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This Week's Citation Classic

Lieberman J. Heterozygous and homozygous alpha$_1$-antitrypsin deficiency in patients with pulmonary emphysema. *N. Engl. J. Med.* **281**:279-84, 1969.
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Measurement of the serum trypsin inhibitory capacity (STIC) in 39 relatives of a homozygous proband for alpha$_1$-antitrypsin (α_1AT) deficiency and in 66 patients with pulmonary emphysema at a Veterans Administration hospital revealed that there is an increased prevalence of both homozygous and heterozygous α_1AT deficiency in patients with pulmonary emphysema. [The *SCI*® indicates that this paper has been cited in over 225 publications since 1969.]

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"The studies reported in this paper were performed while I was a clinical investigator and section chief at the Long Beach, California, Veterans Administration (VA) Hospital. My research had involved studies of blood and tissue proteolytic enzymes, making me especially interested in the reports by Laurell and Eriksson[1,2] of an association between severe alpha$_1$-antitrypsin (α_1AT) deficiency and pulmonary emphysema. A phone call informed me of a 50-year-old patient with far advanced pulmonary emphysema and a strong family history of this disease. I rapidly set up an assay to measure the serum trypsin inhibitory capacity (STIC) in this patient, and, as expected, found a severe deficiency of α_1AT. To my delight, 39 relatives were also available for a pedigree study revealing three with documented pulmonary emphysema and STIC levels in the *intermediate* deficiency range. At that time, only a severe deficiency of α_1AT was thought to predispose to pulmonary emphysema. However, if an intermediate deficiency also predisposed to the development of emphysema, the number of susceptible individuals in the population would increase from 0.04 to five percent. I therefore undertook an investigation of the STIC levels in patients at the Long Beach VA Hospital who were coded as having pulmonary emphysema.

"The manner in which I undertook this study was fortuitous; I obtained names and phone numbers from the charts, then called the patients to come to my laboratory from their homes to provide blood samples. By so doing, I inadvertently avoided acutely ill hospitalized patients with severe infection. α_1AT is an acute phase reactant protein whose serum level fluctuates in response to bodily stresses such as acute infection. Had I utilized acutely ill patients, I probably would not have detected the 15.2 percent with intermediate α_1AT deficiency.

"Some investigators who initially attempted to confirm my report failed because they studied hospitalized patients in whom a rise of STIC to low normal had occurred, or they studied patients with emphysema in old age homes. We had found that α_1AT deficiency is seen mostly in younger patients with emphysema so that a study of patients over 60 years of age would discover few with the deficiency.

"The reasons for this article becoming a *Citation Classic* are: 1) it renewed interest in α_1AT deficiency as a significant predisposing factor to pulmonary emphysema rather than a mere medical curiosity; 2) it initiated an ongoing controversy as to whether the heterozygous, intermediate deficiency state of α_1AT actually predisposed to pulmonary emphysema. Current work indicates that an *acquired* relative deficiency of α_1AT can also develop in heavy cigarette smokers (increases neutrophilic elastase and decreases elastase-inhibitory activity) and contribute to the development of pulmonary emphysema.[3] If so, the lower baseline levels of α_1AT found in heterozygotes would make them even more prone than others to develop a protease-inhibitor imbalance, so that any argument regarding whether or not an intermediate deficiency of α_1AT may predispose to emphysema in smokers is unwarranted. Thus, I believe that this paper still relays an important and practical message: SMOKING IS BAD FOR YOUR LUNGS, ESPECIALLY IF YOU INHERIT AN *INTERMEDIATE OR SEVERE* DEGREE OF α_1AT DEFICIENCY."[4,5]

1. **Laurell C B & Eriksson S.** Electrophoretic α_1-globulin pattern of serum α_1-antitrypsin deficiency. *Scand. J. Clin. Invest.* **15**:132-40, 1963.
2. ----------. Serum α_1-antitrypsin in families with hypo-α_1-antitrypsinemia. *Clin. Chim. Acta* **11**:395-8, 1965.
3. **Janoff A & Dearing R.** Alpha$_1$-proteinase inhibitor is more sensitive to inactivation by cigarette smoke than is leukocyte elastase. *Amer. Rev. Resp. Dis.* **126**:691-4, 1982.
4. **Gelb A F, Klein E & Lieberman J.** Pulmonary function in nonsmoking subjects with alpha$_1$-antitrypsin deficiency (MZ phenotype). *Amer. J. Med.* **62**:93-8, 1977.
5. **Lieberman J, Gaidulis L & Roberts L.** Racial distribution of α_1-antitrypsin variants among junior high school students. *Amer. Rev. Resp. Dis.* **114**:1194-8, 1976.