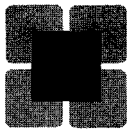

Inherited deficiency of α_1-antitrypsin and emphysema

Prospects and promise of research

THE STORY of the investigation of the inherited deficiency of α_1-antitrypsin and its role in panacinar or familial emphysema is a noteworthy example of the success of the modern biomedical research enterprise. It was only 26 years ago that Laurel and Erikson made their astute observation, establishing an association between this deficiency and early onset of airflow limitation due to emphysema. Together with the demonstration that intratracheal instillation of proteases (eg, papain and other elastolytic enzymes) could induce emphysematous lesions in experimental animals, this led to the development of the protease-antiprotease imbalance hypothesis to explain the pathogenetic process underlying emphysema. Since then, very substantial progress has been made toward the goal of defining the detailed structural and molecular basis of the pathogenesis of emphysema.

■ *See Stoller (pp 683–689)*

The first major breakthrough was demonstration and purification of elastase from neutrophils, thus identifying the source of a potent protease capable of digesting most major structural proteins of the lungs. During the next decade or so, scientists purified both elastase and α_1-antitrypsin; they also crystallized elastase and established its three-dimensional structure. The corresponding genes for both proteins have now been isolated, cloned, and sequenced. Several other molecular variants of α_1-antitrypsin besides PiZ (eg, Pi-null) have also been shown to cause severe deficiency of antitrypsin. The corresponding genes have been sequenced to identify the specific underlying base substitutions.

Parallel lines of investigation during this period revealed the complex nature of the pulmonary extracellular matrix. The emphysematous lesion was shown to be caused by an irreversible breakdown of the lung structure formed by this matrix, with the resultant loss of the histoarchitecture of the alveolar wall.

These findings have molded the current research on preventive treatment for emphysema in subjects with deficiency of antitrypsin. Several approaches to augment the antiprotease shield in the lung are discussed by James K. Stoller, MD, in this issue. Two of the most promising ones are augmentation therapy and the potential use of synthetic elastase inhibitors. Successful development of a commercial method to produce α_1-antitrypsin concentrate from pooled human plasma has led to augmentation therapy, which was approved by the Food and Drug Administration in January 1988. Synthetic inhibitors are, at present, in the developmental phase, and most candidates have not proceeded beyond the toxicity testing in laboratory animals or the earliest phases of human safety testing. However, the availability of a detailed three-dimensional structure of elastase, permitting a clear definition of its active site, has made it possible to design many new inhibitors rationally. Perhaps, in the not too distant future, nontoxic synthetic inhibitors that mimic biological and biochemical properties of α_1-antitrypsin will be available for clinical use.[1]

Recombinant DNA and genetic engineering research now offer another therapeutic possibility, somatic gene therapy, to correct inherited disorders. The underlying principle of somatic gene therapy is to introduce a normal gene into a target cell of a patient who has the deficient gene so as to allow expression of the normal form of the protein. This would compensate for the missing or

defective protein. In vivo introduction of the gene would require development of synthetic viral vectors capable of homing to the desired cell type and delivering the gene to the cell's interior. The inserted gene then would become part of the protein coding machinery—the DNA—of the cell. In vitro introduction of the gene would require tissue culture of target cells from the patients, transfection of the cells with the normal gene, and reintroduction of these cells in the patient's body in a manner that would permit their productive perpetuation. Such gene therapy is theoretically possible for genetic deficiencies due to single-gene defects. α_1-Antitrypsin deficiency would potentially qualify for the approach. It would require, by one of the two means discussed, introduction of the M gene into an appropriate cell of the PiZ patient. However, the technical problems are formidable, and many ethical issues need to be resolved. Gene therapy will be applied initially to diseases that are fatal in childhood. However, this therapy may also be available in the future to correct α_1-antitrypsin deficiency.[2–4]

Unfortunately, clinical research to define the natural history of the α_1-antitrypsin deficiency has not kept pace with the remarkable success of basic research in the field. Few large studies of patients with classic PiZ deficiency have been published. The main reason for this shortfall has been the unavailability of sufficient numbers of known PiZ individuals for a single study. With an estimated homozygote frequency for the Z gene of 0.03% in the U.S., screening a large number of people would be necessary to identify sufficient PiZ individuals for a statistically meaningful natural history study. Without a coordinated effort among several large hospital clinics, patient recruitment would be logistically impossible. The recently initiated Registry of Patients with Deficiency of α_1-Antitrypsin (sponsored by the National Heart, Lung, and Blood Institute), which is a multicenter effort, provides a unique opportunity to fill this void in information about the clinical and laboratory course of the deficiency.

From being mere registries of minimal data about patients, such as age, sex, and morbidity/mortality, the modern registries of diseases have evolved into sophisticated, versatile tools to conduct a variety of clinical studies. Contemporary registries are carefully designed to collect complex, standardized information about many aspects of a disease on a well-defined set of patients, often from many clinical centers. The registry of patients with deficiency of α_1-antitrypsin, for example, will obtain data from more than 20 clinical centers across the U.S. These data will be collected over a five-year period in accordance with a standardized protocol. Analysis of these data should help define the natural history of the deficiency condition and may also provide clinically useful information about augmentation therapy. The registry also provides an opportunity for a stringent correlative standardization of spirometric procedures among the participating clinics.

NATURAL HISTORY

As noted above, there are few large studies defining the natural history of PiZ deficiency. Thus, little information is available on the rate of decline of pulmonary function, age of onset, and codeterminants, if any, associated with development of emphysema in these individuals. Most analyses have been on retrospective data, which were not collected in a coordinated and standardized manner. Also such data were often collected on subjects with known chronic obstructive pulmonary disease. This has introduced bias in the analysis, because healthy PiZ subjects were seriously underrepresented. Despite the limitations, these data have served a useful purpose by showing that the association between α_1-antitrypsin deficiency and early onset of emphysema is far from absolute,[5–8] pointing to a need to collect standardized prospective data on a sufficient number of patients to provide statistically significant results. The ongoing registry of α_1-antitrypsin deficiency provides an ideal tool for this purpose. One goal of the study is to gain a better understanding of its natural history and to enable identification, early in life, of a subset of PiZ subjects who are most likely to develop lung disease. Such information is crucial for identifying candidates for preventive treatment. Also, to design better clinical trials for therapies in future, there is a need to learn more about rates of decline of lung function (and its variability) in emphysematous subjects with antitrypsin deficiency.

EVALUATION OF AUGMENTATION THERAPY

Augmentation therapy was approved on the basis of its biochemical efficacy, ie, augmentation of α_1-antitrypsin levels in plasma and in the alveolar epithelial lining fluid to protective levels. A clinical trial to ascertain the ability of antitrypsin administration to prevent the emergence of the disease would be ideal, and this issue has been examined.[8,9] Unfortunately, the proportion of PiZ individuals who develop emphysema is unknown, and the age of onset of frank disease appears to be variable. Thus, it has been very difficult to determine the

patient sample sizes needed to determine efficacy of the therapy. Considering the number of categories that would be required for various clinical variables, a very large number of subjects would be required for the trial.

Though the researchers working with the registry plan to collect information on subjects receiving augmentation therapy, it is not a clinical trial. Registry data collection is not blind, nor is there a preselection of the type of patients to be studied based on the stage of the disease, age, sex, or other factors related to confounding variables. Barring striking effects of the therapy, definitive statements are usually not possible from analysis of such a database. However, the treatment data collected by the registry could be clinically useful. For example, analyses of the data could help resolve the issue of whether the patients with severe pulmonary function impairment (FEV_1 <30% of predicted) would benefit from augmentation therapy, provided the data on such patients are collected for the appropriate length of time needed for statistical analysis. The registry data base would also be invaluable for designing future clinical trials of augmentation therapy or other protease inhibitors by providing a rational basis for determining the number of patients, classifications needed, etc.

STANDARDIZATION OF PULMONARY FUNCTION TESTING

In multicenter longitudinal studies, not only are reproducible laboratory tests important but data obtained at each center should also be comparable (within acceptable limits of error) to those obtained from other centers. Several reports on standardization of pulmonary function testing have been published.[10,11] Multicenter studies, such as the registry of α_1-antitrypsin deficiency, provide excellent opportunities to field test existing standards for spirometric as well as nonspirometric pulmonary function tests, such as the measurement of the functional residual capacity (FRC) and related lung compartments and the single breath diffusing capacity (S.B. DLCO). Examination of test results generated by different technologists using a variety of models and makes of equipment will allow field testing of existing and proposed methods of standardization. Limitations imposed by hardware, software, and the patients themselves may make compliance with some standards impossible, even when instructions, understanding, and cooperation are maximal. Dissemination of the analyses of such large-scale, high-quality lung function data, their collection, and associated variabilities and problems should provide a basis for continuous improvement in spirometric technology and wider dissemination of the standardized spirometry.

Exploration of α_1-antitrypsin deficiency-associated emphysema may also be applicable to emphysema in subjects without the deficiency. Hence the registry data analysis may better define the codeterminants of emphysema in general. The availability of a large number of clinically well-studied patients, especially with respect to their pulmonary function history, provides an unique opportunity to launch relevant satellite studies. Studies to gain a better understanding of liver disease in patients with antitrypsin deficiency could also be initiated using this cohort.

Clearly, as with research on other topics, the investigation of α_1-antitrypsin deficiency, as with research on other topics, has provided answers to many questions about the disease and has also raised new ones. The cost of augmentation therapy and its chronic nature require that the need for therapy be carefully defined; developing criteria for this probably would require more clinical studies. Also, additional clinical data providing a better profile of PiZ subjects may make possible other preventive measures to thwart development of emphysema in patients with α_1-antitrypsin deficiency. Another important issue is whether neonatal screening for the deficiency would be useful for preventing the disease. Significant information to answer many of these questions will come from well-designed clinical studies, such as those from the above-described registry, with participation of many clinical centers. The success of such studies, to a large extent, would depend upon the support of pulmonary clinicians in office practice who would refer patients for enrollment.

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Monitoring hospital readmissions

SEVERAL recent studies have established that readmissions to an acute care hospital occur relatively frequently and they are responsible for a significant proportion of inpatient hospital spending. Anderson and Steinberg,[1] for example, examined readmissions in the Medicare population between 1974 and 1977 and found that 22.5% of the Medicare beneficiaries discharged from an acute care hospital were readmitted within 60 days and that 49.7% were readmitted within one year. They also found that hospital expenditures could be reduced substantially if the readmission rate could be reduced. Zook and associates[2] examined high-cost patients in Boston-area hospitals and found that, over one year, most of these patients incurred high costs because of multiple admissions and not because of a single catastrophic illness.

■ *See Farmer et al (pp 704–708)*

Since these articles were written, concern over readmissions, especially in the elderly population, has increased primarily as a result of the Medicare Prospective Payment System (PPS). PPS has created new financial incentives for hospitals to discharge patients prematurely and also to discharge and then readmit patients with multiple problems.[3]

Most of the initial studies of hospital readmission rates were primarily descriptive. One of their major values has been to prompt clinicians to ask a whole series of additional questions about readmissions. Two important questions that warrant further investigation are 1) why do readmissions occur and 2) what, if anything, can be done to lower the readmission rate?

In this issue Farmer and associates identify four reasons why readmissions might occur and classify a sample of patients from the Cleveland Clinic into each category. They find that 53% of the readmissions were planned, 17% were the result of complications of a previous admission, 11% were for a recurrence of the illness, and 16% involved conditions unrelated to the previous admission.

As with any good study, this paper raises several new questions that will require further analysis. The authors examine the reasons for readmissions in three services of the Cleveland Clinic Hospital: cardiology, cardiovascular surgery, and gastroenterology. The study will cause most readers to wonder whether the results are generalizable to other settings. Would the classification system work in other hospitals and other departments? Would the percentage of patients falling into each category be the same in other departments and other hospitals? These questions are certainly worth exploring.

In this study more than half of the readmissions were planned. It is unclear whether all the planned readmissions were absolutely necessary. Further analysis of these planned readmissions should investigate whether medical practice could be modified to reduce the number of planned readmissions. It might be time to reevaluate certain treatment protocols, especially in the field of oncology, where planned readmissions occur most commonly. Changes in medical practice could generate considerable cost savings, improved quality of care, and greater patient satisfaction.

Farmer and associates suggest that readmissions are