



α_1 -Antitrypsin deficiency and augmentation therapy in emphysema

JAMES K. STOLLER, MD

■ Since the first description of α_1 -antitrypsin deficiency as a cause of emphysema in 1963, major strides have been made in understanding the structure and function of this important antiprotease, its role in the defense against emphysema, and in new treatment strategies. In order to elucidate the pathogenesis of α_1 -antitrypsin-associated emphysema and recent developments in therapy for this disease, this paper considers current understanding of the pathogenesis of emphysema, recent information regarding the structure and function of the molecule, and more recent developments in augmentation therapy. The author also discusses the national registry that has been organized for better understanding of the natural history of α_1 -antitrypsin deficiency in a relatively unselected population.

□ INDEX TERMS: ALPHA 1-ANTITRYPSIN; EMPHYSEMA □ CLEVE CLIN J MED 1989; 56:683-689

EMPHYSEMA remains a major source of disability and death in the United States today. Researchers at the National Center for Health Statistics estimate that at least 2.07 million Americans are afflicted by emphysema, and chronic ob-

To promote understanding of the pathogenesis and inform physicians about recent developments in therapy for α_1 -antitrypsin deficiency, this paper considers current understanding of the pathogenesis of emphysema, current information about the structure and function of α_1 -antitrypsin, and recent progress in augmentation therapy for patients with α_1 -antitrypsin deficiency.

■ See the editorial by Bengali (pp 671-674)

structive pulmonary disease remains the fifth leading cause of death in the United States and accounts for 3% of all deaths.¹ Approximately 2%-3% of all cases of emphysema can be ascribed to α_1 -antitrypsin deficiency, and current estimates suggest that 20,000 to 40,000 Americans have significant α_1 -antitrypsin deficiency.²

From the Section of Respiratory Therapy, Department of Pulmonary Disease, Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195. Submitted May 1989; accepted June 1989.

Address reprint requests to J.K.S., Head, Section of Respiratory Therapy, Department of Pulmonary Disease, Cleveland Clinic Foundation, One Clinic Center, 9500 Euclid Avenue, Cleveland, Ohio 44195.

PATHOGENESIS OF EMPHYSEMA

Current concepts of the pathogenesis of emphysema favor a protease-antiprotease model,³⁻⁷ which holds that the degree of alveolar destruction is determined by a balance between endogenous proteases (especially neutrophil elastase) and alveolar antiproteases, the most important of which is α_1 -antitrypsin.⁸ To the extent that neutrophil elastase activity is increased and/or unchecked by an antiprotease screen (as happens when smoking recruits neutrophils to the alveoli or with deficiency of antiprotease activity), imbalance will favor destruction of the extracellular alveolar matrix and emphysema will ensue.

Several lines of evidence support this model:

1. Emphysema is associated with α_1 -antitrypsin deficiency, and epidemiologic studies suggest that the magnitude of emphysema risk increases in individuals whose serum levels of α_1 -antitrypsin fall below a protective threshold (11 μ M), using a purified laboratory standard for α_1 -antitrypsin.⁹

2. Emphysema can be produced in animals by instilling proteolytic enzymes (capable of degrading elastin, a key component of the alveolar extracellular matrix) into the airway.¹⁰⁻¹²

3. Cigarette smoking, a major risk factor for emphysema, is associated with marked alveolar inflammation, ie, recruitment of neutrophils (bearing neutrophil elastase) to alveoli. At the same time, cigarette smoke can hamper antiprotease activity by oxidizing the methionine³⁵⁸ residue of α_1 -antitrypsin, which occupies a crucial position on the active site responsible for elastase binding and inactivation.⁶

4. Serum α_1 -antitrypsin is the source of alveolar α_1 -antitrypsin, and persons with deficient levels of circulating antiprotease also show a diminished antiprotease screen in the alveoli (eg, in epithelial lining fluid sampled by bronchoalveolar lavage), where emphysema evolves. Based on this pathogenetic model of emphysema, the importance of an alveolar antiprotease screen is evident. Neutrophil elastase, which is capable of degrading many components of the extracellular matrix of alveoli (eg, elastin, collagen types I, II, and III, and laminin), poses the major proteolytic threat to alveoli, and 95% of the protective screen against neutrophil elastase is provided by α_1 -antitrypsin.⁸ The association between emphysema and deficiency of α_1 -antitrypsin was first recognized in 1963 by Laurell and Eriksson,¹³ and in the ensuing 26 years, extensive study of α_1 -antitrypsin and α_1 -antitrypsin deficiency has greatly advanced understanding of this molecule's structure and function.

STRUCTURE AND FUNCTION OF α_1 -ANTITRYPSIN

α_1 -Antitrypsin is a 394-amino acid glycoprotein with three complex-carbohydrate side-chains (molecular weight 52,000 daltons) that is capable of inactivating several serine proteases, including neutrophil elastase, trypsin, cathepsin G, plasmin, thrombin, tissue kallikrein, Factor Xa, and plasminogen. However, the association rate constant for α_1 -antitrypsin with neutrophil elastase is 25-fold higher than for other serine proteases, so that α_1 -antitrypsin exerts a preferential inactivating function for neutrophil elastase, the primary proteolytic

threat to the alveolus.¹⁴ The antiprotease activity of the α_1 -antitrypsin molecule rests in an active site (methionine³⁵⁸-serine³⁵⁹) that occupies an exposed loop on the molecule and that tightly binds the active region of neutrophil elastase, rendering both molecules inactive. Binding of α_1 -antitrypsin to neutrophil elastase in the alveolus is both very rapid and strong (association rate constant $8-12 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$). Notably, oxidation of the methionine³⁵⁸ residue in the active site (as by oxidants in inhaled cigarette smoke or by toxic products of inflammation) can reduce this association constant 2,000-fold, resulting in slower and less avid anti-neutrophil elastase activity, further tipping the balance in favor of net alveolar damage.

α_1 -Antitrypsin is synthesized in mononuclear phagocytes (including alveolar macrophages) and in hepatocytes, which are the primary synthetic site. In humans, 34 mg/kg of α_1 -antitrypsin is produced daily, resulting in normal serum levels of 20–48 μ M (or 150–350 mg/dL using a commercial standard that overestimates serum levels by approximately 35%). Alveolar α_1 -antitrypsin diffuses from the serum into the lung and normal levels in epithelial lining fluid are 10-fold lower than in plasma, or 2–5 μ M. Deficiency states in which serum levels are lower than expected show commensurately reduced alveolar levels of α_1 -antitrypsin.⁹

The α_1 -antitrypsin gene is highly pleomorphic, with over 75 separate alleles described to date.¹⁴ To classify the observed spectrum of α_1 -antitrypsin phenotypes, a Pi (for protease inhibitor) nomenclature has been devised, which is based on the migration of the α_1 -antitrypsin protein during isoelectric focusing of plasma between pH 4.2 and 4.9. Clearly, amino acid substitutions may alter the net charge of the molecule, changing its position in isoelectric focusing and its Pi type. By the same token, allelic changes may occur without a change in total charge, causing several different alleles to migrate identically during isoelectric focusing. The α_1 -antitrypsin genes are inherited co-dominantly, so that each person's Pi phenotype reflects the separate contributions of each parental allele, for example PiMZ for parental contributions of an M and Z type respectively.

Because the α_1 -antitrypsin phenotype determines the serum level of α_1 -antitrypsin, it is sometimes possible to identify phenotypes by measuring serum levels, just as it may be by isoelectric focusing. This variation in serum levels of α_1 -antitrypsin is responsible for the deficiency states that may predispose to associated disease, most commonly emphysema but also liver disease, which most often presents in childhood. A large number of other illnesses (eg, panniculitis or nephropathy) puta-

TABLE 1
CLASSIFICATION OF ALPHA₁-ANTITRYPSIN VARIANTS

Allele by category	Estimated allelic frequency*	Serum α_1 AT level (%)†	Function as an inhibitor of neutrophil elastase††	Risk for disease§§
Normal				
M1(Ala ²¹³)	0.20–0.23	100	Normal	None
M1(Val ²¹³)	0.44–0.49	100	Normal	None
M2	0.14–0.19	100	Normal	None
M3	0.10–0.11	100	Normal	None
M4	0.01–0.05	100	?	None
B _{alhabra}	Rare	100	?	None
X _{christchurch}	Rare	100	?	None
Others‡	All rare	100	?	None
Deficient				
Z	0.01–0.02	10–15	Decreased	Lung, liver
S	0.02–0.04	40–70	Normal	None
M _{procida}	Rare	<10	Normal	Lung
M _{heerlen}	Rare	<10	?	Lung
M _{malton}	Rare	<10	?	Lung, liver
M _{duane}	Rare	<10	?	Lung, liver
Others§	All rare	<10	?	Lung
Null				
Null _{bellingham}	Rare	0‡‡	—	Lung
Null _{granite falls}	Rare	0	—	Lung
Null _{mattawa}	Rare	0	—	Lung
Null _{hong kong}	Rare	0	—	Lung
Null _{procida}	Rare	0	—	Lung
Others	All rare	0	—	Lung
Dysfunctional				
Pittsburgh	Rare	Normal	Decreased	Hemorrhagic diathesis

* Allelic frequencies for USA Caucasians; "rare" = allelic frequency <0.001.

† Normal α_1 AT levels = 20 to 48 μ M (see text for discussion of standards used to determine normal values); 100% = normal level; % values assumes homozygous state.

‡ Includes: B, B_{saskatoon}, C, D, E, E_{lemburg}, E_{franklin}, E_{matuse}, E_{cincinnati}, E_{tokyo}, F, G, G_{cler}, J_{houyao}, L, L_{heijne}, M5_{germany}, M_{chapel hill}, M_{salle}, N, N_{adelade}, N_{nagoto}, N_{hampton}, N_{yerville}, N_{grosogre}, N_{letrai}, P_{budapest}, P_{santlouis}, P_{castoria}, P_{oki}, P_{clifton}, P_{kyoto}, P_{wesht}, R, T, V, W_{salerio}, W_{finneytown}, X, X_{fergeng}, X_{altan}, X_{bagi}, Y_{brighton}, Y_{toronto}, and Z_{pratt}.

§ Includes: I, M_{hike}, M_{rouen}, P, and Z_{augsbu}.

†† "?" = function unknown.

‡‡ By definition, the null gene has no associated α_1 AT protein in serum.

§§ For the prediction of risk, assumes the homozygous state; since only the heterozygous state has been observed for several of the rare alleles, the predicted risk for the homozygous state is theoretical.

Modified, with permission, from Crystal RG, Brantly ML, Hubbard RC, Curiel DT, States DJ, Holmes MD. The α_1 -antitrypsin gene and its mutations. Chest 1989; 95:196–208.

tively have been associated with α_1 -antitrypsin deficiency, but other than panniculitis these associations are unusual and are largely unproven.⁴

In categorizing the observed α_1 -antitrypsin variants, investigators at the Pulmonary Branch of the National Heart, Lung, and Blood Institute have proposed a useful scheme (Table 1) of four categories¹⁴: 1) normal variants (in which allelic changes do not alter serum levels), 2) deficient variants (in which serum levels are decreased to varying degrees), 3) null variants (in which allelic changes prevent production and/or secretion of the α_1 -antitrypsin protein), and 4) dysfunctional variants (in which the protein activity is altered from its usual anti-neutrophil elastase role). In view of co-dominant inheritance, an individual's phenotype will be determined by

the contributions of each parent's alleles, so that combinations of variants may occur, eg, PiSZ or PiM-null. The phenotype defines both the magnitude of risk for developing emphysema (by determining the serum level of α_1 -antitrypsin) and the risk of associated liver disease. As shown in Table 2, the risk of emphysema increases for phenotypes associated with serum levels below a putative protective threshold of 11 μ M (or 80 mg/dL using the commercial standard). Also, risk of neonatal jaundice and cirrhosis appears to be confined to patients with the PiZZ phenotype, in whom liver disease occurs with a prevalence of approximately 10%.

The deficient and null types of α_1 -antitrypsin variants are most commonly associated with clinical disease and warrant most discussion.

TABLE 2
 "THRESHOLD" PROTECTIVE LEVEL CONCEPT BASED ON
 EPIDEMIOLOGIC ASSESSMENT OF α_1 AT LEVELS AND THE
 RISK FOR THE DEVELOPMENT OF EMPHYSEMA

Phenotype	Serum level (mg/dL)*	Emphysema risk
MM†	150–350	Background
SS	100–140	Background
MZ‡	90–150	Background
SZ	45–80	Moderate: 20–25 percent risk
ZZ	15–50	High: 80–100 percent risk
Null-null§	0	High: 100 percent risk**

* Commercial standard; see text.

† Includes all combinations of normal M-family alleles, including M1 (Val²¹³), M1 (Ala²¹³), M2, and M3 alleles.

‡ Includes all combinations of M-family alleles with the Z allele.

§ Includes all combinations of null alleles.

** Risk of emphysema is 100 percent by age 30 years.

Modified, with permission, from Hubbard RC, Crystal RG. α_1 -antitrypsin augmentation therapy for α_1 -antitrypsin deficiency. *Am J Med* 1988; 89 (suppl 6A):52–62.

The Z variant of α_1 -antitrypsin is common among Northern European whites and accounts for 1%–3% of all alleles in this patient group. The Z type of α_1 -antitrypsin results from a single amino acid substitution (lysine³⁴² instead of glutamine³⁴²). This single residue change results in variation in the protein's charge (causing the Z variant to migrate differently during isoelectric focusing). This residue substitution also has several clinically important consequences¹⁴:

1. Serum levels in PiZZ homozygotes are reduced approximately 10-fold compared with normals (serum levels of 2–5 μ M v 15–48 μ M seen in normal variants).

2. The anti-neutrophil elastase activity of the Z variant protein is reduced, as a result of a lower association rate constant of the Z protein with neutrophil elastase.

3. Abnormal release of Z variant molecules from the hepatocytes results in the accumulation of aggregated Z variant molecules within the hepatocyte. This phenomenon is thought to result from instability of the tertiary structure of the Z molecule, with resultant aggregation and interruption of hepatocyte release. This aggregation accounts for the intrahepatic globules that are seen in liver biopsy specimens from individuals homozygous for the Z variant protein. That such intrahepatocyte aggregation is not seen with other deficient variants of α_1 -antitrypsin may explain why the risk of neonatal hepatitis and cirrhosis is unique to PiZZ individuals.

The S variant of α_1 -antitrypsin is the most common deficient type, accounting for 2%–4% of all alleles in Northern European whites.¹⁴ Like the Z variant, the S

protein results from a single amino acid substitution (valine²⁶⁴ replaces the normal glutamine²⁶⁴). Individuals who are homozygous for the S variant have low serum α_1 -antitrypsin levels (13–19 μ M), but the serum levels are higher than for PiZZ individuals and S homozygotes do not have an increased emphysema risk because their serum levels exceed the protective threshold. Similarly, liver disease is not associated with the S variant. However, individuals with the PiSZ variant have serum levels (9–15 μ M) that are lower than S homozygotes. Because these lower serum levels straddle the protective threshold, PiSZ individuals are at increased risk for developing emphysema.

The null α_1 -antitrypsin alleles are very uncommon (estimated to occur in less than 0.1% of Northern European whites), and result in complete absence of α_1 -antitrypsin production. Persons who are homozygous for null alleles have no circulating α_1 -antitrypsin, and therefore are at the greatest risk for developing emphysema, though liver disease does not occur in these persons. The null variant may result from several different molecular mechanisms, all of which result in the absence of α_1 -antitrypsin synthesis, with similar clinical consequences.

STRATEGIES FOR AUGMENTATION THERAPY

Because emphysema results from deficiency of serum and alveolar α_1 -antitrypsin in affected individuals, efforts to minimize the risk of emphysema have been directed at increasing circulating α_1 -antitrypsin levels. Two general strategies have been considered⁴: 1) elevating endogenous production of α_1 -antitrypsin either pharmacologically (eg, danazol, tamoxifen, or estrogen/progesterone combinations) or by liver transplantation, and 2) exogenously augmenting α_1 -antitrypsin levels by either intravenous infusion or other routes (eg, inhalation^{15,16}). Liver transplantation has proven a successful strategy, but carries the usual transplantation risk, and availability is limited. Pharmacologic means of augmenting endogenous α_1 -antitrypsin production have been effective, but the elevation of serum levels has been marginal and often inadequate to raise circulating levels above a protective threshold. Because of the inadequacy of strategies to augment endogenous production, more recent attention has focused on exogenous augmentation therapy, especially by intravenous infusion.^{2,9,17,18}

The first report of augmentation of α_1 -antitrypsin levels by intravenous infusion was by Gadek et al in 1981.¹⁷ Five persons with PiZZ α_1 -antitrypsin deficiency

TABLE 3
SAMPLE SIZE REQUIRED (IN EACH OF TWO EQUAL SIZED
SAMPLES) TO DETECT REDUCTION IN MORTALITY

Year of follow-up	Reduction		
	50%	40%	30%
2	544	915	1757
3	388	644	1209
4	248	413	782
5	192	315	584

Modified, with permission, from Idell S, Cohen AB. α_1 -antitrypsin deficiency. Clin Chest Med 1983; 4:359-375.

TABLE 4
SAMPLE SIZE REQUIRED (IN EACH OF TWO EQUAL SIZED
SAMPLES) TO DETECT ANNUAL RATE OF DETERIORATION
IN FEV₁

Year of follow-up	Reduction		
	50%	40%	30%
2	170 (251)	266 (392)	473 (696)
3	135 (218)	211 (341)	377 (606)
4	126 (209)	197 (327)	352 (581)
5	123 (206)	193 (323)	344 (574)

Modified, with permission, from Burrows B. A clinical trial of efficacy of antiproteolytic therapy: can it be done? Am Rev Respir Dis 1983; 127 (suppl 1):S42-S43.

received weekly infusions of 4 g of purified α_1 -antitrypsin (from pooled human plasma) for four weeks. This preliminary experience showed that serum levels of α_1 -antitrypsin could be augmented, that nadir (or trough) levels remained above a theoretical protective threshold (11 μ M), and that intravenous infusion of α_1 -antitrypsin could augment both epithelial lining fluid α_1 -antitrypsin levels and anti-neutrophil elastase activity.

A larger and more recent study of intravenous augmentation therapy was published by Wewers et al,¹⁸ who administered weekly infusions of purified human α_1 -antitrypsin (60 mg/kg) to 21 persons with PiZZ α_1 -antitrypsin deficiency over six months. As in the earlier preliminary experience by Gadek et al,¹⁷ weekly infusion therapy was effective in augmenting both serum and epithelial lining fluid α_1 -antitrypsin levels as well as anti-neutrophil elastase activity in serum and epithelial lining fluid. In addition, monthly assessment of pulmonary function and chest radiographs in these 21 patients showed no evidence of progression of emphysema over the six-month study period. Finally, the augmentation therapy was found to be safe and unassociated with serious sequelae.

TABLE 5
CLINICAL CENTERS AND RESPECTIVE PRINCIPAL
INVESTIGATORS PARTICIPATING IN THE α_1 -ANTITRYPSIN
REGISTRY (AUGUST 1989)

Clinical Center	Principal Investigator(s)
Arapahoe Pulmonary Consultants Pulmonary/Critical Care Medicine	Robert A. Sandhaus, M.D., Ph.D.
The University of Arizona Division of Respiratory Sciences	Benjamin Burrows, M.D.
University of California San Diego Medical Center	Jack L. Clausen, M.D.
University of California Davis Medical Center	Carroll Cross, M.D.
Cleveland Clinic Foundation Department of Pulmonary Disease	Andrew Chan, M.D.
Columbia University College of Physicians and Surgeons	David Meeker, M.D.
Graduate Hospital Pulmonary Division	Atul Mehta, M.D.
Henry Ford Hospital Division of Pulmonary and Critical Care Medicine	Gerald Turino, M.D.
Lahey Clinic Medical Center Department of Pulmonary Medicine	E. Eden, M.D.
University of Minnesota Hospital and Clinic Pulmonary Medicine	Paul E. Epstein, M.D.
Mayo Clinic Jacksonville	Michael S. Eichenhorn, M.D.
Mayo Clinic Rochester	Lester D. Paul, M.D.
University of Nebraska Medical Center Pulmonary Section	Peter Bitterman, M.D.
National Heart, Lung, and Blood Institute Division of Lung Diseases	Michael J. Krowka, M.D.
National Naval Medical Center Pulmonary Department	Vdya B. S. Prakash, M.D.
Ohio State University Pulmonary and Critical Care Division	Bruce Staats, M.D.
Oregon Health Sciences University Pulmonary and Critical Care Medicine	Stephen I. Rennard, M.D.
Pacific Presbyterian Medical Center Department of Medicine	Richard A. Robbins, M.D.
University of Rochester Pulmonary and Critical Care Unit	Ronald G. Crystal, M.D.
The University of Texas Health Center Tyler	Richard Hubbard, M.D.
University of Utah Health Sciences Center Department of Internal Medicine	Bruce M. Meth, M.D.
Washington University Medical Center Department of Internal Medicine	Mark Wewers, M.D.
	James E. Gadek, M.D.
	A. Sonia Buist, M.D.
	Alan F. Barker, M.D.
	Robert J. Fallat, M.D.
	Richard W. Hyde, M.D.
	James M. Stocks, M.D.
	Allen Cohen, M.D.
	Richard E. Kanner, M.D.
	Jack A. Pierce, M.D.
	Edward J. Campbell, M.D.

A more recent report by Hubbard and Crystal⁹ has extended this experience with weekly infusion therapy of α_1 -antitrypsin. In this most recently available report, 28 α_1 -antitrypsin-deficient persons (25 PiZZ individuals and three with Pi null-null phenotype) received weekly infusions of purified α_1 -antitrypsin (60 mg/kg) for up to

18 months. As with the earlier experience, such infusions were found to be biochemically effective and safe. No significant change in pulmonary function (vital capacity, total lung capacity, FEV₁, diffusing capacity, ventilation/perfusion scans, chest radiographs) was observed in any of these 28 patients, though definitive evidence of clinical efficacy of infusion therapy still awaits longer follow-up in a larger number of patients.

As an alternative to weekly augmentation therapy, Hubbard et al² recently reported results of once-monthly infusions of purified human α_1 -antitrypsin. Studying nine persons with α_1 -antitrypsin deficiency (eight PiZZ homozygotes and one with PiZ-null phenotype), these investigators showed that monthly infusions at a dose of 250 mg/kg successfully raised serum α_1 -antitrypsin levels and anti-neutrophil elastase activity, as well as α_1 -antitrypsin levels and anti-neutrophil elastase activity in epithelial lining fluid. Specifically, serum levels were augmented above the protective threshold of 11 μ M for a mean of 25 days out of the 28-day infusion interval, with a mean nadir serum level of 9 ± 1 μ M after the twelfth monthly infusion. Nadir levels of α_1 -antitrypsin in epithelial lining fluid were consistently maintained above a theoretical protective threshold (1.3 μ M) over the entire duration of monthly therapy, and nadir anti-neutrophil elastase activity in epithelial lining fluid was maintained at a mean of 1.93 times the pretreatment baseline value. Furthermore, as with the studies of weekly infusion therapy, monthly α_1 -antitrypsin infusion was unassociated with adverse clinical events. Specifically, no changes were noted in hematologic, clotting, or renal parameters, nor were changes in serum chemistries observed. No patients showed evidence of hepatitis B or HIV infection, and no antibodies to α_1 -antitrypsin or immune complexes were observed. Preservation of the serum half-life of the infused α_1 -antitrypsin at four to five days throughout therapy further suggests that no antibodies to infused α_1 -antitrypsin developed.

Overall, current experience suggests that exogenous augmentation of α_1 -antitrypsin by either weekly or monthly intravenous infusion can effectively augment levels of serum and epithelial lining fluid α_1 -antitrypsin and anti-neutrophil elastase activity. Infusion therapy appears safe and clinically effective, though longer fol-

low-up in a larger number of patients is required before the clinical efficacy of infusion therapy is established.

Though the most venerable way to study the clinical efficacy of augmentation therapy would be a randomized clinical trial, the requirements for large numbers of patients over a long follow-up period have precluded such a trial to date. Specifically, when the Working Group for Evaluation of Elastase Inhibitor Therapy in Pulmonary Emphysema convened in 1978, sample size calculations were developed^{19,20} and are presented in *Tables 3 and 4*. For the most liberal estimates, assuming augmentation therapy had 50% efficacy in reducing the rate of FEV₁ decline and that all participants were compliant with follow-up for five years, a trial would require at least 246 participants. More stringent assumptions (eg, a smaller difference between FEV₁ decline on treatment and control and/or a shorter follow-up) raised the sample size requirements markedly. As shown in *Table 4*, sample size requirements were equally formidable when mortality was considered as the study endpoint.

As an alternate strategy to characterize the nature and course of α_1 -antitrypsin deficiency in up to 1,000 patients, the National Heart, Lung and Blood Institute (NHLBI) has sponsored a national registry of patients with severe α_1 -antitrypsin deficiency (serum levels < 11 μ M) with two purposes in mind: 1) to assess the natural history of severe α_1 -antitrypsin deficiency, and 2) to assess whether the disease course differs in recipients of augmentation therapy. Adult patients (≥ 18 years) are eligible once severe deficiency of α_1 -antitrypsin has been confirmed by measurement in the Central Registry Laboratory, located at the Pulmonary Branch of the NHLBI. Patients are eligible whether or not they are receiving augmentation therapy (which is dictated by their referring physicians) and study registrants will be tested at least once yearly (spirometry, routine blood tests, and urinalyses) for up to five years at one of 22 participating Clinical Centers (*Table 5*). The study is being conducted under the guidance of a steering committee composed of authorities in the field and chaired by Dr. Ronald G. Crystal. Data will be analyzed at The Clinical Coordinating Center, located at The Cleveland Clinic Foundation.

REFERENCES

1. Statistical compendium on adult lung diseases. American Lung Association, 1987; pp 47-97.
2. Hubbard RC, Sellers S, Czerski D, Stephens L, Crystal RG. Biochemical efficacy and safety of monthly augmentation therapy for α_1 -antitrypsin deficiency. *JAMA* 1988; 260:1259-1264.
3. Tobin MJ, Hutchison CS. An overview of the pulmonary features of α_1 -antitrypsin deficiency. *Arch Intern Med* 1982; 142:1342-1348.
4. Gadek JE, Crystal RG. α_1 -antitrypsin deficiency. [In] Stanbury JB, Wyngaarden JB, Frederickson DS, Goldstein JL, Brown MS, eds. *Metabolic Basis of Inherited Disease*. New York, McGraw Hill, 1982; pp 1450-1467.
5. Pierce JA. Antitrypsin and emphysema. *JAMA* 1988; 259:2890-

- 2895.
6. Brantly M, Nukiwa T, Crystal RG. Molecular basis of α_1 -antitrypsin deficiency. *Am J Med* 1988; **84**(Suppl 6A):13-31.
7. Wewers M. Pathogenesis of emphysema. *Chest* 1989; **95**:190-195.
8. Gadek JE, Fells GA, Zimmerman RL, Rennard SI, Crystal RG. Antielastases of the human alveolar structures. *J Clin Invest* 1981; **68**:889-898.
9. Hubbard RC, Crystal RG. α_1 -antitrypsin augmentation therapy for α_1 -antitrypsin deficiency. *Am J Med* 1988; **84**(Suppl 6A):52-62.
10. Giles RE, Finkel MP, Leeds R. The production of an emphysema-like condition in rats by the administration of papain aerosol. *Proc Soc Exp Biol Med* 1970; **134**:157-162.
11. Sloan B, Abrams WR, Meranze DR, Kimbel P, Weinbaum G. Emphysema induced *in vitro* and *in vivo* in dogs by a purified elastase from homologous leukocytes. *Am Rev Respir Dis* 1981; **124**:295-301.
12. Lucey EC. Experimental emphysema. *Clin Chest Med* 1983; **4**:389-403.
13. Laurell CB, Eriksson S. The electrophoretic α_1 -globulin pattern of serum in α_1 -antitrypsin deficiency. *Scand J Clin Lab Invest* 1963; **15**:132-140.
14. Crystal RG, Brantly ML, Hubbard RC, Curiel DT, States DJ, Holmes MD. The α_1 -antitrypsin gene and its mutations. *Chest* 1989; **95**:196-208.
15. Smith RM, Spragg RS. Production and administration to dogs of aerosol of α_1 -proteinase inhibitor. *Am J Med* 1988; **84**(Suppl 6A):48-51.
16. Hubbard RC, Stephens L, Crystal RG. Delivery of α_1 -antitrypsin by aerosol: direct augmentation of lung anti-elastase defenses in α_1 -antitrypsin deficiency (abst). *Clin Res* 1988; **36**:625A.
17. Gadek JE, Klein HG, Holland PV, Crystal RG. Replacement therapy of α_1 -antitrypsin deficiency. *J Clin Invest* 1981; **68**:1158-1165.
18. Wewers MD, Casolaro MA, Sellers SE, et al. Replacement therapy for α_1 -antitrypsin deficiency associated with emphysema. *N Engl J Med* 1987; **316**:1055-1062.
19. Idell S, Cohen AB. α_1 -antitrypsin deficiency. *Clin Chest Med* 1983; **4**:359-375.
20. Burrows B. A clinical trial of efficacy of antiproteolytic therapy: can it be done? *Am Rev Respir Dis* 1983(Suppl); **127**:S42-S43.

