensure that these drugs move forward will be to consider participating in these studies, if you qualify. As these studies get closer to starting, expect to receive more information about the specifics of participation. If you are not enrolled in the Research Registry and would like to participate in future studies, please contact the Research Registry at 1-877-886-2383.

FEATURED ALPHA-1 CENTER
Alpha One Foundation Ireland (A Very Brief History)
By Larry Warren, Dublin, Ireland

This article is to introduce you to a newly created Alpha-1 organization - the Alpha One Foundation Ireland. The reason for entitling this "a very brief history" is that we are in existence only for the past few months - since May 1, 2001. Therefore we are more full of expectations than achievement. And yes, we do have great expectations. The Management Committee of the Foundation consists of Professor Gerry McElvaney, Professor Shane O'Neill, Dr. Richard Costello and Mr. Larry Warren, CEO.

Although resources are limited, I am already employed on a part time basis at the Foundation. However that in no way diminishes our hopes and aspirations. Since the formation of the Foundation we have had two very good meetings with our patients and plan another meeting in September. I also had the opportunity to participate as an intern at the Alpha-1 Foundation in Miami, which proved extremely interesting and useful during the formation of the Foundation in Ireland. It also gave me the chance to meet many hospitable friends. Both Dr. McElvaney and I also attended the 3rd International Scientific Conference at Airlie and met many more Alphas and a number of prominent researchers and clinicians in the Alpha-1 Research Network.

The Irish Foundation has written up a very detailed proposal for a screening and detection programme in Ireland. We estimate that there are at least 1,000 Alphas in Ireland, which leaves approximately 950 undiagnosed. The Irish Foundation was assisted more than a little by our U.S. counterparts, the Alpha-1
Foundation, whose expertise we utilized when writing the proposal. It was then presented to the Department of Health for recognition and funding.

Our second area of focus will be meetings and conferences to raise awareness of Alpha-1 in Ireland and highlight current research in the field. We will be holding our inaugural conference on October 12-13, 2001. This conference aims to achieve the following:

- Publicly launch the Alpha One Foundation Ireland
- Provide some very learned and interesting lectures on AAT Deficiency
- Raise awareness of Alpha-1 in Ireland
- Celebrate the Irish/U.S. Alpha-1 Alliance

Among those participating at the conference will be John W. Walsh, Alpha-1 Foundation; Mark L. Brantly, M.D. and Terence Flotte, M.D., University of Florida College of Medicine; Gordon Snider, M.D., Boston VA Healthcare Systems; John McCormick, M.D., FDA-Office of Orphan Drug Development; James Kiley, M.D., NIH-NHLBI, as well as Drs. Muris Heuston and Aidan McCormack of Ireland.

Ireland plans to be at the cutting edge of European research, diagnosis, trials and therapies for Alpha-1. Our center for all these endeavors is at the Alpha 1 Clinic in Beaumont Hospital, Dublin. We hope you will visit us when you are in Ireland!

MEETINGS, CONFERENCES AND WORKSHOPS IN 2001

4th Annual Alpha-1 Research Forum, May 21, 2001, San Francisco, CA

The Alpha-1 Foundation was pleased to host the 4th Annual AAT Deficiency Research Forum during the American Thoracic Society (ATS) Annual Meeting in May 2001. Each year, since 1998, the Foundation has brought together experts and young investigators in the field of AAT Deficiency research to share the latest findings, to stimulate interaction among the many diverse researchers in the field, and to encourage young investigators to focus on AAT Deficiency research. This year there were over 75 participants at the Forum from 12 countries representing academia, government, industry, genetic consumers and clinical centers. Each year the number and types of presentations at the Forum has increased. This year a very broad spectrum of research topics was presented including 18 posters, 2 slide presentations and 2 videos. This expanded range of topics and the success of these forums reflect an ever-increasing interest and involvement of a greater number of investigators in Alpha-1 research.

Presentation topics in 2001 included detection among targeted populations, inflammatory processes in the lung and airways, gene transfer technologies, CT scan for thoracic imaging, drug design to prevent polymerization, conformational changes and neutrophil function, functionality of alveolar macrophages in AAT Deficiency, pathogenesis of emphysema, chemotactic activity of sputum, lung morphology in AAT Deficiency, and marital coping in families with AAT Deficiency. The Forum was moderated by Robert A. Sandhaus, M.D., Ph.D., Medical Director and Executive VP, Alpha-1 Foundation and Robert Fallat, M.D., California Pacific Medical Center. Travel awards were presented for the two best posters to Marianne de Groot, M.D., National Jewish Medical & Research Center for her presentation on myobacteria and AAT Deficiency, and to J.S. Parmar, M.D., University of Cambridge for his presentation on modulation of neutrophil function.
Alpha-1 Events

- The Long Island Kayak for the Kids, sponsored by the Alpha-1 Alliance, took participants on a 200+ mile kayak marathon along the coast of Long Island from May 4-14, 2001 to kick off Alpha-1 Awareness Month. Tom Dailey, diagnosed with Alpha-1 and living with 50% lung capacity, led the challenging way, joined by Team Alpha-1 Captain, Mary Pierce, a double-lung transplant, and Patty Prehm. Bridget and Mike Costello were the "land team" that coordinated the events along the way culminating in a final event on May 12 that brought hundreds of people including government officials, community leaders and Alphas together to celebrate the efforts of Tom and his team.

- The Salem, MA, Whale Watch 2001 for Alphas, families and friends, hosted by Kim Spires, was held August 25. Passengers had unique access to whale sightings aboard the M/V Super Ranger. The vessel sailed from historic Pickering Wharf in Salem, MA, and ventured out to Jeffrey's Ledge, approximately 12 miles south of Boston. The event, organized in collaboration with the Norfolk County Lung Association, members of the Alpha Community and the Alpha-1 Foundation, raised $4,500 to benefit education and research toward a cure for Alpha-1.

Alpha-1 Education Days

- March 2001, The National Jewish Hospital in Denver, Colorado. Event organizers: Kay Kinsel and Janice Behren. The Alpha-1 Alliance, National Jewish Hospital, Bayer Corporation, and AlphaNet sponsored this Alpha-1 Education Day.

- May 2001, The University of North Carolina at Chapel Hill. Event organizer: Jeanie Mascarella, R.N. The Alpha-1 Alliance, University of North Carolina at Chapel Hill, and AlphaNet sponsored this Alpha-1 Education Day.

- August 2001, Northeast Alpha-1 Research and Education Day at Dartmouth Hitchcock Medical Center in Lebanon, New Hampshire. Event organizers: Vicki Cameron, Richard O'Brien and Mary Turco. The Alpha-1 Alliance, Dartmouth Hitchcock Medical Center, AlphaNet, Aventis, Bayer Corporation and Chad Therapeutics sponsored this Alpha-1 Education Day.

Alpha-1 Education Days are held in geographically diverse regions of the U.S. to provide education and support to individuals with Alpha-1 and their families.


An important and timely conference, Alpha-1: The Challenge of a Genetic Condition, was hosted by the Alpha-1 Foundation at the Airlie Conference Center. Conference Co-Chairs were bioethicist, Arthur Caplan, Ph.D., Center for Bioethics, University of Pennsylvania and noted genetic researcher Diane Cox, M.D., Department of Medical Genetics, University of Alberta. Over 100 medical researchers, social scientists, members of government, industry and genetic consumers were in attendance.

The conference provided a forum to promote greater understanding among social scientists and public policymakers of the direction genetic research is heading and investigate how ethical issues may affect further development of scientific knowledge. The social science sessions focused on how advances in genetics research will affect public health issues such as the risks and benefits of genetic testing, resource allocation, employment discrimination and health privacy issues. The scientific sessions provided an overview of the clinical variability characteristic of many single gene disorders that can be
caused by different mutations in the gene, or by the influence of what scientists call genetic modifiers. These can include environmental or occupational stressors and oxidative stress that impacts individuals on a molecular level. How these modifying factors impact a genetic condition such as AAT Deficiency needs to be more fully understood in order to develop appropriate preventative measures and therapeutic protocols. And it may help in understanding why some with AAT Deficiency become ill and others are asymptomatic.

An update on therapeutic approaches for Alpha-1 was provided, including U.S. and European study outcomes on augmentation therapy, progress in the development of aerosolized AAT, and new bi-functional therapeutic approaches, which have the potential to benefit individuals with both lung and liver disease. The following are two articles written by participants.

The first is a story written by Mary Pierce, an Alpha who attended the conference. It provides her personal impressions of the meeting and its relevance to the Alpha Community. The second article is by Magne K. Fagerhol, M.D., the scientist who developed the original method to determine Alpha-1 levels and who helped name the phenotypes. Dr. Fagerhol was the recipient of this year’s Eriksson Award for Distinguished Scientific Achievement in Alpha1-Antitrypsin Deficiency Research, which is presented annually at the international conference.

Airlie 2001 Conference – An Alpha’s Perspective
by Mary Pierce

I’ve been asked to share my impressions of the 3rd International Scientific Conference on Alpha-1 at Airlie, Virginia June 19-22. I have been involved with the Alpha-1 Association and the Alpha-1 Foundation since I was diagnosed with Alpha-1 in 1987. It’s been a privilege to serve on the boards of both organizations, to serve on the staff of the Alpha-1 Foundation and now on the AlphaNet staff. I am presently the AlphaNet Coordinator serving 180 Alphas who live in Ohio, Kentucky and the District of Columbia.

Beginning with the first Alpha-1 educational conference in 1991, I was blown away by the personal involvement of the physicians (the ‘Alpha-docs’). As I recall, Drs. Gadek, Sandhaus, and Stoller were speakers and Dr. Brantly was there in the following years. Their presentations were excellent but the impressive part was that they were available to us one-on-one. This was new to me: doctors who mingled with patients. They stayed for the entire conference, ate dinner with us, answered our questions late into the evening and joined our struggle. This personal commitment by the ‘Alpha-docs’ continued over the next decade and the number of doctors working on Alpha-1 expanded. New faces appeared at conferences and education days. Alpha-1 became an important topic and research funding became available from a variety of sources due to the hard work and vision of John Walsh and the Alpha-1 Foundation.

On June 19th I had the opportunity to be blown away again. This time by how far we have come. I was invited, along with several other Alphas, to attend the Alpha-1 Foundation’s 3rd International Scientific Conference as a representative of the genetic consumer community. This yearly event is
designed to bring together the best and the brightest from around the world that has had an impact in the field of AAT Deficiency research. About 100 people with an interest in the specific topic of that year’s conference are gathered in an isolated spot, and asked to describe to the others how their work impacts our overall understanding of AAT Deficiency. You can almost see the sparks as new ideas take shape and erupt and new lines of thought develop over tuna salad and soup.

I will admit to being somewhat intimidated by the scientific credentials surrounding me. Midway during the first day I realized my purpose was to simply represent the Alpha Community by asking and answering questions the best I could and trying to personalize a disorder many of them knew only from the laboratory.

As with Alpha meetings, in the evenings after the scientific sessions we drifted toward the Pub where Alphas, docs, government folks, and industry representatives all mixed together. On several occasions I heard comments or concerns voiced by Alphas over the peanut bowl that strayed into the formal discussions the next day. I came to realize that as much as the docs impressed us, we were also making impressions upon them, and they were listening to us.

Nationally known ethicist Arthur Caplan opened the conference by discussing the science and risks of testing for genetic defects. He emphasized the importance of privacy and confidentiality in genetic testing and the related stigma and discrimination that is possible in employment and insurability issues Alphas are critically aware of.

Next, Dr. Diane Hoffman explained that state laws vary widely in their protections of our right to privacy. She suggested that the first priority for every Alpha is to get a copy of their own state’s Insurance Laws. Twenty-seven states have laws about genetic discrimination by employers. Some 38 states prohibit rating insurance premiums based on genetic tests or canceling insurance because of them. Alphas who lose their benefits need to be aware of the laws of their state.

Dr. Hoffman also cited a change in military benefits that may be important to our veteran Alphas, specifically “after 1999, anyone with eight years active duty military experience may receive disability coverage whether or not their disability occurred during active duty – genetics notwithstanding.” This may have a huge impact for Alphas with no disability protection except Social Security.

The next session, led by ethicist, Evan De Renzo, Ph.D., covered Public Health issues relative to resource allocation – an issue Alphas face every day. The first question is always “do the benefits of treatment justify the cost?” Another question is whether a situation is unfair or just unfortunate. How far does public policy have to go to protect and provide? Who pays for genetic testing? There are no simple answers – only more questions.

The second day opened with a discussion about identification of AAT deficient individuals. Dr. Sveger presented an interesting history and overview of the natural history of individuals identified at birth in Sweden and followed through childhood and early adulthood. This is the only study of its kind and invaluable for our understanding of the natural history of AAT Deficiency. It will need additional funding to continue.

The afternoon was devoted to identification of risk factors and other genetic disorders such as Cystic Fibrosis. Dr. Danielle Morse discussed oxidative stress on the liver and lung and presented her studies of antioxidant properties of vitamins E and C. She has shown reduced airway reactivity with vitamin C, and decreased peroxidation with vitamin E. She also found that deficiency of Coenzyme Q10 causes muscle and nervous system degeneration.

However, when asked, she was not able to recommend supplementation of vitamins E and C, or Co Q10 in Alpha-1 patients because the clinical research has not been done with living subjects. In my humble opinion, this would be a very important study for the MASAC Committee to consider promoting. If supplemental vitamins E and C were shown to protect the lung it would be an inexpensive, non-invasive therapy to add to our arsenal of weapons. Many Alpha-1 liver patients are already taking additional Vitamins A and E as prescribed by their doctors.

Other presentations included talks by David Perlmutter, M.D., who discussed his research on sub groups of ZZ Alphas to determine who is susceptible to liver disease.
Diane Cox, Ph.D., and Joanne Levy, M.D., reviewed their respective work relative to Copper in Wilson’s Disease and Toxic Iron in Hemachromatosis. Dr. Cox also described some conditions associated with AAT Deficiency such as liver and pulmonary disorders and immune response disorders such as rheumatoid arthritis, aortic aneurysm, anterior uveitis, panniculitis, and membranoproliferative glomerulitis.

The final day of the conference was devoted to therapeutic approaches to Alpha-1. Sandy Sandhaus, M.D., Ph.D., reviewed what is known about intravenous augmentation therapy in the United States. He also reported on Dr. Jack Lieberman’s Chest article taken from Internet interviews with Alphas that provides anecdotal evidence that Prolastin augmentation has a positive effect on exacerbation incidence among Alphas. Marion Wencker, Dr. Med., reviewed the European experience with intravenous Prolastin. The studies are small and inconclusive but she did report that the use of CT scan as a measure of lung changes was much more sensitive and a better measure of lung density in pulmonary evaluation than the more commonly used FEV1.

Dr. Brantly, Dr. Flotte, and Dr. Zern provided an overview of what new therapies are being developed to treat AAT Deficiency. This includes continued development of aerosolized AAT, which will address the lung disease associated with AAT Deficiency. However, other therapies in development are geared to address the impact of both the liver and lung disorders associated with AAT Deficiency.

This includes the use of recombinant adeno-associated virus vectors as gene therapy, which is being studied at the University of Florida in Gainesville. This method uses a harmless virus and splices some of the Alpha-1 gene to it. The virus is then injected into the body where it can begin to make healthy AAT. Human trials are scheduled to start this fall. Other studies discussed included the trans-retinoic acid studies that show promise of damaged lung cells. Stem cell therapies, and artificial organs are also in process but will have a longer time line before they can be used as therapies.

As the conference closed, I felt exhilarated and hopeful. I left for home comforted in the knowledge that there were many brilliant people working behind the scenes to uncover the secrets that will “fix” the problem of AAT Deficiency. The search is on for the tools to repair damage already done inside our bodies—in our lungs, livers, skin, veins—all the places where AAT Deficiency causes chaos. I believe that they will do it in the next decade.

I wish to express a deeply felt thank you to John Walsh, the Board and staff of the Alpha-1 Foundation, the MASAC Committee, the researchers and financial supporters and others unnamed who will continue to make a lifetime commitment to solving the puzzle that is Alpha-1—that is our lives.

With gratitude and love,

Mary Pierce

[Editor’s Note. Mary Pierce is an 8-year, double lung transplant recipient and cycling Gold Medalist in the International Transplant Games.]
starch gel electrophoresis, and just across the street in Oslo, I found Mikael Braend at the Veterinary College who had been one of Smithies students. He was running the technique to study plasma protein polymorphisms in animals, and allowed me to work in his lab. I am therefore proud to be a third generation indirect pupil of Oliver Smithies.

There are many important variables in the starch gel technique, and of course endless combinations of these. But after a while I started to see some sharp bands in the prealbumin region, and different mobility patterns were found. Testing family members showed that these patterns were inherited. These data were written up and a manuscript was sent to the prestigious journal Science. Our work was published in 1965 as a new polymorphism in man, and we called it the Pr system for pre-albumins.

Science accepted the manuscript even if it did not have a method description: we simply stated that details of the starch gel electrophoresis would be reported separately. But in fact, we were in trouble: when we had finally got the nice, sharp band patterns, we decided to “celebrate” and replace the old, muddy electrode buffers that had been used for many weeks, because in the midst of all the variables, a few things had to be kept constant. But that change gave a big surprise: the band patterns disappeared. Since we knew that buffers used many times worked, I simply had to run some 20 miserable gels before the buffers were “conditioned” so that the system worked again.

Clearly, we could not ask the readers of Science who wanted to try our method, to first run 25 miserable gels before distinct patterns could be seen. So I had to find out what was the principle involved in our peculiar method. Soon we also had serious doubts that the band pattern was due to Alpha-1 Antitrypsin rather than prealbumins.

Before long I realized that the critical factor was generating a suitable pH gradient in the gel during electrophoreses. We had simply invented isoelectric focussing without really knowing! Once we were able to achieve this we found we could subsequently prepare buffers with the right composition and have nice patterns from day one.

Among other critical factors was the quality of the potato starch, so I visited several factories to get the best raw material, and worked out the optimal conditions for hydrolysis of the starch and preparing the gels.

Admittedly, the starch gel technique included elements of “art” which I shared with many research groups during visits and practical demonstrations. It was therefore a welcome improvement when a suitable pH gradient could be obtained by more consistently reliable substances which is the method used widely now.

To document that our band patterns represented AAT, I got in touch with professor Carl-Bertil Laurell in Malmö Sweden with whom I exchanged antiserum against Alpha-1 and a collection sera from deficiency patients. With support from the Pasteur-foundation in Oslo and a Council of Europe scholarship, I spent four months in Carl-Bertil’s laboratory working out the quantitative aspects of the Alpha-1 band patterns. After consulting with Schultz and Heremans, authors of the famous textbook on Human plasma proteins, and Sten Eriksson, we decided to propose the name Pi-system for the AAT polymorphism. We also decided to give the variants letter names so that the positions in the alphabet indicate relative
electrophoretic mobilities. Thus the most common deficiency gene was called Pi Z.

Among the best aspects of getting into the Alpha-1 field was to meet so many nice and inspiring people. I had the opportunity to travel a lot in Europe, America and Canada and provide people with the selected, hydrolysed Norwegian potato starch for the Pi typing method and learn from their insight and projects.

I am ever grateful for the constructive discussions with and advice from Carl-Bertil Laurell, Diane Cox, Tobias Cedde-Dahl Jr., Jan Olov Jeppson, Thomas Sveger, Jack Pierce, A. Myron Johnson, Robin Carrell, Dick Talamo, Charles Mittman, Jack Lieberman, Philip Arnaud, Jean-Pierre Martin, Aldur Eriksson, and Bob Senior among others.

So I again thank the Alpha-1 Foundation for the award and for inviting me to come to the 3rd International Scientific Conference on Alpha-1 and meet so many prominent scientists and good old friends. The program at the conference shows clearly that there is a next generation of scientists, using new methods, continuing the work on how to understand and find ways to prevent and treat the diseases associated with Alpha-1-Antitrypsin Deficiency.

I wish them and the Foundation all the best for the future.


This conference brought together representatives of the European Alpha One Registry as well as researchers from over 12 countries to discuss the latest findings in Alpha-1 Antitrypsin (AAT) Deficiency research. Presentations included discussion of the epidemiology, biochemistry and genetics of AAT, as well as explorations of the pathogenesis of lung and liver disease, animal models of emphysema, AAT polymerization, surrogate markers, inhalation therapy, synthetic inhibitors and chaperone molecules, gene transfer and lung transplant. Presentations also included updates on AAT Deficiency registries and patient group organizations. The Conference was chaired by Robert A. Stockley, M.D., and coordinated by Maurizio Lusetti, M.D. (Italy), and Marc Miravitlles, M.D. (Spain). The Scientific Committee consists of Drs. Edward Campbell (USA), Asger Dirksen (Denmark), Nedim Hadzic (UK), Noor Kalsheker (UK), David Lomas (UK), Robert A. Sandhaus (USA), Jan Stolk (The Netherlands) and Jeffrey Teckman (USA).

The Alpha One International Registry, American College of Physicians, Bayer Corporation, and the Alpha-1 Foundation sponsored the conference. Several of the Foundation's Medical And Scientific Advisory Committee members presided or presented at the conference including Drs. Robert A. Sandhaus, Edwin Silverman, Gordon Snider, and Gerard Turino. For more information, please check the website at www.congressteam.com

<http://www.congressteam.com>
First Siena International Conference on Animal Models of Chronic Obstructive Pulmonary Disease

The First Siena International Conference on Animal Models of Chronic Obstructive Pulmonary Disease (COPD) took place from September 30 - October 2, 2001 in Siena, Italy. The conference consisted of six inter-related thematic sessions that discussed Etiological Factors in COPD, Animal Models, Cigarette-Smoke Induced Lesions, Transgenic Technologies, Developmental and Acquired Lesions, and Potential Therapeutic Approaches.

The primary purpose of a conference on animal models and COPD is to promote use of new technologies and to encourage complete description and evaluation of the significance of each of the models. It is likely that this will require collaborative research among investigators, which the conference was designed to promote.

The conference was chaired by Professor Giuseppe Lungarella, University of Siena. In addition to Professor Lungarella, the organizing committee included Professor Piero Martorana and Eleonora Cavarra of Siena and Gordon Snider of Boston.

The Alpha-1 Foundation provided organizational support and sponsorship for the event, as part of its long-term objective to hold conferences that examine various aspects of research related to AAT Deficiency in sequential focused forums. Since interest and expertise in AAT Deficiency research is international, the Foundation supports and promotes events that allow for participation of relevant experts from as many countries and institutions as possible.

For additional information please refer to the Conference website at:
<http://www.unisi.it/eventi/copd2001>
**Alpha-1 Foundation Critical Issue Workshops Series 2002**

The Alpha-1 Foundation will hold several Critical Issues Workshops in 2002. These focused workshops will investigate some of the rapid changes in biotechnology and the most critical issues related to AAT Deficiency research.

- **The Natural History of AAT Deficiency - What Do We Know, What Do We Need To Know?** The purpose of this workshop would be to bring together epidemiologists, pulmonologists, and geneticists to briefly summarize available information on the natural history of AAT Deficiency. Consideration will be given to the need for additional information on the natural history of never-smokers with homozygous AAT deficiency as well as the heterozygous state. Available information on acute exacerbations of AAT-COPD will be reviewed. The anticipated outcome of this workshop is a recommendation as to the feasibility of undertaking the necessary epidemiologic research to answer the questions posed, using the Alpha-1 Clinical Resource Centers and Research Registry.

- **The Pathogenesis of Emphysema (AAT and Usual) - Can We Speed Up Progress in Developing New Treatments?** The modern era of research in the pathogenesis of emphysema began about 50 years ago. However, while new treatment initiatives have come from information on the pathophysiology of emphysema, not a single new therapy has come from information on pathogenesis. The purpose of this workshop is to bring together investigators in human and experimental emphysema and investigators of inflammation from other fields to review the state of the art. The intent would be to identify collaborative initiatives that would speed up acquisition of knowledge from targeted investigations in humans and experimental animals.

- **Stem Cell Research Applicable to AAT Deficiency.** Research with adult and embryonic stem cells has been carried forward with a view of attempting to alleviate a number of diseases - primarily disorders of the bone marrow and lymph nodes and the nervous systems. It seems logical that stem cells established in the liver might serve as carriers of genes that could restore blood levels of AAT. Stem cells might also play a role in lung regeneration. The purpose of this workshop would be to bring together scientists working on stem cells to review their work and suggest possible initiatives for curing AAT deficiency.
A discussion of transplantation must also include liver transplants for Alpha-1. The overall survival rate following liver transplantation adults is better than for lung: 94% survive 1 month, 86% survive 1 year, and 76% survive 3 years. Infants and kids have slightly lower survival rates but still better than lung transplant recipients. In 1999, the same year there were 877 lung transplants performed nationally, there were 4,696 liver transplants performed. There are many more patients on the waiting list for liver transplants than for lung. Unfortunately, Alpha-1 is not one of the diagnoses collected and so it is not possible to determine the number of liver transplants done for Alpha-1. Alpha-1 liver transplant recipients would most likely be listed under the diagnoses non-cholestatic cirrhosis, cholestatic cirrhosis, metabolic liver disease, or possibility acute hepatic necrosis.
Only the Registry Coordinator and myself will have access to test results. After test results are received, participants are asked to fill out and return the two-page post-test questionnaire. Once the Registry Center has received the second questionnaire, identifying information can be deleted from ACT Trial records.

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

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

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**Alpha-1 Education Day-The Oregon Health & Science University**
Portland, OR 97201
Sunday, October 14, 2001
Contact Linda Alms (503) 494-7680

**Alpha-1 Education Day-Jean Bennett Conference Cleveland Clinic Foundation**
Cleveland, Ohio
Saturday, October 27, 2001
Contact Dan Laskowski (216) 444-3702.

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

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

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

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

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