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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 of an association between severe alpha1-antitrypsin (a1AT) deficiency and pulmonary emphysema. A telephone 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 a1AT. 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 a1AT was thought to predispose to pulmonary emphysema. However, if an intermediate deficiency also predisposes 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 doing so, I inadvertently avoided acutely ill hospitalized patients with severe infection. a1AT 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 a1AT deficiency.

"Some investigators who initially attempted to confirm my report failed because they studied hospitalized patients in whom a rise of STIC to normal had occurred, or they studied patients with emphysema in old age homes. We had found that a1AT 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 a1AT 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 a1AT actually predisposed to pulmonary emphysema. Current work indicates that an acquired relative deficiency of a1AT can also develop in heavy cigarette smokers (increases neutrophilic elastase and decreases elastase-inhibitory activity) and contribute to the development of pulmonary emphysema. If so, the lower baseline levels of a1AT 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 a1AT 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 a1AT DEFICIENCY."**