

Alpha 1 Antitrypsin Deficiency

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What is the physiology of emphysema?

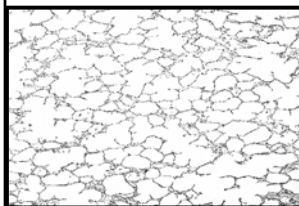
Two basic functional changes:

1. Loss of elastic recoil
2. Loss of membrane surface area

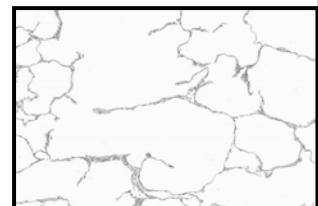
Pulmonary Emphysema

- Permanent enlargement of airspaces distal to the terminal respiratory bronchioles which involves destructive changes in alveolar walls
- Affects as many as 5-10% of adults in U.S.

Normal

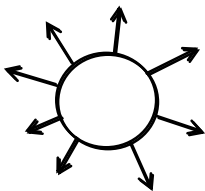


Emphysema

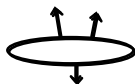


Elastic Recoil Important for Airway Patency

Normal Airway



Emphysematous Airway



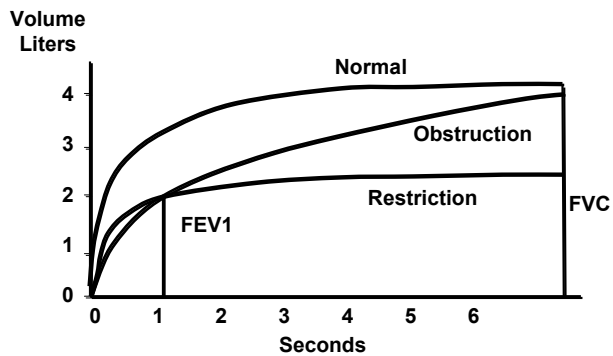
Normal



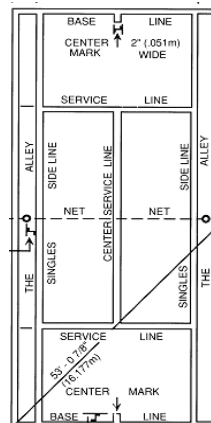
Emphysema



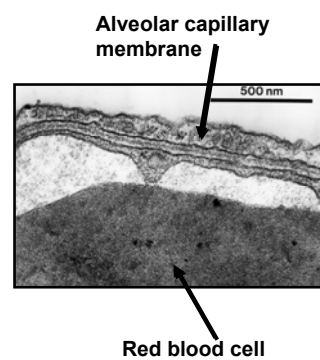
Spirometry



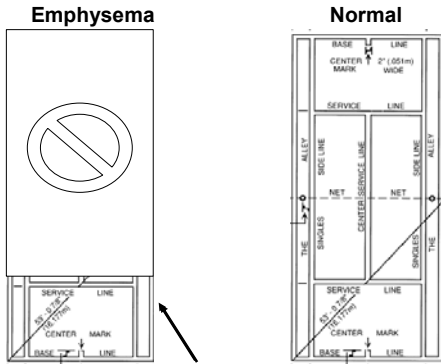
Doubles Tennis Court



Alveolar Capillary Membrane



Alveolar Capillary Membrane



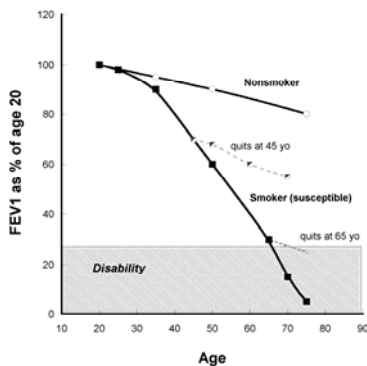
Symptomatic at minimal exertion

Emphysema

How Does It Happen?

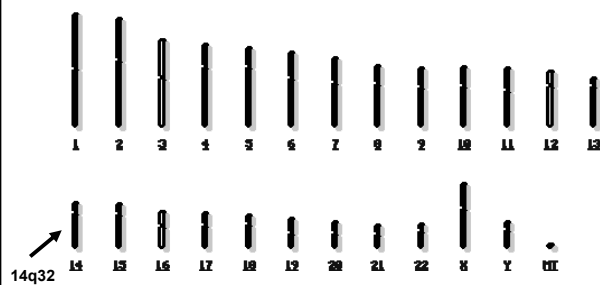
Lessons from alpha 1-antitrypsin deficiency

Smoking Effects on Lung Function



Fletcher, Peto, Tinker, Speizer. Oxford Press, 1976

A1AT Genetic Defect



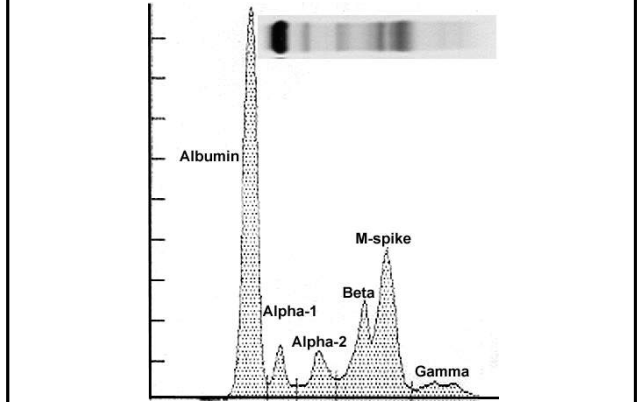
Z Mutation for Alpha 1-Antitrypsin

Glu342 (GAG) → Lys342 (AAG)

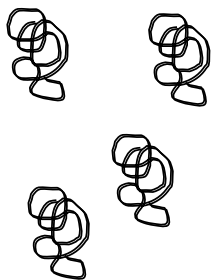


Alpha 1-Antitrypsin Gene

Serum Protein Electrophoresis

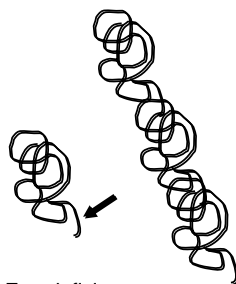


Monomeric Forms



M or normal type

Polymeric Forms



Z or deficient type

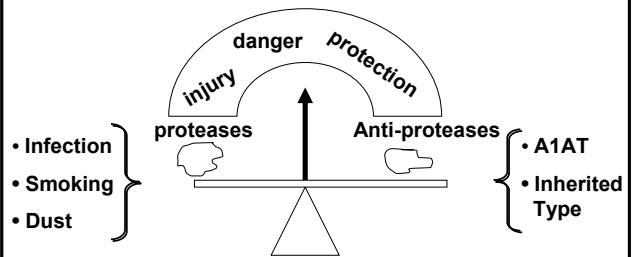
Alpha 1 and Emphysema

- 5 patients found to have deficient alpha 1 peaks on their serum protein electrophoresis
- 3 of the 5 had severe emphysema

Laurell, C.-B. and Eriksson S. The electrophoretic alpha1-globulin pattern of serum in alpha 1-antitrypsin deficiency. *Scandinav. J. Clin. and Lab. Investigation.* 15:1320140, 1963.

How does this defect cause disease?

Protease-Antiprotease Imbalance Hypothesis



Protease/Antiprotease Hypothesis

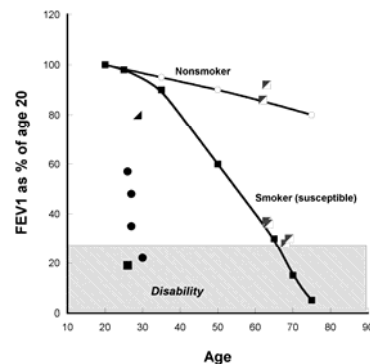
• Laurell and Eriksson, 1963, *Scand.J.Clin.Lab.Invest.*

- ✓ 3/5 cases had emphysema
- ✓ "Some connection between degenerative pulmonary disease and α 1-antitrypsin deficiency is suggested."

• Gross P. et al., 1965, *Arch.Environ.Health.*

- ✓ Papain into silicotic rats
- ✓ Induced emphysema

A Few Case Histories: Patients with A1AT Deficiency



Fletcher, Peto, Tinker, Speizer. Oxford Press, 1976

Alpha₁ a Rare Disease?

1972-1974 All newborns in Sweden screened finding 127 of 200,000 with Pi ZZ.

	1 in 1600
Oregon	1 in 5097
St. Louis	1 in 2857
New York	1 in 3694

~ 1 in 3000
in US

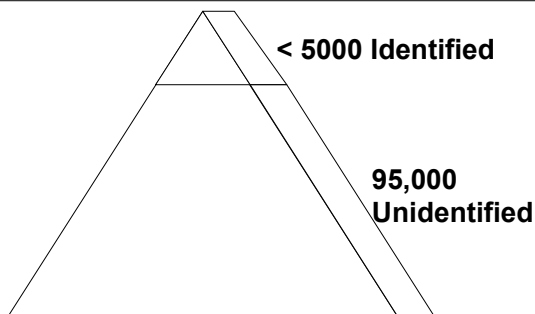
Sveger, Pediatrics 1978; 62:22
O'Brien J Pediat 1978; 92:1006
Silverman ARRD 1989; 140:961
Cobb Chest 1993; 103:812

AATD: Recommendations from the AAT Deficiency Task Force

- Genetic testing is recommended for
 - ✓ Absent alpha-1 peak on SPEP
 - ✓ Early onset pulmonary emphysema (regardless of smoking history)
 - ✓ Family members of known AATD patients
 - ✓ Dyspnea and cough occurring in multiple family members in same or different generations

AATD, alpha-1 antitrypsin deficiency.
American Thoracic Society, European Respiratory Society. Am J Respir Crit Care Med. 2003;168:818-900.

AATD Individuals Identified

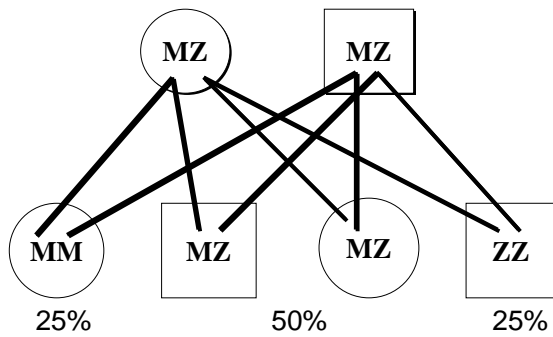


AATD: Recommendations from the AAT Deficiency Task Force

- Genetic testing is recommended for
 - ✓ Liver disease of unknown cause
 - ✓ All subjects with COPD
 - ✓ Adults with bronchiectasis without evident etiology
 - ✓ Patients with asthma whose spirometry fails to return to normal with therapy
 - ✓ Unexplained panniculitis and anti-proteinase 3 vasculitis

AATD, alpha-1 antitrypsin deficiency.
American Thoracic Society, European Respiratory Society. Am J Respir Crit Care Med. 2003;168:818-900.

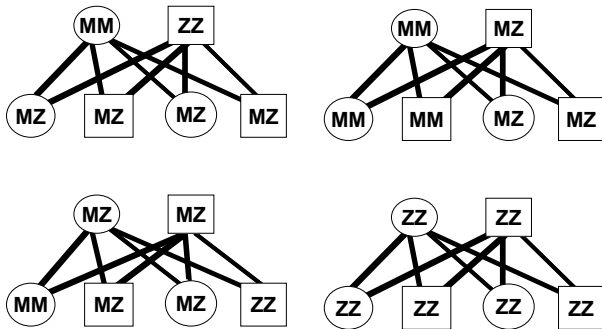
AAT Genetics



Clinical Manifestations

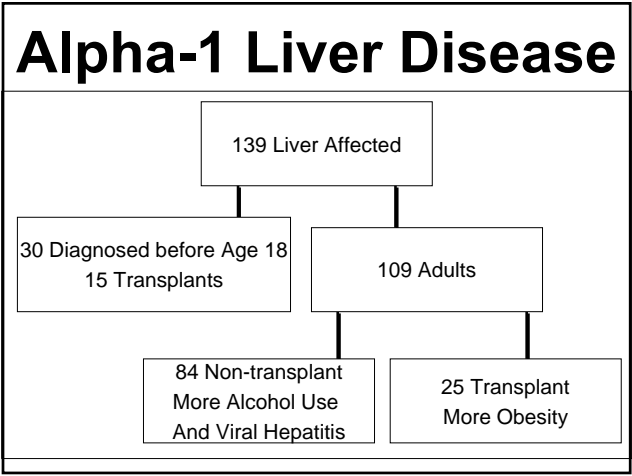
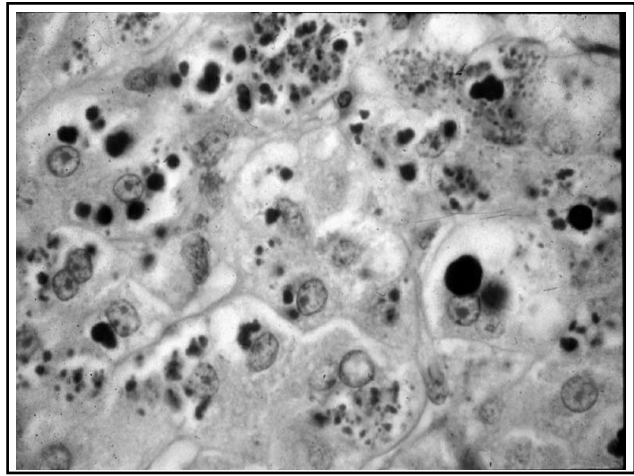
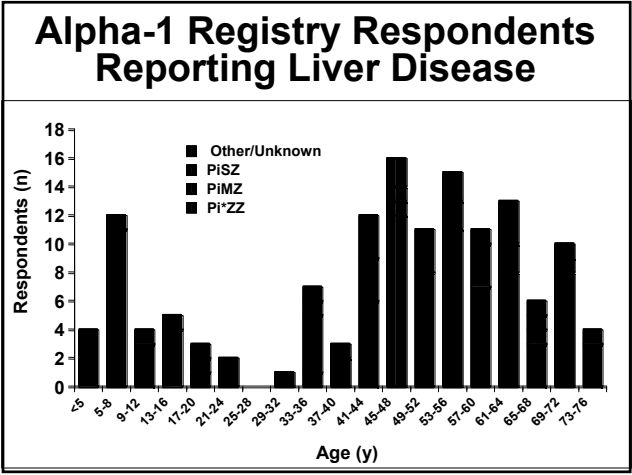
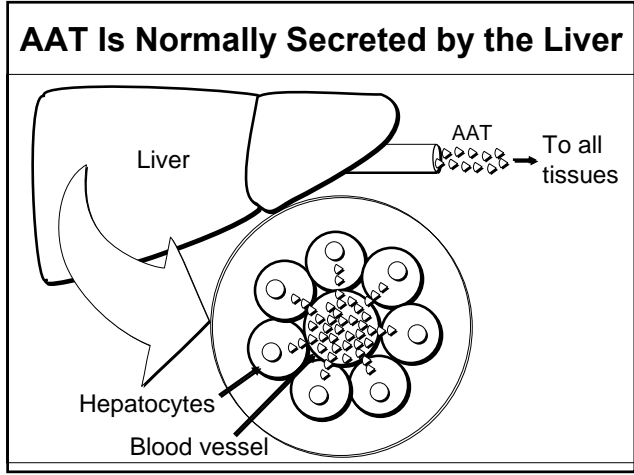
- **Panacinar Emphysema**
 - ✓ Early onset
 - ✓ Most common in current or past smokers
- **Bronchiectasis**
 - ✓ Atypical Mycobacterial Disease
- **Hepatic insufficiency**
 - ✓ Both Infant and after age 50 predominant

AAT Genetics



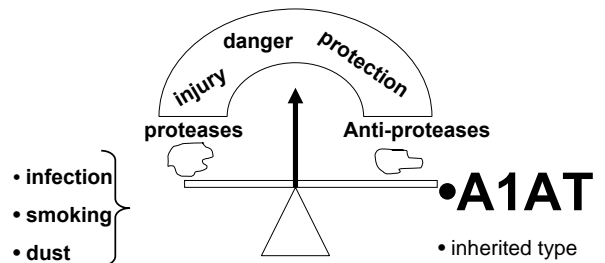
Clinical Manifestations

- **Panniculitis**
- **Association with Anti-proteinase 3 vasculitis**
- **Association with Connective Tissue Diseases**
- **Poorly responsive HIV**
- **Association with Lung Cancer**

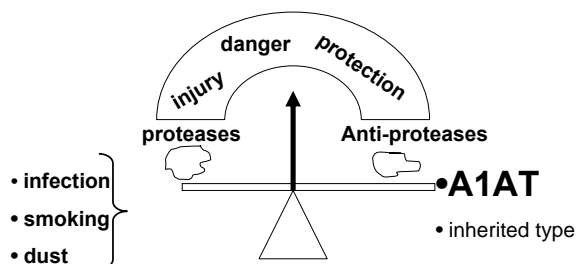


What are the treatment options?

Protease-Antiprotease Imbalance Hypothesis



Protease-Antiprotease Imbalance Hypothesis



First Infusions of Alpha 1-antitrypsin

- Gadek JE, *J Clin Invest.* 68:1158, 1981.
✓ 5 patients for 4 weeks

Replacement Therapy of Alpha 1-Antitrypsin Deficiency
REVERSAL OF PROTEASE-ANTI-PROTEASE IMBALANCE WITHIN THE ALVEOLAR STRUCTURES OF F1Z SUBJECTS

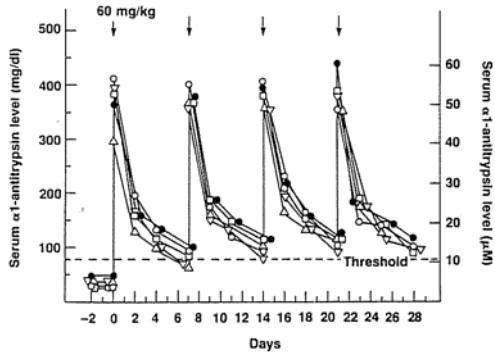
JAMES E. GADEK, HARVEY G. KLEIN, PAUL V. HOLLAND, and RONALD G. CRYSTAL, Pulmonary Branch, National Heart, Lung, and Blood Institute and Blood Bank, Clinical Center, National Institutes of Health, Bethesda, Maryland 20895

- Wewers, MD. *NEJM* 316:1055, 1986.
✓ 21 patients for 6 months

REPLACEMENT THERAPY FOR ALPHA₁-ANTITRYPSIN DEFICIENCY ASSOCIATED WITH EMPHYSEMA

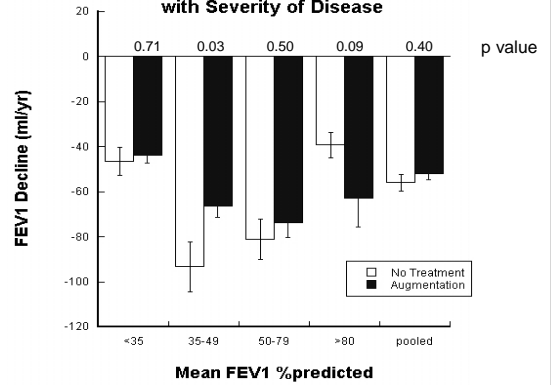
MARK D. WEWERS, M. ANTHONY CAROLARO, STEPHANIE E. SELLERS, SONIA C. SWAYZE, KATHLEEN M. McPHAIL, JANET T. WITTES, AND RONALD G. CRYSTAL

A1AT Infusion Therapy



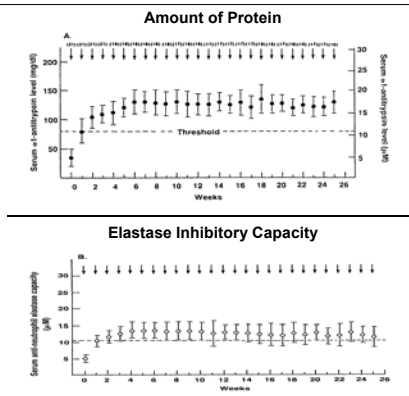
NEJM 1987; 316:1055-62

Relationship Between Augmentation Therapy and FEV1 Decline with Severity of Disease



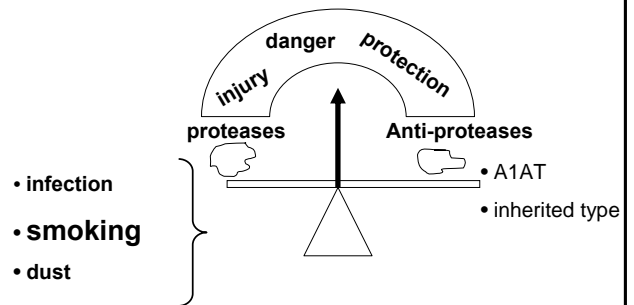
AM J RESPIR CRIT CARE MED 1998;158:49-59.

A1AT Trough Levels Over 6 Months of Therapy

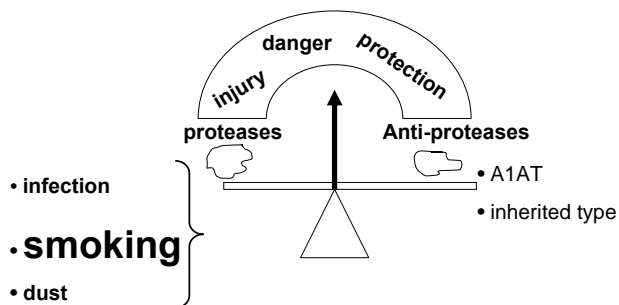


NEJM 1987; 316:1055-62.

Protease-Antiprotease Imbalance Hypothesis



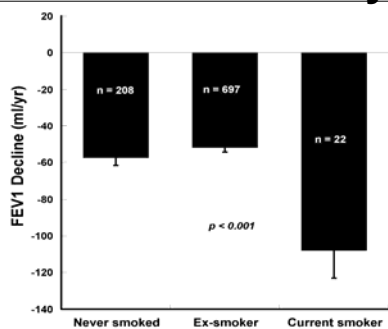
Protease-Antiprotease Imbalance Hypothesis



Treatment Options

- Smoking cessation
- Avoid dusty occupational exposures and passive smoking
- Preventive measures: handwashing; vaccines for influenza and pneumonia
- Treat infections early
- Augmentation therapy with alpha 1 antitrypsin (\$\$)

Smoking Cessation and FEV1 in A1AT Deficiency



AM J RESPIR CRIT CARE MED 1998;158:49-59.

Future Hopes for Therapy

- Genetic manipulation to remove the PiZZ gene from hepatocytes and replace with functioning PiMM gene
- Enhanced antitobacco legislation to help prevent institution of tobacco habit

Some of the Not For Profit Faces

<p>Member-based organization: Support and Education Advocacy Genetic Counseling Center</p>	<p>Research-focused organization: Increase research Improve health Worldwide detection Cure for Alpha-1 Registry DNA and Tissue Bank</p>	<p>Health management organization: Health maintenance and disease prevention Outcome studies Clinical research Health Management Coordinators</p> <p>Not-for-Profit but revenue generating</p>
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Registry Newsletter

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, Alpha-1 Antitrypsin Deficiency and Other Conformational Diseases. The conference was held at the Airline Conference Center in Virginia this past June. It examined the newly recognized class of disorders collectively known as diseases of abnormal protein conformation.

Using Alpha-1 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 stimu-

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

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



Why should we detect individuals with AATD?

- Assist in smoking cessation
- Assist in occupational decisions
- Meaningful genetic data to family members
- Disease specific support
- Allow therapy specific for AATD