LETTER FROM THE MEDICAL DIRECTOR By Robert (Sandy) Sandhaus, M.D., Ph.D.

THE LAST SEVERAL MONTHS HAVE BEEN EXCITING ONES AT THE ALPHA ONE FOUNDATION: The big event was the second annual International Conference, Alpha1-Antitrypsin Deficiency and Other Conformational Diseases. The conference was held at the Airlie Conference Center in Virgina this past June. It examined the newly recognized class of disorders collectively known as diseases of abnormal protein conformation.

Using Alpha1-Antitrypsin Deficiency (Alpha-1) as the paradigm, researchers from a broad range of disciplines gathered to discuss their work and learn from each other. Many had never heard of Alpha-1 before. All agreed it was one of the most stimulating conferences they had ever attended. At the opening dinner of the conference, the Foundation awarded two new Young Investigator Award Grants and the American Liver Foundation awarded two Alpha One Foundation Innovative Seed Grants.

Work has already begun on the third International Conference, which will be called, Alpha-1: The Challenge of a Genetic Condition. The conference will focus on the ethical, legal and social issues facing individuals and institutions in dealing with genetic conditions and on the application of gene based technologies in simple inherited diseases.

Early in 2001, the Foundation will be sponsoring an international scientific workshop evaluating thoracic imaging techniques in the early diagnosis and follow-up of pulmonary emphysema. This has become an especially important topic as companies attempt to bring new drugs to market to treat Alpha-1 and emphysema. Finding the most sensitive and reproducible test to detect disease and evaluate its progression will allow clinical trials to be completed with fewer subjects over a shorter time period. In addition, such technology may help identify patients with destructive lung disease while still in its earliest stages so intervention can be initiated in a timely fashion. We are very excited as this workshop nears and as we see the warm reception to our invitations.

I'd like to address the role of the Clinical Resource Centers (CRCs) which compose the Alpha One Foundations Research Network. These Centers are among the top pulmonary and hepatology centers in North America. This group of experts participates at Foundation sponsored conferences and workshops and regularly receives Foundation publications such as this newsletter and the recently published educational pamphlets. Patients requesting referral to clinicians with expertise in Alpha-1 are referred to these CRCs. The Foundation also directs announcements of new research funding opportunities to the Centers so that those investigators with expertise in Alpha-1 research or clinical care can have access to funding opportunities to support their work. The percentage of applications that are funded to CRC's is currently very high. We are especially interested in attracting bright young investigators into looking at Alpha-1 related questions and work with the Centers to identifying investigators who could apply for research grants.

Finally, the Foundation, in conjunction with the Cleveland Clinic Foundation, is developing a new Centers of Excellence Program in Alpha-1. Within this framework, CRC's with a total program that includes expertise in pulmonary and liver clinical care, pulmonary and liver basic and clinical research, and a broad patient base can apply for this designation. The Centers of Excellence in Alpha-1 will serve as international magnet centers for the care of patients and the training of healthcare professionals in Alpha-1.
Creating a Community for Research
By Charlie Strange, M.D.
Director, Alpha One Research Registry

Research never happens in a vacuum. The ingredients for success include: focused and dedicated researchers, an infrastructure of support (Gregor Mendel’s garden or a rapid genetic sequencer depending on the mission), and in the case of research into human disease, a dedicated group of individuals who are willing to advance science.

The Alpha community is unique in every sense of the word. The Alphas that formed and sustain the Alpha-1 Association are a community. They share stories and legends, pass knowledge to their younger members and reverently pay homage to the memories of those that have gone before. There is growth, occasional failure, empathy, competition, happiness, and sorrow that are palpable within the Alpha to Alpha network.

Researchers also need to have a community. Often a researcher finds his support within university or pharmaceutical firm walls. These large facilities can share expensive equipment and speak a molecular language that is foreign to the uninitiated. They can also provide the needed infrastructure for development of long-term projects or research programs, and buoy short-term failures. But these institutions may also steer researchers away from focused research on Alpha-1 in favor of other areas of study.

For the Alpha-1 community to sustain enlightened research on their disease, the Alpha One Foundation has risen to the occasion with grant support for young investigators, endowed chairs of research, and has assembled a renowned group of scientists to consult with them on their mission (the Medical And Scientific Advisory Committee). The Foundation supports a large yearly scientific meeting (this year’s Airlie conference was a success) and brings together researchers traveling to the yearly American Thoracic Society Meeting.

So where is the cure? I can remember the beginning of the celebrated war on cancer that still struggles on 30 years later. And while some cures are now achieved, the research agenda has been to expand beyond the molecular science of oncogenes to the social sciences of why people don’t get their screening sigmoidoscopy to detect colon polyps at age 50.

In their wisdom, the founders of the Alpha One Foundation knew that a successful cure for Alpha-1 might come in many forms. Just as critical as a cure for the deficiency is a network of social sciences built on early detection of the deficiency, implications of genetic information sharing, and impact of disease on quality of life. The Alpha One Research Registry was formed to support all these missions.

By now most Alphas have heard of the Alpha One Research Registry. Alphas willing to hear about the latest research project are contacted and given the option of participation. Past studies have evaluated the impact of work environment on lung disease, the effect of Alpha-1 on marital stress and the economics of Alpha-1. So why are less than 25% of Alphas enrolled in the research registry? I’m sure the reasons are varied and include combinations of denial, fear, apathy, security concerns and a busy life.
What may be missing is a community approach to research that links the individuals most likely to benefit (Alphas) themselves. What do I mean? I realize that most Alphas will not turn out to be molecular scientists, (even though the IQ of this group is greatly above average). But the social sciences of this disease can be influenced by thoughtful Alphas asking difficult questions.

In today's world of rapid communications and a highly mobile population, a new face of the Research Registry will need to emerge. We need a data interface with firewalls and passwords as secure as a bank, participant profiles that can be updated by the participant, and most importantly, an interface where the Alpha-1 community can influence the research agenda if they desire.

In short, the Alpha-1 community can extend itself towards the world of research while the world of research extends itself into the social sciences of Alpha-1. The shared vision of a cure involves all of us! The transition from researchers doing things to us, to researchers doing things with us is one more way to keep the research agenda alive in Alpha-1. Please send in your Alpha One Foundation Research Registry form today. Feel free to mail or e-mail your comments or thoughts for research to the Registry at alphaone@musc.edu.

**Alpha One Foundation**

**Research Advocacy Priorities**

By Miriam O'Day, Director, Government Relations & Regulatory Affairs

Since its inception, the Alpha One Foundation has made remarkable progress in raising awareness about Alpha-1. The Foundation's work in the area of blood safety and availability, conducted primarily through its representation on the Department of Health and Human Services, Advisory Committee on Blood Safety and Availability, collaboration with consumer coalitions and the Plasma Protein Therapeutics Association, has allowed Foundation the opportunity to raise our specific issues to a level of national concern. The Foundation's leadership has been instrumental in encouraging the government and industry to find positive solutions to product shortages and insurance reimbursement issues.

Over the course of the past six months, the Foundation has engaged in a strategic planning process that has included numerous representatives from government institutions and agencies as well as members of the Alpha community. The input received from this process has been invaluable in forging public policy issues.

The Foundation is committed to tackling Federal and State public policy issues with the aim of improving the lives of individuals within the Alpha-1 community, and their physicians. To this end, AOF is expanding its Advocacy Program as an essential component of a comprehensive three-year strategic plan. The following priorities have been established for the advocacy program: expanding research funding; advancing the development and licensure of new therapeutics; promoting the recommendations of the Screening and Detection Working Group; access to care, medical privacy and genetic discrimination; and blood product safety.

Part of the new advocacy plan will be to establish a close and effective collaboration with the Alpha-1 Association on issues of common concern. These joint efforts were kicked off in July with the release of a press kit produced for a Congressional hearing on genetic discrimination. In addition, AOF is pleased that Nancye Buelow, President, Board of Directors, Alpha-1 Association has been honored by the Genetic Alliance with Board membership. Representatives from the Alpha community and Genetic Alliance recently visited Capitol Hill to discuss genetic discrimination.

The new advocacy plan will continue to generate opportunities for public testimony and grass roots initiatives. We are looking forward to reaping the rewards of our joint efforts as we continue to work together to improve the lives of all Alphas.
By Lynn Overson, R.N., Oregon Health Sciences University

For the last five summers, the University of Colorado School of Medicine has held a conference in Aspen, Colorado on genetics and ethics. This year's conference focused on genetics in the workplace. The Foundation provided funding for the conference and sent several participants from the Alpha-1 community as part of its ongoing commitment and focus on ethical issues. "Alpha" participants included: Sandy Sandhaus, M.D., Ph.D., Mark Yarborough, Ph.D., Richard Sharp, Ph.D., Evan DeRenz, Ph.D., Symma Finn, M.A., Nancy Buelow, Terry Scargent and myself. Other attendees included scientists working on decoding the human genome, ethicists, doctors, nurses, lawyers, a labor union representative, epidemiologists, legislative leaders, representatives from the health care industry, biotechnology corporations and community organizations that serve an educational and advocacy role for workers and for individuals with genetic-related diseases.

The course was meant to help us understand and explore the interaction between genes and the environment, and how this information applies to the workplace. Because the group was such a diverse one, the first speaker, Dr. Raymond Gesteland, took us (quickly) through the basics of genetics. The idea was to make sure that those without Ph.D.'s in molecular biology had some understanding of the biology underlying genetic issues.

We moved from this session to a series of presentations that didn't provide answers, but certainly raised a lot of questions.

Lewis Maltby, a civil rights lawyer, began by challenging us with the question of whether decoding the human genome was "moving us into a brave new world, or plunging us into the dark ages of medicine." Mr. Maltby described cases of people who had been identified as having genes that put them at risk for developing various illnesses or disorders. For a variety of reasons these people then became the victims of discrimination (an employer may not want to hire people who might get sick later, they may not want to pay for this employee's future medical costs, or they, out of ignorance, may be afraid that they would "catch" the disorder). Over the next two days, we would be repeatedly drawn back to considering how genetic testing might affect an individual's employability and insurability.

Rich Sharp, who is the director of the NIH's Environmental Genetics Project, then introduced the concept of genetic responsibility. He noted that with knowledge of any kind, (in this case knowledge of an individual's genetic makeup), comes responsibility. Once we know that an individual is genetically susceptible to certain disorders or diseases, who is responsible for making sure that the person stays as healthy as they can? Is the individual responsible? If they are, are they obligated to not take a job that might put them at risk of getting sick? What obligation do employers have to protect their genetically vulnerable worker? Should they know who is genetically susceptible and work to protect those people? Is the responsible thing to do to simply not hire people who might get sick under certain working conditions? What role does the government have in protecting these individuals? There are no clear answers to any of these questions for one rather simple reason -- we may be able to identify people susceptible or at risk for certain diseases or disorders, but we are not able to tell them, with certainty, when or even if they will develop these disorders.

We then heard a rather sobering talk by Dr. Lee Newman describing what we know about how genetics affects risk for occupational diseases. Dr. Newman emphasized that knowing that a person has genetic susceptibility to a disease or a disorder does not necessarily make us able to predict whether certain working conditions will affect that individual. The question of whether current workplace safety standards (OSHA regulations) are adequate to protect the geneti-
cally susceptible individual was raised. We then began our descent down the slippery slope of the ethics of mandatory workplace testing.

Another presentation, by Dr. David Deubner considered genetic testing for employees applying for jobs in a beryllium manufacturing plant. The advantages of pre-employment genetic testing from the standpoint of the potential employee, that individual's family and the employer were looked at from all angles; and the question of responsibility was again raised. Another issue touched upon in this presentation, was economic, i.e., who should take responsibility (i.e. pay for) the treatment of this illness? 

We also heard from Terry Seargent who helped turn the discussion from philosophical to personal when she described to the group her experience of being fired by her employer because of the cost of her treatment for Alpha-1. She was able to articulate her feelings about the experience, while at the same time express empathy for her employer’s financial dilemma.

The conference also included the opportunity to participate in a mock exercise involving genetic testing in the workplace. We were assigned to play the role of members of a Board of Directors for a manufacturing company called "Dustco". Several of the audience members had been given roles, such as: Board President, Company Doctor, Human Resources Director, Company Lawyer, Ethicist at a local university, etc. The Dustco folks presented a proposal to the board members for approval of a policy of mandatory testing of—you guessed it—Alpha-1. It was quite an experience to try to filter this information from the standpoint of an average citizen board member, not from the standpoint of a healthcare provider. A very lively discussion that lasted several hours ensued. The company managers were very persuasive and very convinced that they had the best interest of their employees at heart. We were then asked to vote on whether to accept the proposal both from the standpoint of the role we were playing as a board member and from a personal standpoint. The results were not the same for these two votes.

Mapping the human genome and the increasing knowledge of our genetic makeup is one of the most fascinating stories of our time. At this point in time though, it is the basis of a cautionary tale. We are rapidly learning how to identify genes that cause disease or increase our susceptibility to disease. What we don't know is what this really means to any one individual. Knowing that you have a genetic disorder has many benefits, but may carry enormous risks in terms of future employability and insurability. Current anti-discrimination laws are not adequate to protect individuals identified to have abnormal genes. Adequate protection for individuals must be in place before widespread genetic testing is done. Individuals seeking genetic testing should make sure that they understand all the potential risk and benefits of being tested.

The Alpha One Foundation sponsored the second annual poster session on Alpha-1 on Saturday, May 6, 2000 in Toronto, Canada during the American Thoracic Society annual conference. Since Alpha-1 related abstracts are often presented in a variety of different sessions at the ATS, the forum provides participants the opportunity to review current research being performed by chest physicians at one time. Presenters competed for travel awards of $1,000 for the two best poster presentations on Alpha-1 research.

Interest in Alpha-1 research has grown since the first poster session, and this year's forum attracted a larger group of attendees and more poster presentations than the previous year. The forum also brought together those researchers who have been working on Alpha-1 topics but were not previously involved with the Alpha One Foundation's research network. Abstracts included presentations on ribozyme mediated gene therapy, determination of phenotypes by capillary isoelectric focusing, identification and formation of pathogenic AAT polymers, gene therapy using adeno-associated vectors (AAV), aerosolized therapy, the role of methionine to inactivate AAT, and the use of 4PBA to increase secretion of AAT. The latter two posters by Clifford Taggart, Beaumont Hospital, Ireland and Natalia Novoradskaya, formerly of NIH were awarded the Alpha One Foundation's travel awards.
The speakers and poster presenters included leading experts in molecular and cellular biology, pathology, neurology, biochemistry, endocrinology, gastroenterology, and genetics. These scientists are separately investigating the underlying causes of protein misfolding and the diseases that result from this type of inherited condition (such as Alzheimer’s, Parkinson’s disease, ALS, Cystic Fibrosis and Alpha-1-Antitrypsin Deficiency). So although there were many familiar "Alpha docs", this conference attracted a more diverse group of scientists and heightened interest from government because it touched upon a scientific theme common to these many genetic disorders. One of the most promising outcomes of this conference was an increased interest on the part of the National Institutes of Health and the Food and Drug Administration on the research necessary to develop therapies for these conformational diseases. Since Alpha-1 is one of the better understood and studied of these diseases, advances in Alpha-1 research may benefit other related conformational diseases. Similar to advocacy efforts, when scientific efforts are coordinated, there can be strength in numbers.

The conference was a success on many levels. It provided a forum, based on the theme of conformational diseases, for those investigating the formation and transport of protein from the liver to compare notes and arrive at a greater mutual understanding of these basic cellular processes. Although the presentations were often very technical, it was easy to see the growing excitement among the scientists about the applicability of the research being presented to their own fields. Each presentation was followed by a question and answer period, which were often lively exchanges between the various experts in the room. Typical of these exchanges was a suggestion to follow up on a promising experiment with a slight variation that would produce better results. These discussions continued during breaks, in the evenings and even in the vans going back to the airport. The conference also successfully put a face to the term "conformational disease" and served to remind the researchers that it is people we know, individuals sitting in the room with them, who need the new therapies, and who are hoping for a cure. Thanks to all the Alphas who participated. You helped make this scientific gathering keep at its heart the people it serves.

The participants included representatives from prominent research institutions in England, Ireland, Scotland, Sweden, Austria, Switzerland, Germany, Italy, Canada, Australia and the United States. It represented a cross section of the Alpha medical, scientific and patient communities. In attendance were representatives from the FDA, NIH, American Red Cross, Alpha 1 Association and pharmaceutical companies.

This year's conference also included several scientific editors and media representatives who will work with the conference chair to publish a scientific summary of the conference in Nature Cell Biology, a scientific journal.
Research Goals

At the conclusion of the presentations the conference organizers requested that participants propose research goals that would continue to advance our knowledge in the field of conformational disease, especially in the area of new therapeutic approaches for those suffering from these inherited disorders.

Airlie Awards Dinner

One of the conference highlights was the awards dinner held on the first evening. Mr. Leopoldo Fernandez and Mrs. Marilina Fernandez attended to receive recognition for their $1 million grant in support of the Foundation's research programs and to announce the newly established Fernandez Liver Research Initiative. This grant will fund basic science and clinical research projects totaling $300,000 in its first year.

The awards dinner was also the opportunity for the Alpha One Foundation to announce the recipients of this year's Young Investigators Awards. A grant award of $50,000 over two years was presented to conference participants Jon Burrows, Ph.D. of Washington University and Priya Choudhury, Ph.D. of Baylor College of Medicine. The 1999 recipients, Drs. Sihong Song and Alexei Guerassimov were also recognized for their ongoing studies and presented with an award by the Foundation. An additional highlight of the evening was the presentation of the Sten Eriksson Award for Scientific Excellence in Alpha 1-Antitrypsin Deficiency Research, which was presented to Dr. Harvey Sharp by Dr. Sten Eriksson, one of the initial discoverers of Alpha-1. Dr. Eriksson gave a vivid description of Dr. Sharp's pivotal discoveries of the connection between Alpha-1 and liver disease and noted their long and rewarding friendship.

The Alpha One Foundation and the American Liver Foundation, represented by John W. Walsh and Alan Brownstein respectively, also announced the first recipients of the Alpha One Foundation Innovative Seed Grant in Liver Disease Associated with Alpha-1. Awarded are Jeffrey H. Teckman, M.D., Department of Gastroenterology, Washington University School of Medicine and Mark A. Zern, M.D., Department of Internal Medicine, Director, Transplant Research Institute, University of California, Davis. These awards in the amount of $100,000 over a two-year period are the first matching grant initiative between the American Liver Foundation and Alpha One Foundation. For descriptions of the proposed research projects, see page 13.
Fundación Leopoldo Fernandez Pujals Awards $1 Million for Research in Alpha-1

The Alpha One Foundation is proud to announce the receipt of a $1 million grant award by the Fundación Leopoldo Fernández Pujals, a Spanish foundation located in Madrid and chaired by Cuban-born entrepreneur Leopoldo Fernandez Pujals. This generous gift, to advance research into Alpha1, will have an immediate and significant impact on basic science and clinical research.

Mr. and Mrs. Fernandez have one child that has had a liver transplant due to Alpha-1 and it is likely that Alpha-1 was the disease that took the life of Mr. Fernandez’s mother prior to her fiftieth birthday.

Marilina Fernandez, newly elected board member of the Alpha One Foundation, together with her husband Leopoldo have committed to joining the Alpha One Foundation’s quest for a cure. "This very generous gift will have an immediate and significant impact on both basic science and clinical research,” says John Walsh, President and CEO of the Alpha One Foundation. "We are honored by the confidence in the Foundation demonstrated by this dedicated Alpha family with this extraordinary contribution,” he added.

Proceeds from the Fernandez grant are earmarked for a number of areas that include a liver research initiative, matching grant programs, and screening and detection programs. These funds will also help to establish an Alpha1-Antitrypsin Deficiency Tissue, DNA and Organ Bank at the Alpha One Research Program, University of Florida as a resource for the international scientific community.

Matching Grants
An additional $1,050,000 has been contributed through matching fund initiatives to support research in Alpha-1 as a direct result of the Fundación Leopoldo Fernández Pujals grant. This funding includes $800,000 from the State of Florida, $100,000 from the American Liver Foundation and $150,000 from the Cleveland Clinic Foundation.

Fernandez Liver Research Initiative
The Alpha One Foundation is pleased to announce the RFA for the Fernandez Liver Research Initiative. This initiative was founded to stimulate research into the liver disease associated with Alpha-1 and will provide grants totaling $300,000 for the first year. This initiative includes two grants, one for basic research into Alpha-1 related liver disease and a second grant to promote the development of new therapeutic agents aimed at the clinical treatment of the accumulation of alpha1-antitrypsin (AAT) in the liver of deficient individuals.
Conference Summary – An Alpha’s Perspective
By Joe Reidy

I have been a staunch supporter and active participant of the Alpha 1 Association and Alpha One Foundation as well as my local Alpha support groups since the early 1990s, so I felt it a privilege and honor to be asked to attend the Airlie conference. The other Alphas attending were: Nancye Buelow, Fred de Serres, Bettina Irvine, Cathy Valenti, and John Walsh.

Sandy Brandley, Carol Deanes and Diane Walsh as well as the rest of the Alpha One staff were also there to represent the Alpha community, as were many of the Alpha-1 doctors whom I had previously met at various Alpha One Foundation functions including: Mark Brantly, Sten Eriksson, Robert Fallat, Friederich Kueppers, Robert Sandhaus, Harvey Sharp, Gordon Snider, James Stocks, James Stoller, Charlie Strange and Gerard Turino. Other doctors whose names I recognize but had not met before included Terence Flotte, David Lomas, Gerard McElvaney and David Perlmutter.

As I read the full title of the conference I knew I was in trouble: "Alpha 1-Antitrypsin Deficiency and Other Conformational Diseases". Not only did I have no clue what a conformational disease was, but I dislike calling Alpha-1 a disease, preferring the term "condition". The conference agenda was organized primarily by Richard Sifers of Baylor College of Medicine, and more remotely by David Lomas, University of Cambridge, England. The conference consisted of 10 two hour sessions. Each session focused on a common theme, which was introduced by a prominent scientist in that field.

Although I understood very little of the highly technical scientific talks, 4.8% not 2.6% The rest of the presentation was a piece of artistry with outstanding graphics. We were shown how the PIZZ molecule was constructed and how it easily formed long chains called polymers. To see these outstanding graphics go to the following web site: http://smokeroom.cimr.cam.ac.uk. As Robin Muskett has told us previously, these polymers tend to form much more quickly when the temperature is elevated. This has been demonstrated in experiments run at the elevated temperature of 41 degrees C. During the break I got a chance to talk to Dr. Robin Carrell, the senior man at Cambridge and he confirmed that my numbers were fairly accurate.

I wanted to tell Dr. Lomas that I truly enjoyed his lecture as it was the first one I understood. But then I thought he might take it the wrong way. Dr. Lomas might think "if a layperson can understand the lecture it was probably way too simplistic". So very uncharacteristically I kept my big mouth shut.

The next lecturer that I could understand was Rick Sifers. For the last 10 or 15 years Rick has been studying the cell processes for the manufacturing and release of alpha 1-antitrypsin (AAT) into the blood stream. Rick called the release process "cell Quality Control", a rather appropriate analogy to typical manufacturing procedures. Within the liver cell the AAT molecule would be fabricated according to the DNA instructions. It then would be inspected to see that it met specifications. If it passed inspection the cell would pass the protein into the blood stream. If it failed inspection the severity of the fault would be assessed. Proteins with major
defects would be destroyed. Minor discrepancies would be sent back to the fabrication area for rework. This cyclical process would continue until the protein was released, destroyed or a cellular timer expired. If time ran out the protein would be stored in inclusions within the liver cell.

As you can probably guess the null protein would be fabricated and subsequently destroyed. The M protein would be quickly released. The good ole Z protein for the most part would go round and round and round ending up in the inclusion. Of course the object is to modify those QC algorithms and release more of the Z protein.

The last session of the conference touched upon therapeutic approaches. Presentations were given on 4-Phenyl Butyrate (4PBA), a chaperone used to increase the release of the Z form of AAT. This work has been performed at University of Florida, Washington University, and at John Hopkins University. However, at John Hopkins the target is the release of the deltaF508 protein, which would help those with the most common form of Cystic Fibrosis. It was noted during the presentation that 4PBA is a good candidate for human trials since it has been used safely in humans.

Other interesting presentations included one by Dr. Terence Flotte, University of Florida, who talked about their gene therapy program and Betsy Kren, who works with Dr. Clifford Steers on gene repair. She discussed their investigations on Chimerplasty (gene repair). One of the problems with this therapeutic approach seems to be that the magical chimeric oligonucleotide molecule is very difficult to manufacture in significant numbers. The beauty of this therapy for Alphas is that the cells with repaired genes cease making the “Z” variant and commence making the normal “M” form of AAT.

Each night at about 10 o’clock we were able to relax in a social gathering at the Swan Pub. I was finally in an atmosphere where I could relate. We could discuss all those things we learned. In the pub I had the chance to spend some time with the scientists discussing the cause of Alpha-1 liver disease, prevalence and potential cures. We agreed that to cure the problem we have to understand the process. That is what this conference was all about.

Let me conclude with a conversation I had with Bettina toward the end of the conference. We both noted that all of the research that had been presented had little bearing on our immediate problem, emphysema. But we realized that emphysema was not the focus of this meeting. What we hope and feel may have happened is that this meeting enabled a cross fertilization of research from scientists from diverse backgrounds. This may help each participant view their work from a different perspective, and perhaps, lead to a cure of a number of diseases. We also hope that some of the researchers will choose Alpha-1 as the condition that can be a good candidate to use while studying protein folding diseases.

I hope this summary accurately describes the flavor and uplifting mood experienced by most if not all the attendees and conveys my feeling of elation and gratitude to the Alpha One Foundation for putting together the resources and people to ensure that such conferences occur.
FROM THE RESEARCH BENCH TO THE BEDSIDE

Clinical Trials Update - "We need a few good Alphas"
By James M. Stocks, M.D., University of Texas, Health Center at Tyler

Two clinical research projects involving volunteers from the Alpha One Research Registry are currently underway. One is a study of an intravenous AAT preparation that began this spring and is scheduled to conclude this coming winter. Forty-five volunteers have been recruited and randomized to receive either the study drug or Prolastin® over a twenty-four week period of observation. This study is being conducted at seven different sites across the United States. The actual participating sites and investigators are listed on the Alpha One Foundation’s website (www.alphaone.org) as well as that of the Alpha 1 Association (www.alpha1.org). Enrollment is closed - no additional volunteers are needed for this project.

The second study is very much in need of additional volunteers. This study involves the aerosol administration of plasma-derived AAT using a new inhaled device and a dry-powder formulation of the AAT protein. This early phase project is being conducted at only two sites, The University of Florida in Gainesville under Mark Brantley, M.D., and at The University of Texas Health Center at Tyler under Jim Stocks, M.D. Three to five subjects are urgently needed to complete this study - larger scale testing involving a larger number of alpha volunteers and additional study sites cannot be planned until this stage of the project has concluded and been analyzed. This study requires volunteers to be off of Prolastin for roughly 9 weeks and involves three visits to the respective center. Volunteers are asked to undergo two bronchoscopies (yes, volunteers are sedated for the procedure) to measure AAT levels within the lung air-spaces both before and after a two week period of daily inhaled therapy. Volunteers are reimbursed for their travel expenses to and from the research centers.

This study began this past winter and approximately 24 Alphas have completed their participation in the project. The eligibility criteria are as follows:

- Must be between the ages of 18 and 70,
- Must have severe Alpha-1 deficiency with a serum Alpha-1 level less than 11 μM and appropriate genetic phenotyping (e.g., ZZ, SZ, Null Null),
- Must only have mild to moderate lung disease with an FEV₁ 50-80% predicted (after using a bronchodilator),
- Must NOT be a current smoker,
- Must NOT have a history of serious and active medical conditions like heart disease,
- Must NOT be allergic to human blood products or have lactose intolerance

If any Alphas are willing to be considered for this study please contact either:

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Fax: 352-392-0821
Pager: 352-395-0120 #0395, function 7 followed by your phone number.

If any potential volunteers wish to discuss their participation with a previous participant it can be arranged by calling either center. Delays in recruitment not only put off the day when additional and possibly even better therapies might become available but, more importantly, may actually prevent the development of such newer treatments. Again, this study is in need of "a few good Alphas".
Young Investigators 2000

Afer careful consideration and evaluation by the Medical And Scientific Advisory Committee, the Alpha One Foundation announced the recipients of the Young Investigator Fellowship Awards for 2000 on June 27th, during the international conference. These postdoctoral fellowships encourage a focus on research of AAT Deficiency at an early stage in a scientist's career and stipulate that these studies must be conducted in a laboratory with known expertise in the field. Each grant recipient will receive support for proposed studies relating to AAT Deficiency research which expands upon important early findings and that the Foundation and its advisory committee feel will advance our understanding in the field. We offer our sincerest congratulations to:

Jon Burrows, Ph.D., Department of Pediatrics, Division of Gastroenterology, Washington University School of Medicine and
Priya Choudhury, Ph.D., Department of Pathology, Baylor College of Medicine.

Jon Burrows, Ph.D. has been involved in research on polymer formation since 1990, and more recently has been investigating chemical chaperones and AAT Deficiency as a potential strategy for prevention of liver injury and emphysema in AAT Deficiency. Since 1997, he has been working in one of the Alpha One Clinical Resource Centers at Washington University School of Medicine, a laboratory with recognized expertise in AAT Deficiency research under the guidance of Dr. David Perlmutter and his colleagues in the Department of Gastroenterology. Dr. Burrows proposes to investigate the "quality control" mechanisms associated with α1ATZ and to characterize the signal transduction pathways that are activated by retention of α1ATZ in the ER. Dr. Burrows describes his proposed research as follows:

"Homozygous PIZZ α1-antitrypsin (α1AT) deficiency is the most common genetic cause of liver disease in children. It also predisposes adults to chronic liver injury and hepatocellular carcinoma. Liver injury is thought to be due to the hepatotoxic effect of mutant secretory protein α1ATZ retained in the endoplasmic reticulum (ER). Cell biological studies of α1ATZ as well as other misfolded secretory and membrane proteins have shown that the degree of retention within the ER is determined by multiple interactions with components of the so-called "quality control apparatus". Recent studies have indicated that the cell has specific biochemical mechanisms by which it can respond to retention of abnormal proteins in the ER."

In preliminary studies for his grant application, Dr. Burrows established a model cell culture system with inducible expression of the mutant α1ATZ gene in which ER retention of α1ATZ can be induced experimentally over specific time intervals and in specific concentrations. He will now use these cell lines to characterize the signal transduction pathways that are activated by retention of α1ATZ in the ER, to determine whether there is a difference between acute and chronic retention states. This will also determine whether there is cell type specificity in activation of these signal transduction pathways. These studies will lay the foundation for later studies of whether there is substrate-specificity in activation of these signaling systems/response pathways, whether polymerization of α1AT plays a role in activation, whether the same pathways are activated in genetically engineered mouse models of α1AT deficiency and whether activation of these pathways plays a role in protection from, or even, contribution to liver injury/hepatocellular carcinoma in α1AT deficient patients."

Dr. Choudhury has been investigating the processing of oligosaccharides in the ER and will continue during the grant period to conduct research on proteasome-mediated disposal pathways and the affect of PI Z polymers. Dr. Choudhury has been involved in these investigations since joining the Baylor College of Medicine in 1995 as a postdoctoral associate in the Department of Pathology, where she has worked under the expert guidance of Dr. Richard Sifers. Her previous research includes investigations of quality control of protein folding with a particular focus on the intracellular disposal of an incompletely folded variant of AAT. Dr. Choudhury describes her proposed research as follows:

"Alpha 1-Antitrypsin (AAT) is a secretory glycoprotein synthesized by hepatocytes which functions in protecting the elastin fibres of the lungs from degradation by
elastase. Deficiency of this protein in plasma caused by lack of secretion results in proteolytic destruction of lung elastin by the neutrophil elastase and consequently results in chronic obstructive lung disease. Secretion is impeded by naturally occurring mutations that cause the protein to misfold, leading to accumulation of polymers in the endoplasmic reticulum (ER), that are eventually degraded. Intracellular retention and degradation of AAT is regulated by a quality control system that allows the transport of only correctly folded molecules beyond the ER. The goal of this project is to gain molecular insight into the biosynthetic processing of AAT, which may lead to the development of therapeutic approaches to mitigate the severity of lung as well as the liver disease.

Liver Initiative Grant Recipients

The Alpha One Foundation is pleased to announce the recipients of a joint research initiative with the American Liver Foundation. The goal of the initiative is to foster development of imaginative research studies in AAT Deficiency and/or directly related areas of scientific investigation. Grant awards were offered for clinical research, which is defined as the process by which a novel question is answered by an investigator interacting with human subjects or carrying out laboratory studies using human participants. Topics considered appropriate for funding included pathophysiological studies, clinical trials and applications or assessment of new diagnostic and/or therapeutic modalities. An American Liver Foundation grant review committee with a representative of the Alpha One Foundation was convened, and applicants' research proposals were judged on their scientific merit as well as the strength of current investigative activity and research environment. It is our pleasure to announce the first recipients of the Alpha One Foundation Innovative Seed Grant in Liver Disease Associated with Alpha-1: Jeffrey H. Teckman, M.D., Department of Gastroenterology, Washington University School of Medicine and Mark A. Zern, M.D., Department of Internal Medicine, Director, Transplant Research Institute, University of California, Davis.

Dr. Teckman is one of the leading experts on liver-related AAT Deficiency research. He is an Assistant Professor of Pediatrics at the Washington University School of Medicine, St. Louis Children’s Hospital, St. Louis, Missouri, one of the Alpha One Foundation’s premier Clinical Resource Centers. Dr. Teckman serves on the Medical and Scientific Advisory Committee of the Alpha One Foundation and is a member of the Board of Directors of the Alpha One Association. He is an expert on the care of children with liver disease and is involved in research on the mechanism of liver injury caused by AAT Deficiency. Dr. Teckman has been involved in research on liver disease related to AAT Deficiency since 1995, with a specific focus on the intracellular fate of mutant α1ATZ because of its implications for the development of liver disease. His current projects involve analysis of how cells are damaged under the stress of AAT Deficiency in both the basic science laboratory and in human patients. Dr. Teckman describes his proposed research for the Innovative Seed Grant as follows:

"Studies have shown that although AAT Deficiency affects 1 in 1600 live births, only a subpopulation of PIZZ individuals, 15%, develop liver disease. The liver injury is caused by the hepatotoxic effects that result from defective secretion and retention of the mutant α1ATZ molecule in the endoplasmic reticulum (ER) of liver cells. Previous studies have shown that most PIZZ individuals are protected from liver disease because the quality control apparatus of the ER ensures relatively efficient degradation of retained, mutant α1ATZ. However, in the "susceptible" subpopulation of PIZZ patients, subtle defects in the quality control apparatus of the ER result in delayed degradation of α1ATZ, greater net retention in the ER and a tendency for liver injury. Recent studies suggest that there are likely to be multiple mechanisms involved in the ER degradation, alteration of any of which might lead to susceptibility to liver injury. The proposed research study will focus on understanding how autophagy is induced by ER retention of α1ATZ. The investigation will also
focus on how the autophagic response contributes to ER degradation of α1ATZ to provide new information about susceptibility to liver disease in α1AT deficiency. The study will also explore the possibility of developing clinical diagnostic assays for pre-morbid detection of susceptible patients and even new strategies for preventing liver disease in this subgroup. The investigations will include using morphological techniques to determine how autophagy is induced by the ER retention of α1ATZ in genetically engineered cell culture model systems and in the PIZ transgenic mouse model in vivo, as well as investigating the autophagic response in human liver from patients with α1AT deficiency."

Dr. Zern has recently moved to California from Jefferson Medical College in Philadelphia to serve as Director of the newly created Transplant Research Institute at University of California in Davis. At UC-Davis he will continue his research on bi-functional gene therapy as well as direct the liver transplantation program. Dr. Zern has conducted research on gene expression since 1987 with an emphasis on hepatic injury and fibrotic conditions and the development of gene therapies to address these conditions. Dr. Zern describes his proposed research as follows:

"Alpha-1-Antitrypsin (α1AT) Deficiency is associated with the development of emphysema and chronic liver disease. Whereas the lung disease is thought to be due to a relative lack of the normal α1AT protein in the circulation, the liver disease is generally thought to be caused by the deposition of abnormal α1AT in hepatocytes. Our intent is to develop a strategy that would both inhibit the synthesis of the abnormal protein and provide a means of synthesizing the normal protein, thus ameliorating the liver disease and inhibiting the development of emphysema. The study will employ ribozyme technology to inhibit the gene expression of abnormal α1AT, and provide for the synthesis of the normal α1AT protein by employing a modified α1AT cDNA not susceptible to ribozyme cleavage.

A viral gene delivery vector for liver-directed therapy of genetic diseases should be: stably expressed so that the replaced gene can treat the genetic condition over a prolonged period; relatively nonimmunogenic and non-lytic so as not to induce hepatocyte necrosis and to allow reutilization over time; concentratable in high titers to enable transduction of a large percentage of hepatocytes; capable of transducing resting cells since most hepatocytes are not cycling at any specific point in time, and replication-deficient. To meet these requirements, the study will employ a gene transfer system based on SV40, as previous studies indicated that SV40 was an excellent candidate system for in vivo hepatic gene therapy since it met all the criteria mentioned above, including stable expression for at least one year. The study will seek to optimize the expression and test the specificity of the AT589 ribozyme and modified α1AT cDNA in a novel SV40-based viral vector system in a hepatoma cell line, employ the optimal vectors in a primary human hepatocyte culture system in order to better establish their efficacy, utilize the most effective SV40-derived ribozyme-modified cDNA viral constructs in a transgenic mouse model of α1AT deficiency disease, and ascertain the effectiveness of the optimal vectors in correcting the pathophysiology of the liver disease and in providing adequate inhibition of neutrophil elastase for the lung disease."

FAQs - Questions raised by patients
By Sandy Sandhaus, M.D., Ph.D.

Q: What is this new inhaler called Xopenex®?

A: Xopenex is the same as albuterol . . . sort of. Most organic chemicals are not symmetric (they are "lop-sided"). It turns out that, depending on how the chemical bonds form during synthesis, molecules can be either "left-hand" or "right-handed". If you were to hold the model of a left-handed molecule up to a mirror, you'd see an image of the right-handed version. This is called stereoisomerism.

It turns out that most living organisms like the left-handed version of organic molecules. More than like them, in many biochemical functions of the body, left-handed molecules are the only molecules the body can use. Almost all the amino acids that make up proteins are L-amino acids (left-handed amino acids). This includes the amino acids that make up Alpha-1. But I digress.

Albuterol, as sold in Proventil® or Ventolin® or generic, is made up of a mixture of L-albuterol and R-albuterol. The L-albuterol is active as a bronchodilator, the R-albuterol is ignored as a nonsense molecule. Xopenex is a solution made up of only the left-handed form of albuterol (L-albuterol or levo-albuterol). Nearly 100% of the drug is active and recognized by the lungs as a bronchodilator. Presumably you could take twice as much Proventil and get the same effect as one-times the dose of Xopenex. But this may not be the case because, even though the R-albuterol form of the drug isn't recognized as a bronchodilator, the R-albuterol form may contribute to the side effects of albuterol such as shaking, fast heart rate, etc. So it's not a good idea to double the dose of Proventil to equal a Xopenex dose of L-albuterol.
Q: Is there a connection between Alpha-1 and bronchiectasis? When should patients with bronchiectasis be treated with antibiotics?

A: The connection between Alpha-1 and bronchiectasis is: 1) statistical; and 2) biochemical. The statistical association is that, while virtually all non-Alpha-1 bronchiectasis has an identifiable cause (most commonly: severe childhood or adult lung infections, immune deficiency, congenital abnormalities, fungal infections of the airways), people with Alpha-1 seem to have a higher than expected incidence of bronchiectasis and, in many cases, have no other reason to explain why they have it. There is a large medical literature reporting on the association between bronchiectasis and Alpha-1.

The biochemical association is somewhat theoretical. Since we know that Alpha-1 blocks some of the destructive enzymes of the body's white blood cells and since we know that these enzymes can damage the structural proteins of the bronchi, it is not a large leap to postulate that the reason people with Alpha-1 get bronchiectasis has to do with bronchial damage caused by white blood cell enzymes. Why do some alphas get bronchiectasis and others do not is an unanswered question. Perhaps it has to do with the number of bronchial infections that an Alpha gets during their life.

Since patients with bronchiectasis generally always have infected sputum, the best way to decide whether it's time to treat with antibiotics is when there is a change in the clinical status of the patient (more short of breath, increased sputum, change in the color or consistency or odor of the sputum). The chronic use of prophylactic or suppressive antibiotics, especially by inhalation, has been advocated by some physicians.

The Cleveland Clinic Foundation
Alpha-1 Antitrypsin Deficiency Clinic Center of Excellence: Auspicious Beginnings
By James K. Staller, M.D.

Based on recent generous support from several patients' families and the Alpha One Foundation, we have been invited to develop a model for an Alpha-1 Clinical Center of Excellence at the Cleveland Clinic Foundation.

In designing the clinical center, I envision several key components as follows:

1. A multidisciplinary group of committed physicians,
2. Close interaction with the pulmonary function laboratory,
3. Development and maintenance of an active clinical data base,
4. Development and distribution of educational materials for patients and families,
5. Offering of an annual educational conference directed to patients, family members, and interested colleagues, and
6. Development of a research infrastructure to permit primary investigator-initiated research and participation in multi-center studies of new therapeutic agents.

I am pleased to report that progress towards these goals at our center is nicely underway, with the intention of developing a model that will be helpful to others in developing similar clinical centers of excellence.

Although strong clinical collaboration has been always part of our practice, we are in the process of formalizing internal meetings with adult and pediatric pulmonologists, hepatologists, and the medical genetics group at the Cleveland Clinic Foundation.

With regard to the database, we are currently designing a web-based database that will be exportable to other centers as this model evolves. The database will capture routine visit information as well as functional status measures, the Alpha One Foundation Registry questionnaire, medications, etc.

We are progressing well in developing educational materials. In particular, we are assembling loose-leaf binders that contain a large sample of the available information for patients and their families regarding Alpha-1. Some of this information has been prepared at the Cleveland Clinic and we also are taking advantage of the excellent informational brochures prepared by the Alpha One Foundation. Our intention is to distribute these books as a useful resource to patients.

Plans are evolving to offer the first annual educational conference regarding Alpha-1 at the Cleveland Clinic Foundation. Again, this will be directed to patients and their families and will address salient aspects of Alpha-1, rehabilitation, implications of genetic disease, etc.

Excellent progress in both investigator-initiated research and collaborative research is also being made. We are exploring funding for a trial of trans-retinoic acid in individuals with Alpha-1. We are also collaborating with industry to examine appropriate clinical endpoints for randomized trials to evaluate new therapies.

Overall, our center is developing a model for a multifaceted approach to Alpha-1 that will permit administration of superb clinical care to affected individuals and to develop exportable tools that will be useful to other clinic centers as they adopt a clinical center of excellence model.
UPCOMING EVENTS - CLINICAL RESOURCE CENTERS

Saturday, October 14, 2000
The Cleveland Clinic Foundation
The Jean Bennett Conference on
Alpha1-Antitrypsin Deficiency
James K. Stoller, M.D.
Cleveland, Ohio
Contact: Dan Laskowski (216) 444 3702.

The Alpha One Foundation is pleased to announce that it will co-sponsor with the Alpha 1 Association, Education/Research Days for Alphas and their families at various Clinical Resource Centers throughout the upcoming year. The following programs are being planned at this time:

Fall 2000
Oregon Health Sciences University
Alan F. Barker, M.D.
Portland, OR 97201
Contact: Lynn Oveson, R.N., M.N., A.N.P.
(503) 494-7680

Winter 2001
University of North Carolina at Chapel Hill
James F. Donohue, M.D.
Chapel Hill, NC
Contact: Jeannie Mascarella, R.N. (919) 966-4675

University of Florida College of Medicine
Mark L. Brantly, M.D.
Gainesville, FL
Contact: Gwen Moen (352) 846-3999

Alpha One Foundation:
For information about the Alpha One Foundation activities and sponsored research please check their web site at www.alphafoundation.org or by calling their toll free number at 888-825-7421. You may also contact the Alpha One Foundation Research staff by e-mail at slinn@alphafoundation.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.

Alpha 1 Association:
Information and educational resources related to Alpha1-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.