The first description of alpha1-antitrypsin (AAT) deficiency (AATD) identified by paper electrophoresis was published in 1963 by Laurel and Eriksson. As part of their publication they reported the first 5 individuals who had been identified, 3 of whom had recurrent chest problems and significant evidence of emphysema, the eldest being 42 years of age and 1 of whom also had a family history of emphysema. Because of this high prevalence of emphysema, particularly at a young age, subsequent studies of the family of these index cases identified nonindex cases with the deficiency and also pulmonary emphysema, confirming the inherited nature of the condition.

Because AAT was known to be an inhibitor of proteolytic enzymes, subsequent research was based on the hypothesis that an enzyme normally inhibited by AAT played a central role in the development of emphysema. Senior and colleagues subsequently showed in an animal model that neutrophil elastase was able to reproduce these features of emphysema, as can proteinase 3, another serine proteinase from the neutrophil. These observations led to the proteinase/antiproteinase theory of the mechanism of emphysema, in which proteolytic destruction of the lung interstitium (and particularly lung elastin) resulted in structural changes in the alveolar region, leading to the pathologic changes of emphysema. This concept has continued to dominate research into the pathophysiology of emphysema, exploring several potential mechanisms, namely deficiency of protective inhibitors, poor function of defective inhibitors, modulation of the function of inhibitors by oxidation or proteolytic cleavage, and overwhelming of the inhibitors by excessive inflammatory cell recruitment and/or activation releasing sufficient enzyme to exceed any protective inhibitors.

PREVALENCE

AAT of the Pi Z phenotype is thought to have originated some 2000 years ago in the Baltic region, thereafter becoming spread by Viking migration. The prevalence follows this migration in a dilutional manner and the incidence can vary from 1 in 1600 in some of the Baltic countries to approximately 1 in 5000 in the United States.

AAT is a 52-kDa single-chain glycoprotein with a sequence of 394 amino acids that is synthesized predominantly in the liver and functions as a serine proteinase inhibitor or serpin. The protein is encoded on the serpin α-1 gene and consists of 7 exons on the long arm of chromosome 14. Since the original discovery there have been more than
500 single-nucleotide polymorphisms reported at this gene locus, although many are associated with normal gene transcription, translation, and protein function. However, several mechanisms are recognized as being related to deficiency, including total absence of the gene, frame shift mutations that lead to premature stop codons, as well as point mutations that may lead to no production or production of abnormal AAT phenotypes. The function of the protein depends on a methionine amino acid at position 358 that gives the protein its specificity for interlocking with the catalytic triad of serine proteinases and in particular neutrophil elastase. This interlocking results in inactivation of both proteins and the formation of a stable complex. In the commonest severe Z type of AATD, the gene is normally transcribed and translated although a single point mutation leads to an amino acid change at position 342 (glu-lys). This change affects the mobility of the reactive center loop and produces a gap in beta sheet A. The reactive loop of one molecule can then insert itself into this gap, causing the so-called loop sheet polymerization leading to accumulation of AAT in the hepatocytes, a reduction in secretion of AAT, and a retained tendency to form spontaneous polymers both in the serum and tissues (especially the lung). The most common phenotype of AAT is the normal M form. Affected individuals have 2 genes and these are usually expressed in a codominant form, thus heterozygotes are common (1%–3% of affected populations) such that MZ heterozygotes have partially reduced levels (approximately 60% of normal MM homozygotes) and SZ heterozygotes have levels approximately 40% of the normal MM homozygotes. The level of AAT may be key to the susceptibility to develop pulmonary emphysema (discussed later).

**CLINICAL IMPACT**

The classic presentation for individuals with AATD is early-onset basal panacinar emphysema (compared with the usual later onset apical centrilobular emphysema of chronic obstructive pulmonary disease [COPD]). For these reasons, initially testing for AAT was confined to such patients, leading to an acquisition bias that continued to support the clinical phenotype. Once these index individuals had been identified, family screening identified further deficient subjects as nonindex patients and, in general, these individuals have much less severe disease. Subsequent testing also confirmed that never smokers also had less clinical evidence of lung disease and more often presented later in life. However, in recent years testing has become more widespread and the variability of the age of presentation has become more apparent as well as variations in the clinical phenotype. Patients may present with bronchiectasis and no emphysema, upper zone and centrilobular emphysema, as well as the classic lower zone panacinar emphysema. There may be evidence of airways predominance with little emphysema, which can be reflected in physiologic discordance with some patients having reduced gas transfer alone, and others reduced spirometry alone, which at least partly reflects the emphysema distribution. However, in most cases, both physiologic measures are impaired. This discordance can also be seen within siblings, in whom there seems to be no concordance with spirometry but clearer concordance with both gas transfer and upper zone rather than lower zone emphysema as determined by lung densitometry. This finding raises the possibility that the emphysema and gas transfer abnormalities are more closely linked to the AATD and that airways disease may reflect other modifying or epigenetic phenomena (discussed later).

Smoking plays a key role in the clinical impact of AATD. Patients who present earlier are nearly always smokers and smoking cessation can largely stabilize the disease. In addition, recurrent exacerbations also influence spirometric decline as well as gas transfer decline, and reversibility of airways obstruction is associated with more rapid spirometric decline. Recent studies have not shown a significant reduction in life expectancy in never smokers and such patients often present at a later age.

However, even in smoking individuals, the progression of lung disease can be widely variable. Recent studies have suggested that spirometry in individuals identified at birth remains normal until their 30s despite an increased prevalence of breathlessness. Studies of never smokers have indicated that deterioration in gas transfer and lung densitometry can be identified even in this good-prognosis group in the early to late 20s, whereas spirometric change starts to occur in the 50s and 60s. In addition, in cross-sectional data, the greatest rate of decline of forced expiratory volume in 1 second (FEV1) occurs in the range of 35% to 60% predicted, whereas the greatest change in gas transfer occurs when the FEV1 is lower. Lung densitometry (which is a more direct measure of the emphysema process) seems to show steady progression throughout all stages of the disease, suggesting that the disjunction with spirometry or gas transfer change reflects the parts of the lungs that are undergoing emphysematus
change. Nevertheless, these features suggest that all individuals with AATD should be monitored on a regular basis to determine the nature and degree of progression in order that prognosis and the potential effects of therapy can be predicted and evaluated (discussed later).

Most patients with AATD are treated as for usual COPD with long-acting bronchodilators and inhaled corticosteroids. Many patients with AATD have a degree of reversibility (Fig. 1) and recurrent exacerbations, although no formal trials of usual inhaled therapies have been performed in deficient patients. However, at least one small study has indicated that inhaled corticosteroids have some benefit.

The continuous progression and young age in some individuals leads to lung transplantation being a viable option toward the end of the disease process. Survival data (especially over the period of 2–9 years after transplantation) suggests that this is improved and is associated with an improvement in lung function and health status, although longer term survival is not necessarily better when patients are closely matched for physiologic impairment at baseline.

Lung volume reduction surgery is rarely indicated because most patients have basal emphysema, although studies are ongoing of nonsurgical lung volume reduction.

**PATHOPHYSIOLOGY**

The neutrophil, which is the main source of serine proteinases thought to cause the pathologic changes, is present in large numbers both in the airways and the interstitium of patients with AATD. Early studies suggested that failure to control elastase within the airways led to the stimulation of the neutrophil chemoattractant leukotriene B4 (LTB4) by alveolar macrophages. Studies of airway secretions from patients with AATD confirmed that LTB4 was the major recognized chemoattractant that influenced neutrophil migration.

In an elegant series of experiments Campbell and colleagues described the process of quantum proteolysis, whereby neutrophils migrating in the presence of connecting tissue release concentrations of serine proteinases in excess of the concentration of AAT even in individuals without deficiency. It was thought that this process was necessary to allow neutrophils to migrate through the interstitium of the lung by destroying the connective tissue in close proximity to the cell. This process showed little relationship to the AAT concentration until it decreased to less than 11 μM (Pi Z antitrypsin deficiency has an approximate concentration of 5 μM). At this point there was an exponential increase in the degree of damage seen in the presence of a migrating neutrophil. This concept has major implications concerning the risk of heterozygotes such as the MZ and SZ phenotypes, because in general these phenotypes have AAT plasma levels that are more than the critical 11 μM threshold (discussed later). More recently it has been recognized that polymers of AAT can be chemoattractants in their own right, although they are also proinflammatory. It has been suggested that these properties of the polymers may be more important in driving the neutrophilic infiltration into the lung than the effect of uninhibited elastase on LTB4. Whether this is true remains unresolved. However, AAT enters the lung mainly by diffusion from plasma and the interstitial concentration should be about 80% of that in plasma. Larger proteins (including polymers) would be restricted in this diffusion, leading to a reversed plasma/lung gradient that would thus not act as a conventional chemoattractant. In addition, polymer formation is concentration...
dependent and hence should not increase in the interstitium to more than that in plasma. However, there are potential caveats to this concept. First, lung cells have the potential to produce some AAT locally\(^3^4\) and hence increase polymer formation in situ, establishing a gradient. As an alternative, the proinflammatory nature of polymers may increase local chemoattractant production, providing an alternative gradient. Nevertheless, polymers of AAT are in the interstitium of the lung and this chemoattractant property may be the reason that some neutrophils colocalize with the polymers\(^2^8\) and, if so, are likely to cause even more local connective tissue destruction by retaining them (and their proteolytic activity) in situ. These concepts are summarized in Fig. 2.

There are other factors that may complicate the development of emphysema, including the role of uninhibited proteinases on cell apoptosis (which has also been implicated in the emphysema process)\(^3^5\) and activation of other proteinases in the inflammation cascade and inactivation of cognate inhibitors.\(^3^6\) In addition, MMP-9 (matrix metalloproteinase)\(^3^7\) and IREB2 (iron responsive element binding protein)\(^3^8\) have been implicated as further genetic modifiers in AATD, and, more recently, polymorphism of the tumor necrosis factor alpha gene has also been shown to amplify the inflammation and progression of lung function decline as well as influencing the clinical phenotype.\(^3^9\)

**Susceptibility of Other Phenotypes**

Most information concerning AATD relates to studies of the Pi Z phenotype (usually Pi ZZ genotype) because this is the most common severe variant presenting with disease. There is limited literature on the null variants of AAT, although in a small series the patients seem (if anything) to have worse lung function than Pi Z subjects.\(^4^0\) The null variants have undetectable levels of AAT and hence no circulating polymers, suggesting that the level is more critical than polymers in the pathophysiology of AATD lung disease. This finding is consistent with the quantum proteolysis process described by Campbell and colleagues.\(^3^0\)

With this last concept in mind, the in vitro studies of Campbell and colleagues\(^4^1\) indicated that a prevailing plasma AAT concentration also showed this critical threshold for more extensive tissue damage in the presence of a degranulating neutrophil. For this reason the common MZ heterozygote carriers should not be at greater risk of developing emphysema than the normal MM individuals because their AAT levels are invariably more than this threshold. However, there is some controversy in the literature because MZ subjects have been reported as having evidence of increased elastase activity in 1 study,\(^4^2\) are more likely to have slightly lower lung function as a group\(^4^3\) and more severe COPD than MM subjects,\(^4^4\) as well as greater hospitalization and mortality.\(^4^5\) Although these data do not indicate the MZ as a susceptibility factor, they do suggest that, if a patient is going to develop COPD and also has the MZ phenotype, the disease may become more of a problem. However, these data mainly relate to known patients with COPD or subjects tested or detected as part of family screening, and as such represent a selection bias. The most robust data from epidemiologic studies suggested that, at worst, MZ subjects have a minimal decrease in FEV\(_1\) compared with MM subjects.\(^4^6\) Thus, in general, the MZ phenotype alone is not considered a risk factor.

The SZ phenotype is approximately 3 times as common as the Z phenotype, especially around the Mediterranean. The average AAT level in these individuals is about 14, although a proportion has levels less than the 11 \(\mu\text{M}\) threshold, suggesting

![Fig. 2. Airway neutrophils release elastase (1) which remains active because of AAT deficiency. This stimulates macrophages and epithelial cells to release chemoattractants (2), which leads to neutrophil recruitment (3) and retention in the interstitium adjacent to polymers (4) enhancing tissue destruction. IL8, interleukin 8.](image-url)
A theoretic susceptibility in some individuals. Meta analysis of published data provides credence to this possibility, although again selection bias is likely to have influenced the results. However, patients with the SZ phenotype are more likely to have emphysema with the usual apical distribution of usual nondeficient COPD, which is therefore not typical of the AATD phenotype.

Furthermore, despite the greater prevalence, few patients with COPD and the SZ phenotype have been identified (approximately one-fifth as many as patients with the Z phenotype). Nevertheless, in some countries the SZ phenotype is considered appropriate for augmentation therapy.

Even less information is available for other partial deficiencies including the IZ, PZ, and FZ phenotypes. Although the FZ phenotype has comparable plasma AAT with the MZ phenotype, it is less functional. The F variant has a reduced association rate constant for neutrophil elastase and binds it more slowly once the enzyme is released. This property could provide a mechanism to increase local elastase-induced tissue damage. However, few such subjects have been identified and studied to provide more certainty about the role of the F variant.

AUGMENTATION

Because of the proteinase/antiproteinase hypothesis it became accepted that augmentation of the AAT level would prove beneficial in protecting the lung from progressive damage. Studies in the 1980s showed that purified AAT given by the intravenous route increased and maintained AAT levels in the blood (beyond that of SZ heterozygotes and thus thought to remove the increased risk) and in the airways of deficient individuals, where it remained functional and was subsequently shown to reduce inflammation, in particular the major neutrophil chemottractant LTB4. Although biochemical efficacy was therefore shown, clinical efficacy has been difficult to show. In the early days the FEV1 was the gold standard outcome measure for studies in COPD. Power calculations indicated that it would be impossible to recruit and deliver a clinical trial of augmentation therapy with FEV1 as the primary outcome. For this reason no such trial was deemed feasible or has been undertaken. Evidence for efficacy therefore has come predominantly from indirect observational studies.

The US National Institutes of Health developed an AATD register and eventually analyzed outcomes in individuals who had received augmentation therapy (at least for 6 months) and those who had never received augmentation. Mortality over 5 years was greater in individuals who had never received such therapy. In addition, the decline in FEV1 between the values of 35% and 60% predicted was also greater in individuals who had never received augmentation therapy. This last observation has led to a general belief that augmentation therapy is only effective within this physiologic range, and in some countries augmentation is stopped once the FEV1 decreases to less than 30% predicted. However, there are some problems with the interpretation of these data. First, in the health care systems in the United States, the least privileged individuals are unlikely to receive therapy and individuals of low social class have poorer outcomes for all health care issues. This trend is consistent with the observation that patients who had always or only partially received augmentation therapy seemed to have a similar outcome. Second, in all clinical trials it is easier to detect a benefit on the outcome measure if the outcome measure is highly prevalent and changing most rapidly. As indicated earlier, the FEV1 decline in AATD is most rapid in the 35% to 60% predicted range, which may explain the positive data only in this range. Other observational studies have also shown some benefit on FEV1 decline, namely comparing countries where augmentation therapy is available with those where it is not. Sequential studies of decline in FEV1 before and after therapy, although it should be noted that FEV1 decline is not linear and slows down later in the disease process, which could explain the sequential change. In addition, meta-analysis from reported data on decline in FEV1 in treated and untreated cohorts also suggests an overall benefit in terms of spirometric decline if augmentation was given.

In recent years it has become accepted that FEV1 is generally a poor surrogate of the emphysema process. Because emphysema is thought to be central to the pathophysiology of COPD in AATD, lung densitometry has become the outcome measure of choice. Data show that lung densitometry progresses in a linear fashion throughout the disease process. It is the sensitive parameter to change and thus power calculations for interventional studies with densitometry as an outcome are more favorable for this rare disease group. An initial study between Denmark and Holland confirmed that augmentation therapy had no benefit on spirometry but did show a trend (P = .07) for preservation of lung density and, by implication, stabilization of the emphysema process. The subsequent Exacerbations and Computed Tomography as Lung Endpoints (EXACTLE) study was performed using more sophisticated scanning techniques with densitometry as a primary
outcome. Again, the decline in lung densitometry in
patients receiving augmentation was less than on
placebo using the same analysis as the Danish/
Dutch study, although again it failed to achieve sta-
tistical significance ($P = .07$), but there was a signif-
ciant reduction in severe exacerbations requiring
hospitalization.\textsuperscript{60} Further analysis of the data from
the EXACTLE trial did show a significant reduction
in densitometry progression at the bases of the
lung where the characteristic emphysema oc-
curs,\textsuperscript{61} and combining the data of these two trials
in which densitometry was measured, even when
biasing the data in favor of the earlier and hence
less sophisticated trial, led to a highly significant
difference between treatment and placebo, indicat-
ing preservation of lung density.\textsuperscript{62}

Augmentation therapy is currently licensed in
many countries as a weekly infusion, although
other therapeutic regimens have been used; how-
ever, it is expensive\textsuperscript{63} and this raises the possibility
of providing augmentation through the inhaled
route. However, deposition studies have shown that
the inhaled route does not target the most
affected emphysematous areas\textsuperscript{64} and deposition
is unlikely to occur in the alveolar region (as with
most nebulized drug delivery). Even if such a
deposition could be achieved, the integrity of the
epithelial surface would restrict any movement of
AAT into the interstitium\textsuperscript{65} where the destruction
is occurring. One possible caveat to this physio-
logic problem is that, if the chemoattractant
(LTB4) is generated on the airway side of the
lung, augmentation of the elastase inhibitory ca-
pacity at this site would lead to a reduction in
free elastase activity and hence LTB4 production
by local macrophages, and this in turn would
lead to reduction in neutrophil migration and hence
neutrophil-dependent connective tissue damage.

Nevertheless, the inhaled route may be of more
benefit for individuals having recurrent
exacerbations. About half the patients with AATD
do not have a history of exacerbations but, in
those who do, most have 1 or 2 per year (Fig. 3).
These episodes usually include all 3 of the major
symptoms of such episodes and occur throughout
the year with some preponderance in the autumn
and winter months (Fig. 4). Exacerbations in
AATD are more inflammatory than those in usual
COPD, with higher elastase activity,\textsuperscript{66} and tend
to last longer.\textsuperscript{67} These episodes are related to
the progressive reduction in FEV\textsubscript{1},\textsuperscript{15} AAT by the
inhaled route is predicted to result in a more rapid
reduction in the local proteinase burden of these
larger airways events and may therefore reduce
the proteinase-generated inflammation and fre-
quency, severity, and perhaps length of exacerba-
tions. Such a trial is currently under\textsuperscript{68} and the
results will be informative in terms of the fre-
quency, severity, and pathophysiologic processes
involved. At worst, the treatment may change
episodes requiring treatment to less severe/sym-
tomatic ones not requiring intervention (Fig. 5).

It would also be possible to give intravenous bol-
uses of AAT at the start of an exacerbation, which
may have the same (although less efficient) effect
of increasing airways AAT by diffusion from
plasma. However, this would require an ability to
predict early whether the episode would be mild
or severe; perhaps limiting to episodes at admis-
sion to hospital may prove most beneficial if length
of stay or mortality were to be influenced. Never-
thless, at present, even if the overall efficacy of
augmentation therapy is accepted, it is largely un-
known whether all patients should receive such
therapy or whether it is possible to identify a sub-
set for whom it would be important and hence in
whom there is likely to be a greater cost/benefit.

At best, effective augmentation therapy slows
down the progression of emphysema and its phys-
ibologic markers. Thus, ideally all patients with

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Fig_3.png}
\caption{The features and frequency of exacerbations is shown as a percent-
age of patients experiencing at least 1 episode per year.}
\end{figure}
AATD who are identified should be monitored so that the natural history in the absence of augmentation can be determined. For smokers this should be done after smoking cessation and in many such patients lung function stabilizes. In others there is a continual progression that may be within or greater than the normal aging decline. It seems logical therefore that, for individuals in whom the decline in either spirometry or gas transfer exceeds that expected as part of the normal aging process, augmentation therapy would be indicated and that the younger the individual the more important this would be to either stabilize disease or prolong the phase until transplantation becomes the only remaining option. In never smokers, the physiologic measurements at presentation related to the age would already provide good evidence of the rate of progression even though life expectancy in such individuals remains normal. In times of austerity, rationalization along the lines of this approach may become critical for the prescription and funding of augmentation therapy.69

For Pi Z individuals without respiratory disease, less information is available of the benefits of augmentation therapy. Acute necrotizing panniculitis can respond dramatically70 but it is unknown whether the vasculitis would also benefit from augmentation therapy, although this is also a proteinase-dependent process in some subjects.71 The cirrhosis caused by liver damage from AAT retention is not expected to respond to or require augmentation therapy because the endogenous polymerization will still continue. Methods to silence gene transcription may prove protective to the liver but potentially amplify the lung damage. Mechanisms to enhance liver AAT secretion by preventing polymerization treat the liver and protect the lung if AAT function can be retained (discussed later).

Fig. 4. Distribution of exacerbations throughout the year for patients with AATD.

Fig. 5. Daily diary card score reflecting severity and duration of symptoms for exacerbations in AATD that did or did not require intervention (data are derived from Ref.68).
NEW TREATMENTS

There are many strategies that can potentially overcome the problems of AATD.

Recombinant A1AT

Because of the cost and limited supply of plasma-derived AAT, recombinant forms of protein have been generated. Initial studies produced nonglycosylated proteins that result in more rapid clearance, and potential problems with structural stability and exposure of immunogenic epitopes normally hidden. A glycosylated transgenic sheep protein induced immune responses because of impurities that were impractical to remove. More recently a sialyzed version has been produced in a human neuronal cell line and it remains to be seen whether this becomes a viable source.

Secretion Strategies

Because at least the Z form of AAT is translated normally, strategies to prevent retention in the hepatocytes would have 2 potential benefits. Release of AAT would reduce the endoplasmic stress in the hepatocytes and thus (potentially) prevent the development of cirrhosis and liver failure. At the same time, the increased secretion would raise the plasma concentration and potentially protect the lung from proteolytic damage. Chemical chaperones intended to stabilize the intermediate forms of Z AAT on the folding pathway were shown to work in animal studies but have proved to be toxic and ineffective in humans.

Small peptides can prevent intrahepatic polymerization in vitro, although there is currently no identified method of delivering these compounds to the endoplasmic reticulum (ER) of hepatocytes. In addition, they inactivate the AAT, which produces a null phenotype. This process would be expected to worsen the lung disease in such naturally occurring individuals.

Gene Therapies

A variety of gene therapies have been explored. In general, these result in minimal and only transient expression and hence production of A1AT. This approach would fail to influence the liver disease. The hepatocyte ER stress could be abrogated by the use of a silencing strategy using Si RNA. This strategy would lead to a null phenotype but potentially can be combined with a transgenic approach leading to normal AAT production to protect the lung as well. An alternative is to correct the gene defect using small DNA fragment technology. However all these methods still depend on the development of effective transfer of gene-modifying agents into the hepatocytes before trials can be undertaken.

A further strategy is to deliver the gene to the lung in a way that minimizes any immune response to the vector and provides significant and sustained AAT production. This strategy would make repeated treatments less frequent and immune activation to the vector less likely. Such a strategy introducing the vector into the pleural space seems to fulfill these criteria in animal models. Further studies including long-term safety in humans need to be undertaken.

In addition, transfection and/or a stem cell strategy to deliver normal hepatocytes to the diseased liver may provide further long-term solutions, although again safety may be a major issue.

Drugs

Specific inhibitors of Neutrophil Elastase (NE) have been developed, although they have not been tested in AATD. Most have failed at the phase 2 development stage because of failure to improve lung function in usual COPD (an outcome that is improbable in phase 2 studies for such agents). Because AAT inhibits other serine proteinases released at the same time as NE (Pr3 and Cat G) having many similar effects on the lung and being increased in AATD, it is possible that a highly selective NE inhibitor may not provide significant or total protection against serine proteolytic attack to the lung. However, in the absence of such a study, the direct role of elastase and, in particular, the contribution of other serine proteinases remains speculative.

In addition, alveolar repair could potentially progress ahead of alveolar damage. Retinoic acid receptor (RAR) gamma agonists are effective in animal models of emphysema. However, this strategy proved ineffective in a 1-year study of patients with AATD and further development is on hold.

Inhibitors of chemotaxis (CXCR 1 and 2 antagonists or particularly on LTB4 receptor antagonists) may have a potential role. These inhibitors would reduce neutrophil reflux and hence proteinase release in the lung. However, these agents have not been studied in AATD.

BIOMARKERS

Biomarkers of disease activity and hence determinants of future progression remain illusive in AATD as in usual COPD. However, the mechanism that leads to the development of emphysema has been accepted as destruction of lung connective tissue and specifically elastin by serine proteinases and most likely elastase. For this reason
elastin degradation products have been proposed and extensively studied as appropriate markers. However, elastin is a widespread connective tissue and little is known about systemic turnover, although in the healthy lung it is minimal. Thus systemic or secreted elastin peptides or cross-linking amino acids may reflect changes in other tissues or even diet. Nevertheless, recent studies have suggested that reassessment of these elastin products may still be useful as an indicator of emphysema progression and the effectiveness of specific, protective interventions. An alternative is to measure elastase directly, although, because of the presence of inhibitors both in the plasma and the airways, enzyme activity is often largely inhibited by the time samples are collected and analyzed. Such data do not inform about the activity at the point of release (ie, where the damage occurs). For this reason a footprint of the local activity would serve all potential needs. Recent studies of a specific cleavage product of fibrinogen may serve this purpose. The peptide is increased in AATD and correlates with physiologic impairment. In addition, it increases during exacerbations, which are known to influence physiologic decline, and responds positively to augmentation therapy. Further validation is required but such an approach may prove invaluable in predicting physiologic decline and in short-term monitoring of drug efficacy.

**SUMMARY**

Since the identification in 1963, understanding of the molecular mechanism, natural history, clinical phenotype, and progression in AATD has improved from simple interpretation in the 1960s to mid-1990s. In general, outcomes are better than originally thought, clinical illness is not a given, and there is a clearer understanding of the expected role of augmentation therapy. However, because of the general rarity of the condition, it is essential that all such patients get referred to centers of excellence, monitored, and treated/not treated. These centers should be located alongside relevant transplant facilities. Nevertheless, further research is required to identify specific epigenetic factors that influence clinical phenotype, markers of progression, and treatment benefit.

**REFERENCES**


42. Weitz JI, Silverman EK, Thong B, et al. Plasma levels of elastase-specific fibrinopeptides correlate with proteinase inhibitor phenotype. Evidence for increased elastase activity in subjects with homozygous and
Stockley


