LETTER FROM THE MEDICAL DIRECTOR

IM VERY EXCITED TO INTRODUCE THE SECOND YEAR OF THE REGISTRY UPDATE NEWSLETTER

and the first issue since I accepted the position of Medical Director for the Alpha One Foundation. What does a Medical Director do? I'm learning the answers to this question every day. As a full-time employee of the Foundation, I am able to concentrate on the scientific and medical goals and direction of the Foundation as well as answer everyday questions from staff, patients, and physicians.

As some of you may know, I've spent the past 30 years working on research related to alpha-1-antitrypsin deficiency (alpha-1) and caring for patients with alpha-1. I worked with Dr. Aaron Janoff on some of the early work showing that enzymes from white blood cells could damage lung tissue and that alpha-1-antitrypsin blocks this destruction. I've cared for a large and growing group of alpha-1 patients and their families for over 20 years at the National Jewish Medical and Research Center in Denver, was a major participant in the NIH Registry of patients with alpha-1, and have been a board member of the Alpha 1 Association, the Alpha One Foundation, and AlphaNet over the years. Many of you know me from the Alpha 1 Association's annual conferences.

For me, the opportunity to devote my total effort to the alpha-1 community is a dream come true. Along with my work at the Foundation, I will be providing medical direction to AlphaNet, co-directing the new Genetic Lung Disease Center at the University of Colorado Health Sciences Center, and continuing to see patients at the National Jewish Medical and Research Center.

You may notice some new abbreviations cropping up in this issue of the newsletter. The Alpha 1 Association and the Alpha One Foundation are trying to standardize the abbreviations used to refer to alpha-1-antitrypsin deficiency and individuals with this condition. This is being spearheaded by board members of both organizations. While nothing is finalized yet, we thought we'd see what it would be like to use some of the proposed abbreviations. For information aimed at the general public, it has been suggested that we consider calling the condition simply 'alpha-1', and also refer the protein alpha-1-antitrypsin as alpha-1. In more scientific presentations, it has been suggested to refer to the protein as AAT and the condition as AAT deficiency. Individuals with the condition will be called Alphas. Please let us know if you think this simplifies or confounds things.

This Newsletter issue includes a broad range of subjects. The historical articles by Jim Travis and Harvey Sharp allow us to examine the recollections of some of the true pioneers in alpha-1 research. Dr. Travis' article is of special interest to me since I was a graduate student in the laboratory of Dr. Aaron Janoff during the years referred to in his article. While many scientists have been involved in the effort to understand and treat alpha-1, personal accounts provide a unique and compelling perspective.

Finally, the Foundation would like to thank the Alpha One Research Registry Data Management Center at the University of Miami for its efforts during the initial years of the Registry.

Continued on back cover, page 16
Relocation of the Alpha One Research Registry

By Charlie Strange, M.D., Associate Professor, Medical University of South Carolina

The Alpha One Research Registry Data Coordinating Center is moving to Charleston, South Carolina. Dr. Charlie Strange in the Pulmonary Division of the Medical University of South Carolina (MUSC) has been entrusted with the important job of facilitating the research initiatives of the Alpha One Foundation by keeping the members of the Registry informed of new research opportunities. Dr. Strange is well known to the Alpha community as one of the principal investigators of the National Institutes of Health Registry and currently directs one of the Alpha One Foundation clinical centers.

The goals of the Registry are to enhance the chance of finding a cure for this disease. Never before in the history of alpha-1-antitrypsin deficiency have so many avenues of meaningful research been available. The National Institutes of Health has realized that chronic obstructive lung diseases are under-funded. The abnormal protein folding of the alpha-1 protein in the liver is driving a new group of protein chemists to examine the pathways of liver transport of AAT. Gene therapy initiatives are continuing forward at a rapid pace. As these opportunities arise, the risk to the alpha-1 community is the scarcity of patients with known AAT deficiency. Researchers with novel treatments will turn to other more common diseases unless patients with this disease willing to participate in research can be easily identified.

The transfer of the data coordinating center to MUSC is designed to increase the number of patients in the Registry. MUSC is among the most vital of the university medical centers in America. Exponential growth over the past decade in the southeast coast has fueled the drive to excellence in clinical research at MUSC. With a research budget yearly of more than 100 million dollars, the university has facilities to handle any mission given it by the Alpha One Foundation.

Dr. Strange will spend much of the next six months enhancing the web interface of the Registry to allow on-line access to research opportunities. As the Registry grows, the opportunities and challenges of rapid communication to the membership are obvious. When asked to comment on his new charge Dr. Strange said, "I am honored to have the important job of safeguarding the vital information of Alpha patients. When I wrote the proposal to transfer the Alpha One Research Registry coordinating site, I knew I wanted to give something of substance back to the Alpha-1 community. It is with pride that I will serve as the intermediary between the world of research and Alpha patients. I will strive to give the Alpha One Research Registry a face that cares and an ear that hears the concerns of every member."

The immediate concerns of the Registry transfer are to assure a smooth transition of the coordinating center from Miami to Charleston. If current members get a new Registry questionnaire from the Alpha One Foundation or the Alpha 1 Association they are encouraged to update the information and send it back to keep the database as current as possible. Since new research initiatives may come at any time, a rapid response is vital. It is important to realize that being a member of the Alpha One Research Registry does not obligate anyone to participate in research. Membership does assure that you will hear about research initiatives as they arise to stay current in the field of AAT deficiency.
Recruitment for the Alpha One Research Registry
By Robert (Sandy) Sandhaus, M.D., Ph.D., Executive Vice President and Medical Director, Alpha One Foundation

One of the greatest potential assets to the Alpha-1 community is the Alpha One Research Registry. Building on the National Institutes of Health’s Registry that was started a decade ago, the Alpha One Research Registry, funded by the Alpha One Foundation, provides a confidential repository of information regarding Alpha-1 patients. The first and primary purpose of this Registry is to foster clinical research studies that lead to new therapies. In order to meet this purpose, it is of vital importance that all individuals diagnosed with AAT deficiency in the US consider enrolling in this Registry.

The Registry is housed and maintained by an independent academic center and is governed by a blue-ribbon committee of scientists, ethicists, and patients. Researchers interested in studying therapies or issues related to Alpha-1 can present their proposed projects to the Medical and Scientific Advisory Committee of the Alpha One Foundation. If approved, Registry participants who might meet the enrollment criteria are contacted by the University and presented with the option of participating in individual projects. Neither the Foundation nor the researchers ever see any identifying information. If the patient agrees to participate, he or she contacts the researcher directly. Currently, Registry participants have the opportunity to participate in three trials involving new therapies.

The registries of other similar patient groups, such as the cystic fibrosis Registry, have provided the information necessary to help in promoting important legislation, setting government research priorities, and promoting new drug development. The Alpha One Research Registry, if large enough to be representative of the population of Alpha-1 patients, can provide an overall view of how well current therapy is being provided. It is our hope that the Alpha One Research Registry will be able to represent the US in an international Registry of Alpha-1 patients.

Your help is needed to increase enrollment and build the Registry into a valuable research tool. There are about 1,000 patients currently enrolled in the Registry. We know that there are many more patients with Alpha-1. Please encourage Alphas in your support groups to complete the Registry questionnaire. Of great importance, if there are individuals not wishing to participate in the Registry, we’d love to know why. Are there things that could be done differently or better that would facilitate your participation?

All Alphas and carriers, as well, are encouraged to contact the Alpha One Foundation for enrollment information. Registry questionnaires are available for downloading from the Alpha One Foundation Website at www.alphaone.org, or copies can be obtained by calling toll free 877-2 CURE A1 (877-228-3721) or by e-mail at Registry@alphaone.org.

Bettina Irwin, Board Member Alpha 1 Association, discussing recruitment with Mary Pierce, Program Director Team Alpha One
Educational and Training Materials: The Alpha One Foundation is proud to announce publication of three pamphlets,
- WHY SHOULD I BE TESTED? with information for those considering being tested regarding the benefits and risks of diagnosing a genetic condition,
- GUIDE FOR THE RECENTLY DIAGNOSED, with information about treatment and resources for alphas and their families, and
- A HEALTH CARE PROVIDER’S GUIDE, written for physicians, nurses and therapists to educate them about alpha1-antitrypsin deficiency, its symptoms, diagnosis and treatment.
To obtain copies of these important resources, contact the Alpha One Foundation at 888-825-7421 or research@alphaone.org

An Up-Date on Bioethics at the Alpha One Foundation
By Evan G. DeRienzo, Ph.D., Bioethics Consultant, Alpha One Foundation
Since its beginnings, the Alpha One Foundation has been on the cutting edge among research foundations. This is exemplified by its approach to ethical consideration of its activities and interests. That is, the Foundation has explicitly and uniquely incorporated bioethics into its general processes. Early in the Foundation’s development it hired me to serve as a consulting clinical research ethicist to the Medical and Scientific Advisory Committee (MASAC). Utilizing a bioethics consultant on such a regular, ongoing basis is unique among research foundations.
At the beginning, my responsibilities were to attend MASAC and Alpha One Foundation Board meetings, to be available to respond to questions as they arose, and to review and comment on the various processes related to setting up the infrastructure of the Foundation. Today, my responsibilities have expanded, and we are, again, pushing the boundaries as we continue to serve as a model of how bioethics can and should be integrated into the life of a foundation that supports and/or stimulates human subjects research.
This evolution has been swift. Initially we created the processes for review of research protocols being considered for support by the Foundation. Next we tackled the ethical complexities of establishing the Alpha One Research Registry and the critical need for informed consent, and privacy and confidentiality protections. Of late, we have turned our attentions to the issue of detection and screening for AAT Deficiency.
The Foundation’s incorporation of bioethics also occurs when considering what research is needed at the basic and clinical levels, developing strategies to stimulate and where appropriate, fund, such research, and simultaneously, consider the ethical, legal, social and economic aspects of these Foundation activities. For, similar to the model created by the Genome Project (now the National Human Genome Research Institute of the National Institutes of Health), the Alpha One Foundation has always understood that examination of the ethical, legal, and socio-economic implications of genomic science must go hand in hand with scientific progress.
Thus, it is my pleasure to report on the newest evolutionary steps for Foundation bioethics. The first is the expansion of involved bioethicists. With the creation of the Detection and Screening Working Group, a group established to develop the Foundation’s scientific agenda on detection and screening for AATD, four more bioethicists have become part of the Foundation’s activities. They are: Richard R. Sharp, Ph.D., NIH, Henry Silverman, M.D., University of Maryland, Robert Wachbroit, Ph.D., University of Maryland, and Mark Yarborough, Ph.D., University of Colorado.
The second evolutionary step is the recent creation of what has been named the Alpha-ELSE Working Group. The Alpha-ELSE is a formalized working group that will include ethicists, physician-investigators, and others who will specifically focus on the ethical, legal, social and economic aspects of Foundation activities and interests.

We welcome the community’s thoughts, suggestions or questions about ethical issues related to Foundation activities. And as issues arise, we will keep you informed through future updates in this newsletter. In the meantime, you can be proud that the Alpha One Foundation is committed to consideration of the ethical aspects of the science it encourages.
Effectiveness of the Alpha Community
By Miriam O'Day, Government Relations Consultant, Alpha One Foundation

There have been a number of positive developments and successful outcomes for the Alpha-1 Community in government relations and advocacy.

The first is the long anticipated ruling from the Health Care Financing Administration (HCFA) regarding the Prospective Payment System for Hospital Outpatient Services published April 7, 2000. Under the new ruling biologics such as Prolastin® will be reimbursed on a special provision (pass-through) equal to 95% of the average wholesale price (AWP). This is cause for celebration because the Balanced Budget Act of 1997 required strategies for cost containment that would have discontinued adequate reimbursement for biologics by bundling them into a single reimbursement (i.e. non pass-through) code (APC906). The Foundation was among those providing public comment on APC906, calling for HCFA to exempt Prolastin from the bundled reimbursement. HCFA received more comments on this proposed rule then any rule to date. This represents a unified effort by the consumer community who worked collaboratively with physicians and the biologics industry to tackle this issue. This hard won victory should be appreciated as an achievement made through effective collaboration from all members of the Alpha-1 Community. This partnership is essential to effectively address the ongoing problems of access to care and adequate reimbursement for therapy.

Thanks in large part to Executive Director Dr. Stephen Nightingale’s leadership and committee member John W. Walsh’s motion on behalf of the plasma consumer, the Advisory Committee on Blood Safety and Availability focused their agenda on this critical issue. This prompted Secretary Shalala to take personal action and affect the aforementioned change. These activities were also supported by the Alpha 1 Association, under the leadership of Nancye Buclow, through a critical letter writing campaign and meetings with HCFA representatives. Through these coordinated and cooperative efforts, Prolastin was included on the list of biologics to receive this special pass-through provision. The Foundation will continue to promote this ruling in order to make physicians aware that their hospitals are able to bill Prolastin as a pass-through. Finally the HCFA ruling has provisions for new technologies giving hope to Alphas that reimbursement will be available for aerosol delivery systems when they become available.

The Foundation has also furthered its goal of ongoing and effective interactions with government through its series of Strategic Planning sessions with all of its stakeholders. The March 3, 2000 session held in Washington, DC focused on government grants and research and included representatives from the NIH, FDA and DHHS. The February 12, 2000 session held in Miami included Executive Directors who are voluntary health agency members in the National Health Council (NHC) marking their commitment to the growth and development of philanthropic organizations such as the Alpha One Foundation. Government and non-profit leaders offered input and guidance during these sessions that will contribute to the development of new ideas and approaches to furthering the success of our mission.
FROM THE RESEARCH BENCH TO THE BEDSIDE

Prolastin: From an Idea to a Useful Product
By James Travis, M.D., Professor of Biochemistry, The University of Georgia

The early discovery by Sten Eriksson, Carl Laurell, and their colleagues in Malmo, Sweden of a relationship between a serum deficiency in alpha_1-antitrypsin (AAT) and the development of both emphysema and liver cirrhosis were certainly the stimulus for research into the function of this proteinase inhibitor. Indeed, the story of how an idea became a product really begins serendipitously with my invitation to the first meeting organized by Chuck Mittman, entitled "Pulmonary Emphysema and Proteolysis" which was held in January 1970 in Duarte, CA. I was invited to this meeting, not because I knew anything about emphysema, but rather to discuss the proteolytic enzymes elicited by the human pancreas. In fact, I was intrigued by this "antitrypsin" molecule, but as an inhibitor of pancreatic enzymes that might be useful against pancreatic diseases.

Since I was trained in classical biochemistry, I came away from the meeting with the immediate notion that we needed to know more about the structure and function of the M form of AAT, which circulates in the blood of the majority of individuals, in comparison to the abnormal Z-form, before we would be able to understand the reasons for the disease states in which the latter predominates. In addition, it was obvious from the fundamental studies of Aaron Janoff that we needed to investigate the role of proteolytic enzymes from neutrophils as the initial cause of tissue destruction in the lung associated with the development of emphysema.

Let me make it clear at the outset that AAT had been purified previously by many investigators, the best job perhaps being done by Norbert Heimburger and his group at Behringwerke. They used a method of purification that I believed would have a lot of denatured inhibitor (turns out I was wrong!). So, instead we started with whole plasma and used non-denaturing technologies. A very sharp student, Ralph Pannell, worked out the details of the purification which at that time was rather novel. Shortly thereafter we characterized the AAT protein and began to examine what its function in plasma might be in terms of controlling neutrophil proteinase activity. It was at this stage that I met and was fortunate to become friends with a terrific competitor, Aaron Janoff. I cannot say enough kind words about Aaron. He died an untimely death just at the height of his career, but his contributions will always be remembered.

Dr. Janoff had been working on neutrophil elastase, and discovered that this enzyme rapidly degraded lung elastin. His theory was that this enzyme was a logical target for AAT and that in deficiency states it would degrade connective tissue proteins within the lung. However, he didn't have good inhibitor available to him and he had not been able to obtain enough enzyme to do proper characterization studies. I was fortunate to have obtained an excellent source of cells. It wasn't long before we purified two of the
major proteinases from these cells, elastase and cathepsin G (we missed out on a third enzyme, proteinase III, which was isolated several years later by John Hoidal’s group). Thus, we were now ready to tackle Aaron’s hypothesis regarding roles for both elastase and AAT in the prevention and/or development of pulmonary emphysema.

As we were pretty simple protein chemists/enzymologists, we were fortunate to also have other friendly competitors, including Bob Senior, Kjell Ohlsson, and the late Allen Cohen all of whom added their expertise to this research area. Concurrent with our investigations, these researchers were able to perform whole cell and whole animal studies using, in some cases, the enzyme(s) and inhibitor that we supplied. It seems like only yesterday that I received a call from Aaron who wanted to know what I had learned from our structure/function experiments. It was clear that he was pretty excited, but so was I because Dave Johnson in my laboratory had just figured out how the inhibitor functioned. After much hemming and hawing Aaron told me that his group had tested both chemical oxidants and the oxidants in cigarette smoke and found that both caused a loss of inhibitory activity. I told him that concurred with Johnson’s data who also found that AAT could be oxidatively inactivated. More importantly, we had identified the specific amino acid required for elastase inhibition. We were both satisfied that we had, in parallel, come to the same conclusion and, in my opinion this opened up a world of possibilities for explaining the importance of oxidants from both neutrophils (utilized to kill foreign organisms during infection) and cigarette smoke to the development of pulmonary emphysema. These oxidants apparently caused conversion of native AAT to an oxidized form that was no longer capable of controlling degradation in connective tissue rich organs, especially the lung.

During this period (1977) I began consulting for Cutter Laboratories (later to become part of the Bayer organization). This was quite timely, as they were looking for new plasma products to supplant those already on the market. I enthusiastically recommended AAT, now referred to as alpha1 proteinase inhibitor (a-1-PI) because of its role in controlling neutrophil enzymes. I was amazed at the number of steps one had to go through to bring a product to the market, particularly the characterization of the molecule, toxicity studies, and animal and human experimentation (the latter performed brilliantly by Ron Crystals’ group at NIH). However, I remember very well being at the final FDA meeting when a-1-PI, now referred to commercially as Prolastin, was approved for use under orphan drug status. Certainly, this was the highlight of my scientific career.

It is clear to me that Prolastin will certainly be used in the future to treat other disease states where excessive neutrophil infiltration and tissue damage is occurring. However, supplies are currently limited and one can only hope that the development of aerosols to deliver the protein directly to the lung will reduce the quantities needed for the Z-deficient individuals. This will then allow wider use of this very important protein. Of course gene therapy, together with the development of alternate procedures for expressing a-1-PI are certain to occur in the near future. At that stage, this protein should find new uses not even remotely considered today.

None of this would have happened as it did had it not been for significant research funding from NIH, dedicated graduate students and post-docs, and a loving and patient family. To all of them I send my heartfelt thanks.
Historical Aspects of the Liver Abnormalities Associated with Alpha One-Antitrypsin (AAT) Deficiency

Harvey L. Sharp, MD, Professor, University of Minnesota Hospital & Clinics

In 1955, Jacobsson documented that 90% of the ability to block trypsin in human serum resides in the protein fraction designated alpha one globulin. Uninhibited trypsin breaks down complete proteins and is one function of this protein subsequently expanded to include the inhibition of other damaging enzymes including elastase. That same year, Schultz et al. isolated and characterized the protein in the alpha globulin fraction which had trypsin inhibitory capacity and in 1962 named this glycoprotein alpha_{1}-antitrypsin (AAT) because of this known function.

The following year in Malmo, Sweden, Dr. Carl Laurell discovered a virtual absence of the alpha one globulin band in laboratory tests performed on certain patients and together with Dr. Sten Eriksson noted that 3 out of 5 patients with this abnormality had pulmonary insufficiency. While looking at another protein separation gel he noted an alpha one globulin band which migrated very slowly that was characteristic of the abnormal form of AAT that predisposes to disease. In the following two years, Dr. Eriksson studied families with AAT deficiency and documented a range values for homozygotes, heterozygotes (carriers), and normals. The findings verified that this is an inherited disorder that in the homozygotes predisposes to familial emphysema. Kueppers and Bearn in the United States confirmed this association with pulmonary emphysema indicating that this was not a local (European) phenomenon. AAT deficient patients presented with dyspnea earlier than the usual 60 years associated with other chronic obstructive lung diseases, were equally distributed between males and females, and the lower lobes of the lungs were more involved with damage.
In adjacent Oslo Norway, Magne Fagerhol demonstrated multiple AAT variants on a special potato acid starch gel. Together with Dr. Laurell they devised the Pi (protease inhibitor) system. The gene allele protein products were lettered according to the alphabet with normal being PiM and with the slowest moving protein designated PiZ. In heterozygotes with both M and Z alleles, both types of protein can be identified in blood, thus the inheritance is "co-dominant" (as opposed to dominant or recessive).

At the University of Minnesota, the techniques published by Dr. Eriksson were replicated by Esther Freier because of the high interest in emphysema at that institution. After screening patients with low alpha one globulin levels, she called Dr. Harvey Sharp concerning the diagnosis of the first two patients detected who turned out to have a familial liver disease of unknown origin. Quickly 10 children from six different kindreds were identified as having cirrhosis of the liver associated with AAT deficiency and with the aid of Dr. Jack Pierce confirmed the PiZZ homozygotes with the parents being heterozygotes except for one homozygous father who subsequently developed liver disease. This report in 1969 was preceded in 1968 by the notation of two adult cases of cirrhosis and one case of hepatocellular carcinoma by Gaffney, Laurell, and Eriksson. Upon examining liver specimens of children with liver disease associated with AAT deficiency under the electron microscope, Dr. Sharp noted retention of protein within liver cells. Granules of retained protein were identified as being contained within the rough endoplasmic reticulum (RER). The protein was identified as retained AAT and this accounts for the low circulating levels of AAT in PiZZ homozygous individuals. The results of these investigations were reported in Hospital Practice in 1971. Lesser amounts of the PiZ AAT accumulation were also documented in the hepatocytes of carriers without liver disease and patients with inherited emphysema indicating the retention of AAT was not a result of the liver disease.

The most common presentation of the liver disease is cholestatic jaundice during infancy. Up to 10% of AAT deficient infants presenting with jaundice have a decrease in the number of bile ducts within the liver. Other than extrahepatic biliary atresia, AAT is the most common reason (13%) for liver transplantation in childhood. Landmark prospective studies by Dr. Tomas Sveger confirmed this by utilizing better and simpler serum techniques and indicated that the incidence of significant liver disease is only 3% up to 18 years of age. Emphysema is extremely rare during this time period and never documented in this series. Therefore the overall risk for significant liver disease in children is quite small although the risk is somewhat higher (projected to be 5%) in families in which one child has already had severe liver disease.

Subsequently a number of other inherited diseases have been found where the protein has a hard time trafficking out of the RER, including the most severe form of cystic fibrosis. In the PiZZ form of AAT deficiency, the gene defect results in aggregation to the point of sticking together of individual AAT proteins in the RER of the liver cells. PiZZ AAT is functional when it is secreted out of these cells. Thus treatment to disrupt the stickiness of this protein in the RER could allow AAT to traffic normally to the serum. An international scientific conference is being held this summer sponsored by the Alpha One Foundation to bring together experts in this field of research in hope that a medical therapy will ultimately be available for AAT deficiency.
Current and Future Clinical Trials
Summary of a presentation by Mark L. Brantly, M.D.
By Symma Finn, M.A., Research Administrator.
Alpha One Foundation

Current Trials: Dr. Brantly, a leading expert on alpha-1-antitrypsin (AAT) deficiency research and patient care, made a presentation on current and future research directions at Texas Research Day in Austin. His presentation included a description of the current clinical trials being conducted on transgenic AAT by PPL, a Scottish pharmaceutical company famous for cloning Dolly the sheep (see Volume 1, Issue 2 for description of this trial), and the upcoming Centeon (Aventis-Behring) trial, which will test aerosolized AAT. Dr. Brantly also described how research studies are designed, so that Alphas who participate in these studies could understand why certain elements are included, and gave an overview of upcoming trials and the trials that are being developed for implementation over the next several years.

Dr. Brantly's explanation of research study design included:
- The rationale for dose escalation
- The rationale for using a placebo
- The rationale for performing bronchial alveolar lavage as part of the trial

Dose Escalation: A well-designed clinical trial will answer some important questions about a new drug or treatment. A Phase I trial is frequently designed as a dose-finding study and is used to determine the safest dose that will still be strong enough to be effective for treating patients. In the Aventis trial, aerosolized delivery of AAT was examined for its potential to deliver a high dose directly to the lungs. It is important to determine how much to use, since it is handled by the body in a different way than an intravenously delivered drug, and therefore the recommended dose cannot be based on intravenous doses. A Phase I trial can also establish the toxicity of a product by determining at what dosage problems and side effects begin to occur. For example, it is possible that asthmatic patients may experience asthma symptoms at very high doses of an inhaled medication.

Use of a Placebo: The importance and necessity of using placebos in trials was also discussed. If a drug is treating a disease where there is no current therapy or the effectiveness of the current therapy is not proven, they may require a placebo be used in order to approve the drug. The rationale used is that placebos prove beyond a doubt that administration of a particular substance has a significant affect on the patient. If patients in both a drug-receiving group and a placebo-receiving group have similar reactions and symptoms, then it is clearer that the drug did not work any better, or at all. If, however, the drug-receiving group shows a statistically significant difference from the placebo-receiving group, the FDA is more willing to consider approving that drug as an effective treatment. The FDA also establishes with researchers at the start of a study what are the exact results (the markers) that will prove the effectiveness of a particular drug. The FDA and other regulatory authorities around the world require that the results evaluated affect the patient in a clinically significant and positive way.

Use of Bronchial Alveolar Lavage (BAL): Dr. Brantly also explained why it was important to conduct BALs several times throughout early clinical trials. Since the lung is the location of the destruction associated with AAT deficiency lung disease, it is the best place to see what is going on. A BAL done prior to aerosol therapy can establish what is going on in the lungs (i.e., how much inflammation, the concentration of neutrophil elastase, the amount of AAT). Testing after administration shows in the most exact way how much of the aerosol reached the lungs, and how much was retained over time. Phase I trials generally use moderately ill patients, but Phase II and III trials of AAT products will use larger groups of people at all different stages of disease to show the effects of the product on all those effected by AAT deficiency. These later trials may not need to include BAL.
Upcoming Trials: Aventis-Behring will conduct Phase II and Phase III intravenous trials in early 2000, which follow up on a Phase I dose comparison study on a newly developed AAT product. This study will be conducted at multiple centers, with University of Texas Health Center (Dr. James Stocks), Tyler and University of Florida College of Medicine (Dr. Mark Brantly) as the first two sites. These trials will require some patients to have BAL procedures to determine if the product inhibits neutrophil elastase activity. To participate please contact moengc@medicine.ufl.edu or kthornto@uthct.edu

In addition, Phase II and Phase III trial results are expected to be submitted to the FDA by Alpha1 Therapeutics seeking the approval of an additional plasma derived product to compete with Bayer’s Prolastin.

National Emphysema Treatment Trial (NETT) Study: This is a national study to determine the usefulness and effectiveness of lung reduction surgery. Subjects are still being recruited for this study and although the study is not specifically for alphas, it is important to get representation of the alpha community in this study. For more information visit the website at www.nih.bi.nih.gov/health/prof/lung/nett/lrsweb.htm

Future Near Term Studies: An All Trans Retinoic Acid Study in Emphysema is being planned by the NIH to determine the effects of a form of vitamin A given to individuals with emphysema. Early animal studies showed some promise for regrowing alveolar tissue. If these study results are confirmed in human trials, this type of treatment may prove to be an effective way to halt lung destruction, and repair it for Alphas as well as those with cystic fibrosis, chronic bronchitis or other lung related diseases. Alphas should consider participating in this study.

4 PBA (Phenyl Butyrate) Pilot Study: This is a new class of therapeutic compounds that act as chemical chaperones to help move proteins through the cell. This concept was used by a researcher at Johns Hopkins, Pamela Zeitlin, M.D. She utilized 4PBA with the cystic fibrosis protein, and was successful increasing the amount of cystic fibrosis protein that found its way to the cell surface. This same process may also be successfully used to increase the amount of alpha-1 that leaves the liver cells of deficient individuals.

Oral Elastase Inhibitors: These substances have been studied since the 1980s. At least two pharmaceutical companies have recently submitted a study designs to the FDA for trials to begin in the near future. A number of other elastase inhibitor compounds are being developed as well.

Future Studies: There are several new therapies being explored by researchers that may eventually lead to entirely new approaches for the treatment of AAT deficiency. They include gene replacement therapy, ribozyme therapy, gene correction, recombinant aerosol AAT, hyaluronic acid protective therapy, and stem cell replacement therapy. Although exciting and promising therapies, their implementation in human trials are several years away. We will describe each of these new therapeutic approaches in an upcoming issue of the Registry Update.
Nutrition and Exercise for Patients with Alpha-1
By Rick Carter, Ph.D., M.B.A., Professor of Medicine and Physiology, The University of Texas Health Center at Tyler

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hronic diseases of the lung, such as Alpha1-Antitrypsin (AAT) Deficiency, increase dyspnea (shortness of breath), reduce an individual’s ability to perform daily activities or exercise and promote an imbalance with respect to nutritional intake and energy expenditure. Aside from treating the disease and fighting acute infections, increasing exercise ability and following good nutritional habits are essential elements for health maintenance.

Nutrition: While shortness-of-breath, even with supplemental oxygen administration, may make eating difficult, an individual still needs to consume adequate amounts of food with the right nutritional blend. One problem Alphas may have with food consumption is the amount of food placed in the stomach at one time. When the stomach is filled, extra pressure from the stomach presses upward on the chest cavity and diaphragm making it harder to breathe. The individual may avoid eating because of the increased dyspnea. To counteract this problem, as many as six or seven smaller meals spaced throughout the day are recommended. This will ensure that adequate caloric needs are satisfied and that dyspnea is minimized. Also important is the composition of the foods consumed. It is recommended that Alphas make sure to consume a balanced diet and take supplemental multivitamins with trace elements along with an ongoing intake of water and other fluids.

Exercise: Many individuals with advancing lung disease enter into what has been described as an activity-limiting cascade because of the unpleasant sensation of increased shortness-of-breath. This inactivity spiral continues, with increasing shortness-of-breath experienced. The most positive, but often the most overlooked counter measure to this inactivity spiral, is to enter in and routinely participate in an exercise rehabilitation program designed to reduce dyspnea, increase exercise tolerance, maintain/increase muscle strength and promote numerous other positive bodily changes.

When designing an exercise program several essential components are required. These include:
• how hard to exercise (judged by heart rate responses or dyspnea),
• how long to exercise (minutes per day),
• how many times per week to participate and
• selection of the different forms of exercise to participate in.

It is important to note that all individuals who train will experience shortness-of-breath during exercise and that with training the amount or severity of this unpleasant sensation will gradually decrease. The difference for Alphas is the severity of dyspnea experienced with exercise. Alphas need to understand that the benefits of exercise are many, and that they need to continue even though shortness-of-breath is present.

By using self-management approaches with input from your physician, your quality-of-life will be greatly improved. Other very important alterations that will result from a program as outlined above include:
• positive changes in blood cholesterol and lipids,
• improved lung and heart function,
• improved muscle tone, balance, and ability to perform work,
• positive biochemical changes throughout the body,
• positive immunologic changes.

Further these programs have been associated with:
• fewer hospital admissions, and physician visits,
• better control over the disease process and
• positive alterations in medication usage.

Exercise can and should be approached with a knowledge base that will make it an effective part of an Alphas daily routine. Simply because you may have a lung problem does not restrict you from exercise. To the contrary, exercise and nutrition should be key components to maintenance of a healthy lifestyle and delaying the negative effects of both disease and aging.
Texas Research Day
By Laurie Lackland, R.N., BSN, The University of Texas Health Center at Tyler

The University of Texas Health Center at Tyler (UTHCT), is one of the nation's leading centers for alpha-1 clinical research, education, and patient support. Our staff is a team of professionals who are dedicated to serving the alpha-1 community. We offer a variety of services, resources, and opportunities for Alphas to maximize their quality of life, as well as opportunities for patients, themselves, to contribute to the development of new therapies.

Dr. James Stocks, Professor of Medicine, and Medical Director for the Center for Clinical Research at UTHCT, leads our alpha-1 team. Dr. Stocks has more than 15 years of experience in clinical research, and has been actively involved with the alpha-1 community since the development of the first U.S. Registry in 1989. Other team members include Laurie Lackland, RN, BSN, who serves as a patient advocate and educational resource, and Kevin Thornton, LVN, who helps in the implementation of clinical research trials.

Each year we host an educational conference for Alphas and their families. This year's conference was held in Austin, Texas, and was attended by Alphas from across the state, and as far away as Maryland and Miami. Dr. James Stocks highlighted the currently available treatment options for Alpha patients and the need for Alphas to become active partners in clinical research, stressing that "Without volunteers, no new therapy will ever become available."

The other talks were by Rick Carter, Ph.D., also from the Tyler Health Center, on exercise rehabilitation, and an update on current and future clinical trials by Dr. Mark Brantley, University of Florida. Many attendees expressed an appreciation for the opportunity to meet these experts on a personal level and to ask questions which directly related to their lives. Another special highlight of the conference was an outstanding performance by Eric Hansen, an Alpha with a wonderful gift of sharing his life through music.

For more information about the University of Texas Health Center at Tyler, please call Laurie Lackland, RN, BSN, at (903) 877-7840.

End of Life Issues and Palliative Care:
By Mark Yarborough, Ph.D., Director, Health Care Ethics, Humanities & Law, University of Colorado Health Sciences Center

Appropriate care near the end of life is an area of vital importance to the Alpha community and the Alpha One Foundation is committed to providing leadership in this area. The Foundation is pleased to announce that researchers with the Program in Health Care Ethics, Humanities and Law and the Division of Internal Medicine at the University of Colorado Health Sciences Center, the National Jewish Hospital and Research Center in Denver, and at the Alpha One Foundation are in the process of planning research projects to study end-of-life issues for those with alpha-1-antitrypsin deficiency.

This research team plans to coordinate their efforts with researchers in the field of Cystic Fibrosis to investigate whether, and to what extent patients, their families, and their care providers know about and access palliative care services. This may include advance care planning, establishing goals for care near the end of life (such as the management of pain and other symptoms), and the psychosocial and spiritual dimensions of care. It is hoped that the results of this research will empower patients, their families, and their care providers to improve care near the end of life.

The research team is actively seeking your input at this early stage of the research study design. What issues are important to you, the Alpha community? Please send your comments or questions to Mark Yarborough, Ph.D., Program in Health Care Ethics, Humanities and Law at email: mark.yarborough@uchsc.edu or by fax at (303) 393-7798.
FAQs*
By Robert A. Sandhaus, M.D., Ph.D., Medical Director, Alpha One Foundation

Q: If I'm getting the same dose of Prolastin® every week (60 mg/kg and my weight hasn't changed) why does my nurse give me 4 vials of Prolastin sometimes and 5 vials other times?

A: While your total dose hasn't changed, the amount of Alpha-1 in each vial of Prolastin does change from lot to lot. The largest vial of Prolastin is supposed to contain approximately 1000 mg of alpha-1 proteinase inhibitor (alpha-1 antitrypsin). However, "approximately" can sometimes mean it contains 823 mg, and other times 1202 mg, for example. Let's assume you weigh 143 pounds (65 kilograms). Your calculated weekly dose of Prolastin should be 65 times 60, or 3,900 mg. Since we "round up" to the total number of vials needed for the calculated dose, if the lot you are using has about 800 mg in each vial, you would need 5 vials to deliver the calculated dose, but you'd need only 4 vials if the lot being used contained 1200 mg per vial.

Q: I'm one of the new kids on the block, and about to start Prolastin any day now. Someone said I need to get my levels checked and adjust my dose of Prolastin but I didn't realize you were supposed to maintain a certain level. I'm very interested in this. The more detail, the better.

A: Although others may disagree, I don't think that Alphas on Prolastin should ever have their levels checked! Why, you ask? Well, let's examine the history of the dosing of Prolastin. Back in the mid-80's, investigators at the NIH were trying to show that you could replace or augment the alpha-1 in someone's lungs by giving intravenous alpha-1 from normal plasma. They had to decide how much to give and looked at a bunch of homozygous and heterozygous individuals (ZZ, MZ, SZ, SS, MS) trying to correlate their blood levels of alpha-1 and whether or not they got emphysema. They decided that people who had levels of 80 mg/dl and above were protected while those with lower levels were not. Thus, the magic level of 80 mg/dl!

So they set out to find a dose of alpha-1 that never let the level go below 80 mg/dl and found that giving a dose of 60 mg/kg to ZZ alpha-1 patients would produce dramatically high levels immediately after the infusion (thousands of mg/dl) and that these levels then fell over time until at the end of the seventh day the levels were just about 80 mg/dl. They also did bronchoscopies on the patients receiving this extra alpha-1 and found that with time, there were higher and higher levels of alpha-1 in the bronchial fluid and that these lung levels didn't vary from dose to dose as much as the blood levels did. The important thing to remember is that for emphysema patients, it's the lung levels that matter!

So, why do I say that levels shouldn't be checked for patients on Prolastin? First of all, the 80 mg/dl magic number is "made up" and should be just a guide. Most Alpha Docs know people with much lower levels than 80 mg/dl who never get any lung disease and individuals with higher blood levels than 80 mg/dl who do get lung disease. Second, the level we should be really interested in is the lung level. Unless you're willing to have a bronchscopy done to measure this, looking at just the blood level is not likely to tell you what the lung levels are AND we know from the original NIH studies that the lung levels tend to remain high after someone's been on regular doses of Prolastin for several weeks.

Chasing blood levels not only wastes resources (and your blood) it also may lead you to get higher doses of Prolastin than you actually need, taking Prolastin from others during a time of shortage.

No one has ever actually tested what the optimal dose of Prolastin is, partly because such a study would involve giving a variety of doses of Prolastin over several years to many patients in order to detect a difference. The closest we can come to an answer at this time might be to look at the results of the NIH Registry. One of the results of the Registry that is often overlooked is that patients who received ANY Prolastin at ANY time while in the Registry did just as well as patients who received Prolastin throughout their time in the Registry. And both of these groups did better than those who never got Prolastin. This suggests to me that the current dosing regimen of 60 mg/kg per week may even be overkill.

*FAQs will be a regular column — please send your questions to Dr. Sandhaus at rasandhaus@alphaone.org
The Alpha One Foundation will be hosting the 2nd International Scientific Conference June 27-30, 2000 at the Airlie Conference Center, Warrenton, VA. The topic of this year’s conference is Alpha-1 Antitrypsin Deficiency and Other Conformational Diseases and will be an exploration of several related genetic disorders, using alpha-1 as one of the most studied inherited conditions. The program has attracted leading scientists from around the world to participate in this landmark conference. These experts will share their concurrent research findings, begin to amass a greater body of knowledge about underlying genetic causes of disease, and explore the possibility for a genetic cure for conformational diseases including alpha-1, cystic fibrosis, Parkinson’s disease, and Alzheimer’s disease among others. For the Alpha community, this conference represents the hope that current research initiatives will uncover a cure that will benefit both liver and lung related AAT deficiency.

The Alpha One Foundation is also pleased to be a co-sponsor of the conference “Genetics and Ethics in the 21st Century: Genetics and the Workplace.” The conference will be held July 21-23, 2000 at the Given Institute in Aspen, Colorado. This conference is the fifth in an annual series begun in 1996 to address current ethical and legal issues related to genetics. The focus of this year’s conference is genetic issues in the workplace. The conference will consider occupational risks, and the responsibilities of both corporations and employees when there is knowledge that occupational risk factors are increased for people with certain genes. The conference will also consider broader issues related to workplace discrimination based on predictive genetic testing. The conference will culminate with a mock exercise using participants as a Board of Directors of a corporation that is considering implementing genetic testing to predict which workers might be at increased risk of preventable illness stemming from workplace conditions. This summer’s conference will use AAT deficiency as the genetic condition for this mock exercise and include representatives of the Alpha One Foundation in the exercise.

The conference is designed to meet the interests and needs of health care professionals, basic scientists, legislative leaders, members of the Bar and Judiciary, ethicists, representatives from biotechnology corporations, and community organizations that serve an educational and advocacy role for individuals with genetic-related diseases. For additional information and to register for the conference, please contact the Office of Continuing Medical Education, School of Medicine, University of Colorado Health Sciences Center at 1.800.882.9153 or at www.uchsc.edu/sm/commnedu/cmecal.htm.
Without the dedicated work of these individuals, much of the research effort currently underway would not have happened. The University of Miami has chosen to change the priorities of its epidemiology department and thus the Alpha One Research Registry was in need of a new home. Dr. Charlie Strange and his program at the Medical University of South Carolina was chosen by the Medical and Scientific Advisory Committee of the Alpha One Foundation following a request for competitive applications. The Foundation could not be more pleased that such a prestigious scientist has agreed to devote a major portion of his effort to the Registry.

I hope you find this Newsletter informative and stimulating. Please don't hesitate to contact me if you have suggestions or questions. My email is rasandhaus@alphaone.org

Alpha One Foundation:
For additional information about the Alpha One Foundation activities and sponsored research please check our web site at www.alphaone.org or contact our offices at 305-567-9888 or toll free at 888-825-7421. You may also contact the Alpha One Foundation Research staff by e-mail at sfinn@alphaone.org for additional assistance in locating resources related to AAT Deficiency research, obtaining information about current research initiatives, participating in the Research Network or Registry, or to receive Foundation publications. We look forward to hearing from you, the Alpha Community!

Alpha 1 Association:
Additional 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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