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MEDICAL GRAND ROUNDS

University of Texas Southwestern Medical School
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α1-ANTITRYPSIN DEFICIENCY:

FROM THE BENCH TO THE BEDSIDE

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In the current edition of Harrison's Principles of Internal Medicine, less than one-half of one page is devoted to a discussion of α1-antitrypsin deficiency (see one paragraph on page 1237 and one paragraph on page 1488). This paucity of coverage is surprising when one considers the following facts: 1) α1-antitrypsin deficiency is a common disorder, occurring in 1 per 25 individuals in the heterozygous form and 1 per 2,500 individuals in the homozygous form; 2) it is among the best understood medical diseases at a molecular level (the basic defect at the cellular level has been identified and the pathogenesis at the whole body level has been explained); and 3) a rational therapy for the disorder has emerged as a result of knowledge of the basic defect and pathogenesis. The lack of adequate coverage of α1-antitrypsin in Harrison's Principles of Internal Medicine is even more remarkable when one considers that 3 times more space is devoted to a discussion of orotic aciduria, which has occurred in a total of 9 patients throughout the world!

The purpose of this Grand Rounds is to provide a supplement to the 9th edition of Harrison's Principles of Internal Medicine by presenting a discussion of α1-antitrypsin deficiency. The following aspects of the disease will be discussed:

1) Historical Aspects
2) Structure of α1-antitrypsin and its genetic variants
3) Physiology of α1-antitrypsin
4) Pathogenesis of destructive lung disease
5) Pathogenesis of liver disease
6) Therapy

I HISTORICAL ASPECTS

1.

α-1-ANTITRYPSIN DEFICIENCY

- **1963** - Association between α-1-AT deficiency and pulmonary emphysema in young adults (Laurall and Erickson)
- **1964-1968** - Elucidation of genetics and polymorphism of α-1-AT locus (Laurall and Erickson; Fagerhol)
- **1969** - Association between α-1-AT deficiency and liver disease in infants (Sharp)
- **1970-1981** - Elucidation of biochemistry and physiology of α-1-AT; unraveling pathogenesis of the deficiency states; development of rational therapeutic approaches

2. **α-1-ANTITRYPSIN**

- Protein that accounts for 90% of α-1-globulins of plasma
- Acute phase reactant – increased by inflammation, infection, liver disorders, pregnancy, oral contraceptives
- Inhibits large number of proteolytic enzymes - trypsin, chymotrypsin, collagenase, elastase
- Major physiological role – to inhibit elastase released from neutrophils

II STRUCTURE OF α1-ANTITRYPSIN AND ITS GENETIC VARIANTS

1. **α-1-ANTITRYPSIN-STRUCTURAL PROPERTIES**

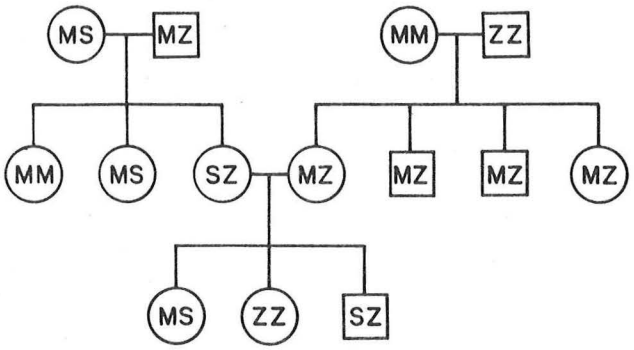
- Glycoprotein - single polypeptide chain
- Molecular weight of 50,000 - 90% protein and 10% carbohydrate
- 4 Carbohydrate chains per 1 protein molecule

2. **CLINICALLY IMPORTANT Pi PHENOTYPES**

	MM	MZ	SS	SZ	ZZ
					
Percent of Normal Serum α-1-Antitrypsin Level	100	60	50	35	10
Frequency in USA	95%	4%	1 per 250	1 per 800	1 per 2000

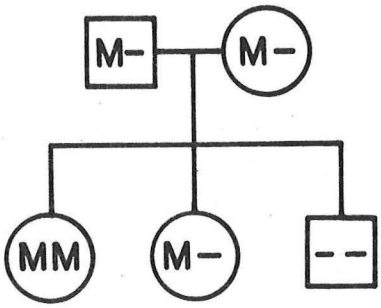
3.

CO-DOMINANT EXPRESSION OF Pi ALLELES



4.

"NULL" ALLELE



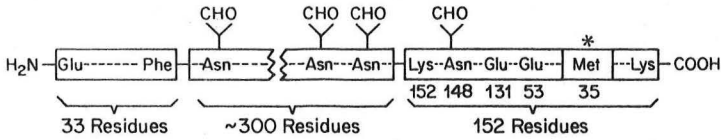
5.

FREQUENCY OF α-ANTITRYPSIN VARIANTS IN NORWEGIANS

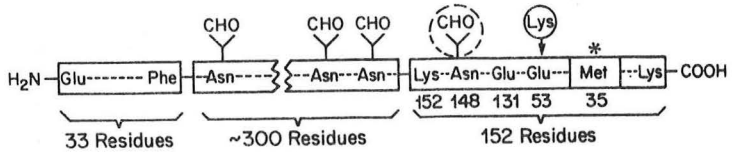
Pi Type	Concentration in Plasma	Population Frequency
	% of normal	per 10,000
MM	100	9,450
MZ	70	470
M-	50	50
SS	60	7
SZ	35	14
ZZ	20	7
Z-	10	2
--	0	0.09

6.

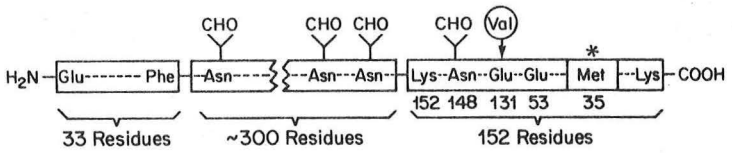
PRIMARY STRUCTURE OF α-1-ANTITRYPSIN-M PROTEIN



7. **PRIMARY STRUCTURE OF α-1-ANTITRYPSIN-Z VARIANT**



8. **PRIMARY STRUCTURE OF α-1-ANTITRYPSIN-S VARIANT**



III PHYSIOLOGY OF α1-ANTITRYPSIN

1. **INACTIVATION OF PROTEASE BY α-1-ANTITRYPSIN**

Protease	Time for 50% Inactivation
	milliseconds
Elastase	0.42
Chymotrypsin	4.2
Trypsin	210
Thrombin	576,000 (9.6 minutes)

2. **NEUTROPHIL ELASTASE**

- Negatively-charged protein with molecular weight of 29,500
- Stored in primary (azurophilic) granules of neutrophils as active enzyme
- Once discharged, elastase is attracted to elastin by electrostatic interactions

IV PATHOGENESIS OF DESTRUCTIVE LUNG DISEASE

1.

CLINICAL MANIFESTATIONS OF DESTRUCTIVE LUNG DISEASE IN ZZ INDIVIDUALS

1. 80% of ZZ individuals have panacinar emphysema
2. Typical age of onset - 30 to 40 years
3. Earliest symptom - dyspnea on exertion
4. Later symptoms - cough, recurrent pulmonary infections, chronic bronchitis
5. Major distinguishing feature - predilection for lower lung

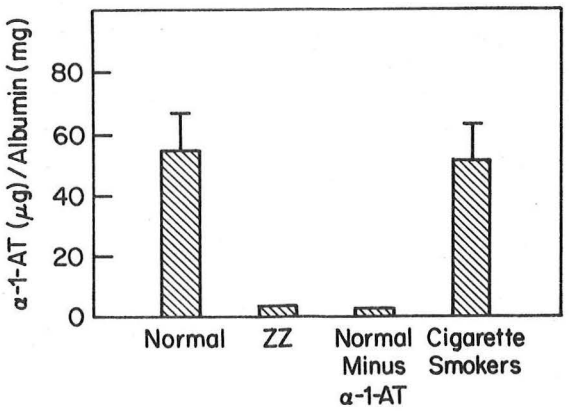
2.

MAJOR DETERMINANTS FOR DEVELOPMENT OF LUNG DISEASE IN α-1-ANTITRYPSIN DEFICIENCY

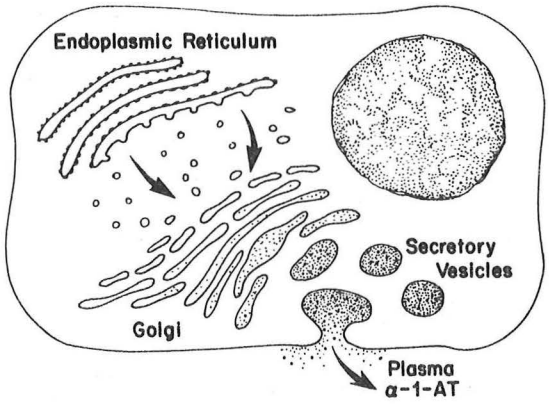
1. Reduced Plasma Level of α-1-Antitrypsin
2. Cigarette Smoking
3. Unknown factor(s)

3.

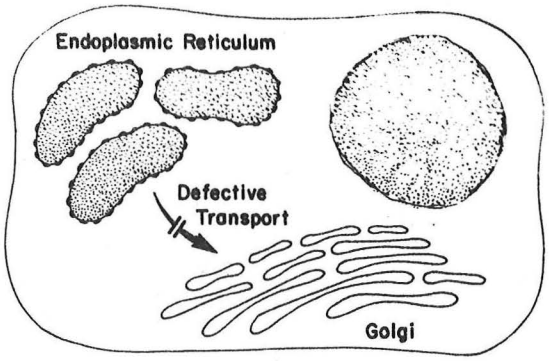
AMOUNT OF α1-ANTITRYPSIN IN LUNG



4. **NORMAL PATHWAY FOR SECRETION OF α-1-ANTITRYPSIN**



5. **ALTERED PATHWAY OF SECRETION OF α-1-ANTITRYPSIN**



6. **HOW DOES SMOKING ACCELERATE PULMONARY DESTRUCTION IN α-1-ANTITRYPSIN DEFICIENCY?**

1. Alveolar macrophages from smokers produce a neutrophil chemotatic factor
   a. ZZ smokers have more neutrophils in lung that ZZ nonsmokers
   b. Elastase burden is increased

2. Smoking inactivates α-1-antitrypsin
   a. MM smokers have same level of α-1-AT in lung as MM non-smokers, but each molecule of α-1-AT is only 60% as active
   b. Elastase burden is increased

V PATHOGENESIS OF LIVER DISEASE

1. **LIVER DISEASE IN α-1-ANTITRYPSIN DEFICIENCY**

1. Spectrum - Neonatal hepatitis, cryptogenic cirrhosis in children and adults, and chronic active hepatitis
2. Present in ZZ individuals but not in null (–) or SZ individuals
3. Neonatal hepatitis occurs in ~ 15% of ZZ infants
4. Emphysema and liver disease are not mutually exclusive in the same ZZ individuals
5. Increased frequency of hepatomas in ZZ and MZ individuals

2. **NATURAL HISTORY OF LIFE EXPECTANCY IN α-1-ANTITRYPSIN DEFICIENCY**

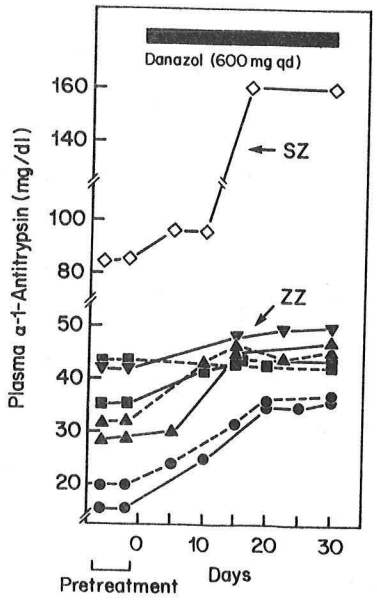
- Swedish study of 246 adults with ZZ genotype
- 141 Males and 105 Females
- 70% had emphysema
- No sex difference in frequency of emphysema
- 70% of Smoking ZZ individuals were dead at age 50, compared to 20% of those who did not smoke

VI THERAPY

1. **APPROACHES TO THERAPY OF LUNG DISEASE**

- Induce Synthesis and Secretion of α-1-AT - Danazol
- Direct α-1-AT Replacement
- Administer Synthetic Inhibitors of Elastase

2.



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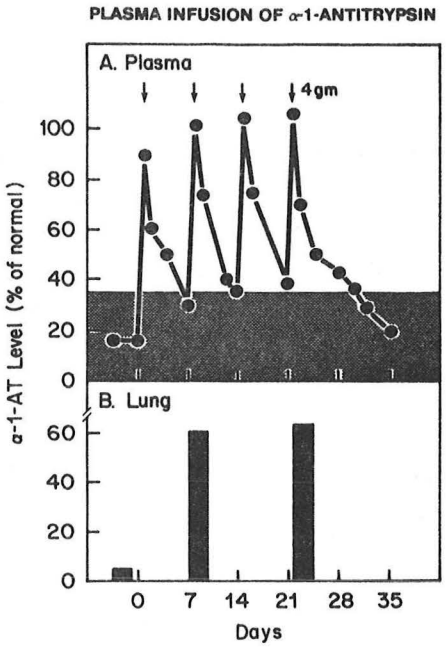
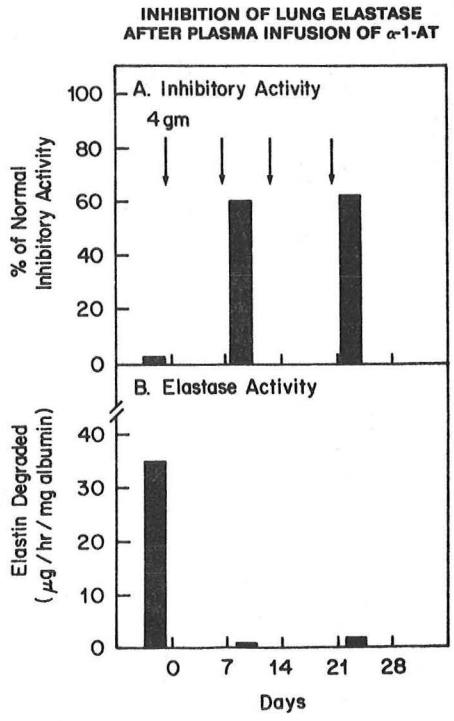

PLASMA INFUSION OF α-1-ANTITRYPSIN
A. Plasma
4 gm
100
80
60
40
20
0
α-1-AT Level (% of normal)
B. Lung
60
40
20
0
0 7 14 21 28 35
Days

4.


INHIBITION OF LUNG ELASTASE
AFTER PLASMA INFUSION OF α-1-AT
A. Inhibitory Activity
4 gm
100
80
60
40
20
0
% of Normal
Inhibitory Activity
B. Elastase Activity
40
30
20
10
0
Elastin Degraded
(μg / hr / mg albumin)
0 7 14 21 28
Days

REFERENCES

I Recent Review Articles

1. Kueppers, F.: Inherited Differences in Alpha$_1$-Antitrypsin. In Lung Biology in Health and Disease: Genetic Determinants of Pulmonary Disease. S.D. Litwin (ed), Marcel Dekker, Inc., New York, pp. 23-74, 1978.

2. Carrell, R.W. and Owen, M.C.: α_1-Antitrypsin: Structure, Variation and Disease. Essays Med. Biochem. 4: 83-119, 1980.

3. Gadek, J.E. and Crystal, R.G.: α_1-Antitrypsin Deficiency. Chapter 64 in The Metabolic Basis of Inherited Disease. J.B. Stanbury, et al. (eds). 5th edition, McGraw Hill, New York. In press, 1982.

4. Lieberman, J.: Alpha$_1$-Antitrypsin Deficiency. Curr. Pulmonary 2: 41-68, 1980.

5. Bohm, N.: α_1-Antitrypsin and its Deficiency States. Path. Res. Pract. 1-16, 1980.

6. Morse, J.O.: Alpha$_1$-Antitrypsin Deficiency. N. Eng. J. Med. 299: 1045-1048 and 1099-1105, 1978.

7. Fagerhol, M.K. and Cox, D.W.: The Pi Polymorphism: Genetic, Biochemical, and Clinical Aspects of Human α_1-Antitrypsin. Chapter 1 in Advances in Human Genetics. Vol. 11. H. Harris and K. Hirschhorn (eds), Plenum Press, New York, pp. 1-62, 1981.

8. Latimer, J.S. and Sharp, H.L.: Alpha-1-Antitrypsin Deficiency. Curr. Probl. Pediatr. 11: 1-36, 1980.

II References of Historical Interest

9. Laurell, C.B. and Eriksson, S.: The Electrophoretic α1-Globulin Pattern of Serum in α1-Antitrypsin Deficiency. Scand. J. Clin. Lab. Invest. 15: 132-140, 1963.

10. Eriksson, S: Pulmonary Emphysema and Alpha 1-Antitrypsin Deficiency. Acta Med. Scand. 175: 197-205, 1964.

11. Fagerhol, M.K. and Laurell, C.B.: The Polymorphism of "Prealbumins" and α1-Antitrypsin in Human Sera. Clin. Chim. Acta 16: 199-203, 1967.

12. Sharp, H.L., Bridges, R.A., Krivit, W., and Freier, E.F.: Cirrhosis Associated with Alpha 1-Antitrypsin Deficiency: A Previously Unrecognized Inherited Disorder. J. Lab. Clin. Med. 73: 934-939, 1969.

13. Jeppsson, J.: Amino Acid Substitution Glu → Lys in α1-Antitrypsin PiZ. FEBS Letters 65: 195-197, 1976.

14. Yoshida, L., Lieberman, J., Gaidulis, L., and Ewing, C.: Molecular Abnormality of Human α1-Antitrypsin Variant (PiZ) Associated with Plasma Activity Deficiency. Proc. Natl. Acad. Sci. USA 73: 1324-1328, 1976.

15. Miller, R.R., Kuhlenschmidt, M.S., Coffee, C.J., Kuo, I., and Glew, R.H.: Comparison of the Chemical, Physical, and Survival Properties of Normal and Z-Variant α1-Antitrypsins. J. Biol. Chem. 251: 4751-4758, 1976.

III Natural History of α-1-Antitrypsin Deficiency

16. Cox, D.W.: New Variants of α_1-Antitrypsin: Comparison of Pi Typing Techniques. Am. J. Hum. Genet. 33: 354-365, 1981.

17. Fagerhol, M.K.: The Genetics of Alpha-1-Antitrypsin and its Implications. Postgrad. Med. J. 52 (Suppl. 2): 73-79, 1976.

18. Langley, C.E., Berninger, R.W., Wolfson, S.L., and Talamo, R.C.: An Unusual Type of α_1-Antitrypsin Deficiency in a Child. Johns Hopkins Med. J. 144: 161-165, 1979.

19. Sveger, T.: Liver Disease in Alpha$_1$-Antitrypsin Deficiency Detected by Screening of 200,000 Infants. N. Eng. J. Med. 294: 1316-1321, 1976.

20. Larsson, C.: Natural History and Life Expectancy in Severe Alpha$_1$-Antitrypsin Deficiency, PiZ. Acta Med. Scand. 204: 345-351, 1978.

21. O'Brien, M.L., Buist, N.R.M., and Murphey, W.H.: Neonatal Screening for Alpha$_1$-Antitrypsin Deficiency. J. Pediatr. 92: 1006-1010, 1978.

22. Sveger, T.: α_1-Antitrypsin Deficiency in Early Childhood. Pediatrics 62: 22-25, 1978.

23. Jeppsson, J-O, Cordesius, E., Gustavll, B., Lofberg, L., Franzen, B., Stromberg, P., and Sveger, T.: Prenatal Diagnosis of Alpha$_1$-Antitrypsin Deficiency by Analysis of Fetal Blood Obtained at Fetoscopy. Pediatr. Res. 15: 254-256, 1981.

24. Hodges, J.R., Millward-Sadler, G.H., Barbatis, C., and Wright, R.: Heterozygous MZ Alpha$_1$-Antitrypsin Deficiency in Adults with Chronic Active Hepatitis and Cryptogenic Cirrhosis. N. Eng. J. Med. 304: 557-560, 1981.

25. Burke, J.A., Kiesel, J.L., and Blair, J.D.: α_1-Antitrypsin Deficiency and Liver Disease in Children. Am. J. Dis. Child. 130: 621-629. 1976.

26. Odievre, M., Martin, J-P., Hadchouel, M., and Alagille, D.: Alpha$_1$-Antitrypsin Deficiency and Liver Disease in Children: Phenotypes, Manifestations, and Prognosis. Pediatrics 57: 226-231, 1976.

IV Recent References Relating to Pathogenesis and Therapy of α-1-Antitrypsin Deficiency

27. Bignon, J., Lenfant, C., Scarpa, G.L.: Emphysema: Past, Present, and Future. Bull. Europ. Physiopath. Resp. 16 (Suppl): 423-428, 1980.

28. Lenfant, C. and Schweizer, M.: Pulmonary Research: Advances and Clinical Implications. Am. J. Med. 70: 1155-1157, 1981.

29. Hunninghake, G.W., Gadek, J.E., Fales, H.M., and Crystal, R.G.: Human Alveolar Macrophage-derived Chemotactic Factor for Neutrophils. J. Clin. Invest. 66: 473-483, 1980.

30. Johnson, D. and Travis, J.: The Oxidative Inactivation of Human α-1-Proteinase Inhibitor. J. Biol. Chem. 254: 4022-4026, 1979.

31. Gadek, J.E., Hunninghake, G.W., Zimmerman, R.L., and Crystal, R.G.: Regulation of the Release of Alveolar Macrophage-Derived Neutrophil Chemotactic Factor. Amer. Rev. Resp. Dis. 121: 723-733, 1980.

32. Eriksson, S.: Proteases and Protease Inhibitors in Chronic Obstructive Lung Disease. Acta Med. Scand. 203: 449-455, 1978.

33. Gadek, J.E., Fells, G.A., and Crystal, R.G.: Cigarette Smoking Induces Functional Antiprotease Deficiency in the Lower Respiratory Tract of Humans. Science 206: 1315-1316, 1979.

34. Harel, S., Janoff, A., Yu, S.Y., Hurewitz, A., and Bergofsky, E.H.: Desmosine Radioimmunoassay for Measuring Elastin Degradation In Vitro. Amer. Rev. Res. Dis. 122: 769-773, 1980.

35. Hood, J.M., Koep, L.J., Peters, R.L., Schroter, G.P.J., Weil, R., III, Redeker, A.G., and Starzl, T.E.: Liver Transplantation for Advanced Liver Disease with Alpha-1-Antitrypsin Deficiency. N. Eng. J. Med. 302: 272-275, 1980.

36. Gadek, J.E., Fulmer, J.D., Gelfand, J.A., Frank, M.M., Petty, T.L., and Crystal, R.G.: Danazol-induced Augmentation of Serum α1-Antitrypsin Levels in Individuals with Marked Deficiency of this Antiprotease. J. Clin. Invest. 66: 82-87, 1980.