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Emphysema Before and After 1963 Historic Perspectives[a]

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By the end of the 1950s research on emphysema had indeed become very active, but it also appeared to have reached an impasse. The disease had been fairly well characterized in clinical, physiologic, and pathologic terms, but its etiology remained obscure. The atmosphere of resignation was apparent in the J. Burns Amberson lecture presented by Dr. George W. Wright at the annual meeting of the National Tuberculosis Association and the American Thoracic Society in 1963. This lecture was later published[1] with Dr. Jerome Kleinerman, a collaborator of Dr. Wright in the experimental induction of emphysema by inhalation of the oxidant gas nitrogen dioxide, as co-author.

In his lecture Wright systematically analyzed a variety of possible etiologic agents according to the revised Koch postulates. He suggested that the causal agent should: (1) act in *all* cases of emphysema in a logical fashion, (2) be recognizable and definable as a specific thing or condition. and (3) reproduce the disease in other susceptible animals. Wright was unable to suggest a putative candidate as agent. He was most inclined at that time to believe that the injury was of a vasculonecrotic nature, leading to necrosis and destruction of tissue with faulty repair, but he concluded his lecture on a pessimistic note, stating that "The current state of knowledge will not permit any summarization that is meaningful. Obviously, we do not believe the necessary causal agent of emphysema has been established."

Wright, in his lecture, emphasized the destructive element in emphysema. It is important to realize that this feature of the disease was first defined and accepted as late as 1958. The word emphysema is derived from the Greek word for inflation and is still commonly used for a state of inflation by gas or air of any tissue of the body. But emphysema is not only inflation. It is "a condition of the lung characterized by increase beyond the normal in the size of air spaces distal to the terminal bronchiole, either from dilatation or from destruction of their walls." This definition, presented at the well-known Ciba Guest Symposium in London in 1958, was further developed in 1961 by a committee of the World Health Organization. They deleted the criterion of dilatation of air spaces. One year later, the American Thoracic Society[2] excluded altogether the concept of overinflation from the definition of emphysema. Emphysema was now defined as "an anatomic alteration of the lung characterized by an abnormal enlargement of the air spaces distal to the terminal, non-respiratory bronchiole, accompanied by destructive changes of the alveolar walls." This definition is retained today with the single qualification that obvious fibrosis should be absent, and it is applicable to both clinical and experimental emphysema.[3]

These anatomic concepts were largely based on new, improved, and simple techniques for preparing lung specimens in the inflated state thanks to work by Heard and by Gough and Wentworth. Their fixation techniques permitted the assessment of emphysema by the naked eye or with the dissection microscope and allowed selection of appropriate blocks for histologic study.[4,5] The panacinar and centrilobular types had been defined and were easily recognized by the use of these techniques.

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Despite the lack of a comprehensive hypothesis to explain the etiology of emphysema, clinical diagnosis could be made with a reasonably high degree of accuracy. In classical correlative clinicopathologic studies based on the inflation techniques just discussed, Thurlbeck[6] could demonstrate an acceptable correlation between clinically diagnosed emphysema and the severity seen at necropsy. The ability to diagnose emphysema during life depended then, as today, on the combined use of history, physical examination, a correct interpretation of chest X-ray findings, and simple lung function tests. Laws and Heard[7] in England and others had defined the criteria for evaluation of the vascular tree in emphysema in 1962. They wrote: "A reduction in the calibre of the peripheral pulmonary arteries, often with an increased transradiancy of the background, due to reduction in the vascular bed, were the most reliable radiological signs of emphysema." The most significant functional abnormalities have been defined as: (a) expiratory air flow obstruction (FV1), (b) increased residual volume (RV), (c) reduced negative intrapleural pressure, and (d) uneven distribution of inspired air. These abnormalities were all compatible with a reduction in elastic recoil of the emphysematous lung, identified as the most specific physiologic abnormality of emphysema.[8] It is understandable that interest in the connective tissue of the lung began to increase.

Laennec had described the clinicopathologic features of emphysema in 1838, and his concepts regarding etiology came to dominate the field for more than 150 years. One main feature of his hypothesis is that there is a constant association between chronic bronchitis (catarrh) and emphysema. The other essential assumption in Laennec's hypothesis is that partial bronchial obstruction raises the pressure in the lung distal to the obstructed bronchus and that this mechanical increase eventually leads to destruction of the tissue.

In the early 1960s several authors[9] voiced concern about the validity of this hypothesis. Several lines of evidence against Laennec's hypothesis were proposed. First, Lindskog's work on collateral ventilation made it seem unlikely that a marked increase in intraalveolar pressure would occur distal to a small bronchus. Secondly, bronchial asthma is generally not associated with emphysema as shown by the postmortem studies of Gough, and finally, experimental attempts to produce emphysema by obstruction of bronchi had been unsuccessful.

Considering the key role of reduced elastic recoil pressure in emphysema. investigators logically began to look for abnormalities in connective tissue, particularly in elastin. Briscoe and Loring[10] found an increasing amount of elastin in the lung with increasing age. Pierce *et al.*,[11] in their study of the collagen and elastin content in emphysematous lungs, could not find any reduction in total amounts. No quantitative abnormality was detected in elastin, and biochemical methods for detecting a putative qualitative abnormality at that time were unsatisfactory. In retrospect, it could be argued that an abnormality in elastin had to be present for loss of elasticity to have occurred. It was also evident from histologic studies that disruption and disintegration of elastic fibers are a frequent finding in emphysema.[12]

Rare conditions with obviously defective connective tissue had been observed to be associated with emphysema, but there was no general agreement that hereditary factors were important in the pathogenesis of emphysema. Some clinicians thought that observations of unusual familial cases or cases with atypical early onset of emphysema would perhaps give clues to the etiology of the disease. Among several reports I will just mention two that seemed important. Wimpfheimer and Schneider[13] in 1961 reviewed the literature on familial emphysema and presented two new families. Seebohm and Bedell[14] from Iowa City presented 10 cases of "primary pulmonary emphysema in young adults." These authors emphasized that shortness of breath was the first symptom, infections and bronchitis were absent, and breath sounds on the lung bases were weak or absent. Their findings did not fit the traditional Laennec hypothesis and again pointed towards a possible inherent defect in connective tissue, but these authors could not identify any biochemical correlate.

Against this background the discovery of alpha$_1$-antitrypsin (AAT) deficiency and its association with emphysema appeared at exactly the right time. The possibility of proteolytic mechanisms gave a completely new insight into the pathogenesis of emphysema. The early history of AAT deficiency has been reviewed in detail.[15] I will briefly return to some of the initial biochemical and clinical observations and the concepts concerning pathogenesis that these patients generated.

Laurell[15] had refined and improved the paper electrophoretic technique for separation of plasma proteins. Paper electrophoresis had gained increasing popularity among clinicians as a helpful diagnostic tool in many clinical settings. When Laurell first observed the missing α_1 band on the strips, he thought that the samples had been bacterially contaminated and that neuraminidase activity was responsible for the lack of a distinct band. Neuraminidase removes terminal sialic acid residues from glycoproteins and retards their electrophoretic mobility towards the anode. But no other glycoprotein was affected. The rest of the α_1 and all other zones seemed to be normal. We could deduce from data published in 1955 by Jacobsson[15] on the partition of antitryptic activity in serum after electrophoretic separation that the missing fraction corresponded to AAT.

This glycoprotein had been isolated 1 year earlier, in 1962, by Schultze *et al.*[15] at the Behring Werke in Marburg, Germany. The protein had the ability to inhibit trypsin activity and was therefore named AAT. Consequently we suggested the name AAT deficiency for the clinical deficiency state. In our first paper in 1963, we also noted that AAT in deficient sera had slightly decreased mobility consistent with a structural abnormality. We know

today that this change of negative net charge is the result of the glutamic acid → lysine substitution in position 342 in the molecule.

In our report[16] in 1963 we described five patients with this deficiency with varied clinical presentations. Only three had obstructive lung disease with chronic bronchitis, bronchiectasis, and emphysema as the main diagnoses. One young and one elderly woman lacked obvious signs of obstructive lung disease. We concluded, however, that an association existed between degenerative pulmonary disease and AAT deficiency. We suggested that the primary cause was an inborn error of metabolism. The hereditary nature of the condition was rapidly confirmed and the type of inheritance was apparent. The first report of a large family was published in 1964.[17] Two homozygous siblings had severe emphysema. Their children had intermediate AAT levels and were thus heterozygotes and carried only one abnormal allele.

In 1965, I had collected a series of 33 deficient homozygous probands and performed extensive family studies.[18] The probands had been traced from a variety of files and hospitals and were in no way representative of an unbiased population sample. Most patients had come to diagnosis because of lung disease, resulting in a considerable ascertainment bias. The series, however, permitted a delineation of the characteristic clinical features of this new entity. It was evident that, as in other inherited conditions, the degree of clinical manifestation in AA T deficiency was highly variable, ranging from complete absence of clinical symptoms to early onset of obstructive lung disease with severe dyspnea. In my series many patients had early "primary" emphysema and resembled in this respect the cases described by Seebohm and Bedell[14] discussed earlier. Tissue destruction was prominent and bullous transformation frequent. The basal predominance was striking. Vascular markings were lacking at the lung bases, and blood flow was redistributed towards the apices. However, patients with bronchitis and even bronchiectasis were also observed. Postmortem examination in single cases using mounted paper sections according to Gough and Wentworth's method confirmed the general clinical impression that these patients had panacinar emphysema. This assumption was first confirmed by Talamo and associates[19] in 1966. Other typical features were pronounced weight loss and lack of hypercapnia until late in the course of this particular obstructive disease.

The most important observation emerging from this series was the concept of emphysema as the *primary defect* in these patients who often had received clinical diagnoses reflecting secondary events such as bronchitis, asthmatic bronchitis, and even bronchial asthma. I focused on the obligate destructive element of emphysema when suggesting the so-called proteolytic theory for its development, at this time a concept that seemed somewhat naive and oversimplified. Two main sources of proteases, namely, neutrophils, which were known to be sequestered in the lungs, and macrophages, were suggested. The true biologic significance of AAT at that time, however, was unknown, so that any attempt to explain the exact causal mechanism of emphysema in these patients remained speculative.

The proteolytic concept received unexpected support from the independent observation in 1964 by Gross *et al.*,[20] demonstrating the experimental production of emphysema after intratracheal instillation of papain, a plant protease with broad spectrum proteolytic activity. A new era of experimental emphysema had begun.

Gradually, but not unexpectedly, considering the well-established abnormal properties of elastic tissue in emphysema just discussed, it became apparent that neutrophil elastase was the probable key enzyme involved in the pathogenetic process. Although several groups of investigators made significant contributions toward focusing interest in this direction, only a few can be mentioned here. Kueppers and Bearn[21] connected clinical and experimental medicine when they demonstrated the ability of AAT to inhibit proteolytic enzymes from neutrophils. They emphasized a possible role for elastase in the development of emphysema. In agreement with earlier work by Heimburger and Haupt,[22] they showed that AAT was an effective inhibitor of pancreatic elastase. Janoff and Scherer[23] first demonstrated elastase activity in the human neutrophil granulae.

Turino and coworkers[24] found serum antielastase deficiency in patients with AAT deficiency. Ohlsson[25] demonstrated the high affinity of AAT for purified neutrophil elastase, and Lieberman[26] induced lung digestion *in vitro* by leukoproteases that could be inhibited by AAT. We and others emphasized the early loss of elastic recoil force in deficient patients, and Senior *et al.*[27] used purified human neutrophil elastase to produce emphysema in animals. However, the most convincing evidence for the key role of elastase came from the kinetic studies on the association rate between AAT and various serine proteinases. In a series of publications in the late 1970s Travis[28] and coworkers could demonstrate a 1,000-fold more rapid rate of association between neutrophil elastase and AAT than between AAT and trypsin. The most important singular function of AAT, therefore, seemed to be to control the activity of neutrophil elastase.

A second important contribution from the biochemists was the demonstration of the oxidative inactivation of AAT. The presence of a methionine residue in the Pi position of the inhibitory site of AAT led to a number of studies on the oxidation of the reactive site of the protein by use of chemical oxidants, myeloperoxidase, or components in cigarette smoke. Oxidation results in a 1,000-fold loss of antielastase activity and a very prolonged half-time of inhibition. These data led to the development of the "oxidation hypothesis," which

attempts to explain the garden variety of emphysema, that is, that seen in smokers with normal plasma levels of AAT.

The protease-antiprotease hypothesis has certainly provided many new directions in emphysema research. It is nonetheless important to realize that most of the evidence that supports this concept is still indirect. No matter how compelling the AAT deficiency state is as a clinical model, it has been difficult to demonstrate an increased rate of elastin breakdown, elastolysis, in these or other emphysematous patients. In the production of experimental emphysema, the best results are obtained with the use of elastases, but a limitation in interpreting the results is the condensed time course of these models as compared to the human situation. Returning to Wright's[1] revised Koch postulates, elastase appears to be a good candidate for a causative agent because:

1. Elastase may well be the causal agent in *all* cases of emphysema.
2. Elastase is well defined and recognizable. Neutrophil elastase has been demonstrated anatomically by electron microscopic study of elastin fibers in the lung interstitium.[29]
3. Elastase reproduces the disease in susceptible animals.

Hopefully, the current availability of replacement therapy[30] for AAT deficiency will allow demonstration of retardation in the development of emphysema. The result of augmentation therapy would thus be a final proof of the proteolytic hypothesis.

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