The Origins of a Concept*

The Protease-Antiprotease Imbalance Hypothesis

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One of the more intense areas of research in lung disease in the past 40 years has been the investigation of mechanisms of lung parenchymal destruction by \textit{in vivo} enzymatic proteolytic enzymes causing pulmonary emphysema and COPD. How this direction of research evolved is worth recounting because it illustrates how quite different experimental approaches done in different parts of the world at approximately the same time can give rise to new conceptual insights that point the way for what were then wholly new directions of research.

The time is May 1958 at a meeting of the Association of American Physicians at the Haddenhall Hotel in Atlantic City. These meetings were annual pilgrimages by young and old alike who belonged to the “young young Turks” (the American Federation for Clinical Research), the “young Turks” (the American Society for Clinical Investigation), and the “old Turks” (the Association of American Physicians). The meeting was not the plenary session of the Association of American Physicians, but was the second day of meetings, where papers were presented to smaller groups in the solarium of the Haddenhall Hotel. On this day, a paper was presented from Lewis Thomas’s Department of Pathology at New York University by Robert McCluskey.\textsuperscript{1,2} The point of the paper was to demonstrate the ability of a crude protease, in this case papain, to degrade cartilage with great rapidity when injected intravenously. A dramatic example of this effect was shown at the meeting on slides showing that the ears of live rabbits could be made to collapse in a matter of hours postinjection through the degradation of cartilage and excretion of chondroitin sulphate in urine (Fig 1). It was also shown that the cartilaginous softening that resulted in ear collapse was reversible in 3 to 4 days, and that the rabbits ears were once again erect after that time, as a result of replenishment of ear cartilage with chondroitin sulphate. Here then was a demonstration of a rather specific effect of an enzyme on cartilage that could be applied to dissect the role of various connective tissue elements to the mechanical behavior of airways in the lung.

While papain could be used to degrade cartilage of the mammalian trachea and bronchi, there were available other enzymes that were reasonably specific to degrade other connective tissue components, such as elastases from porcine or bovine pancreas and collagenase from clostridial organisms. Use of these enzymes in animal lungs demonstrated the rapid potency they possessed to degrade elastin and collagen, as well as cartilage, and the consequences of this degradation in terms of mechanical characteristics of distensibility and rigidity related to the changes in airway morphology.\textsuperscript{3–5}

In 1963, Laurell and Ericksson\textsuperscript{6} published their classic article on the observation that members of families that have low concentrations of serum $\alpha_1$-antitrypsin have a high prevalence of pulmonary emphysema in both male and female family members, and at ages much younger than the usual smoking population that acquired emphysema. Exactly how the inherited deficiency of this serum protein might be related to lung parenchymal destruction was evolving from laboratories in America.

In 1965, Gross et al,\textsuperscript{7} from the University of Pittsburgh, demonstrated that papain and quartz dust degrade lung tissue of rats to produce parenchymal destruction resembling centrilobular and panacinar emphysema. Other enzymes such as $\alpha$-chymotrypsin with quartz dust did not produce emphysematous destruction. Why papain was selected for these studies is not stated, but papain is recognized to have potent elastolytic properties in tissue.\textsuperscript{8}

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By the mid-1960s, Drs. Janoff and Scherer, working at New York University, demonstrated that the normal human neutrophil contained a potent serine elastase. This elastase could therefore act on lung tissue under normal circumstances, by access through the pulmonary vasculature and the normal circulatory cellular constituents traversing the lungs. Later studies were to show that serum from patients with $\alpha_1$-antitrypsin deficiency lacks inhibitory capacity specifically for elastase. Later studies also elegantly demonstrated the morphologic and mechanical effects of elastases in animal lungs to produce a useful model of pulmonary emphysema using papain and neutrophil elastase. Thus, four sets of observations all led to the protease/antiprotease imbalance hypothesis for the development of lung destruction in pulmonary emphysema: (1) a realization of the biological potency of elastases and other elastolytic enzymes for elastin degradation, (2) the identification of a protease that possessed elastolytic properties that could produce an animal model which approximated human emphysema, (3) the recognition that $\alpha_1$ antitrypsin was a major specific inhibitor for neutrophil elastase, and (4) the demonstration that a genetically determined deficiency of serum $\alpha_1$-antitrypsin was associated with the development of pulmonary emphysema at a young age in nonsmokers and smokers.

Needless to say, the protease/antiprotease hypothesis has been a useful scaffold for research over the past 4 decades to define the cellular and biochemical mechanisms underlying pulmonary emphysema. This early work on proteases and the prospect of understanding emphysema through a protease-antiprotease imbalance hypothesis was a strong impetus for the development of new directions of research in lung disease by the newly formed Division of Lung Disease of the National Heart, Lung, and Blood Institute under the direction of Claude Lenfant, and it was part of a landmark task force report in 1972.

At present, it is clear that we still require definition as to which proteases are critical to the development of alveolar destruction in human pulmonary emphysema. Nonetheless, the stage is set for the development of synthetic inhibitors to counteract the effects of neutrophil elastases, as well as new aerosol agents of human $\alpha_1$-antitrypsin or recombinantly produced forms, and matrix components such as hyaluronic acid to protect the pulmonary matrix, specifically lung elastin, from the degradative effect of neutrophil and macrophage elastases. So starting from a series of widely separated laboratory and clinical observations leading to the protease/antiprotease hypothesis as the cause of COPD and pulmonary emphysema, a number of therapeutic agents are likely to evolve.

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21982/)
REFERENCES


