CLINICAL CONFERENCE

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Chronic Pulmonary Emphysema and Cor Pulmonale
A Clinical-Pathologic Conference

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DR. C. BRUCE TAYLOR: The case for discussion is not being presented as an unusual case but instead as an example of a common but poorly understood disease process for which there is no very effective treatment. After presentation of the clinical abstract, Dr. Paul will discuss the clinical findings and differential diagnosis. Following this I shall briefly outline the postmortem findings and then we shall discuss certain problems illustrated by this case.

ABBREVIATED CLINICAL ABSTRACT

This 76-year-old man developed increasing dyspnea during the last 10 years of his life. For many years he had a chronic cough, productive of frothy watery material. During childhood a tracheotomy had been performed. He had had lobar pneumonia at age 50. Examination when he was 66 years old revealed a slightly cyanotic, dyspneic man with a pulse rate of 100 and a normal blood pressure. The veins of the neck were normal. The chest was symmetrical, "barrel-shaped," and hyperresonant. There was more marked hyperresonance and decreased fremitus with absent basilar respiratory sounds in the left chest. Examination of the abdomen and extremities was negative. Roentgenograms showed marked bilateral pulmonary emphysema with large bullous blebs in the left lower pulmonary field. Fluoroscopy showed a low diaphragm with poor excursions. During the final 8 years of his life he entered the hospital 10 times with progressively severe symptoms of pulmonary emphysema and its sequelae. Five years before death the vital capacity was 50 per cent of normal; and 2½ years later it had decreased to 30 per cent of normal. The arterial oxygen saturation was 88 per cent. Hemoglobin was 172 Gm. per 100 ml. and erythrocyte count, 5.9 million per mm.³ Supplemental volume and maximal ventilatory rate were markedly reduced. Electrocardiograms were interpreted as showing right ventricular strain. Clubbing of digits became progressively more pronounced. During the last several months of life he developed atrial fibrillation, moderate hepatic and appreciable cardiac enlargement, and peripheral edema. He improved temporarily after digitalization.

Terminally, cyanosis as well as manifestations of right heart failure became conspicuous. Atrial fibrillation persisted and he had a low grade fever. He became stuporous. Mucus collected in his trachea and pharynx. Suddenly on the tenth hospital day he died following massive hemoptysis.

The other clinical and laboratory findings during the course of the patient's illness were not pertinent to the purpose of our present discussion.

DIFFERENTIAL DIAGNOSIS

DR. OGLESBY PAUL: In reviewing the history briefly, there are a few events that probably are not pertinent to his final illness. One of these is the tracheotomy done during childhood. We do not know the reason for this and I doubt whether it was related to the disease from which he died. I would, likewise, doubt the relationship of lobar pneumonia at the age of 50 to his terminal illness. It was probably an isolated respiratory infection, although perhaps a warning of troubles to come and of an increased susceptibility to bronchopulmonary infection. There are certain things one would like to know that are missing in this record. It is stated that he had a chronic cough for many years. I would like to know whether this man

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Supported by The National Heart Institute, National Institutes of Health (H-1630), The Otho S. A. Sprague Memorial Institute, The American Heart Association, and The Life Insurance Medical Research Fund.
was a smoker, as I believe the use of cigarettes in large numbers may bear a relationship to this type of chronic pulmonary disorder.

**Dr. Taylor:** He smoked about 30 cigarettes a day during most of his adult life.

**Dr. Paul:** Decreased tactile fremitus with absent basilar breath sounds was not observed until about 10 years before his death, although it may have been present earlier. I think it is remarkable that he survived as long as he did, particularly in view of the fact that 10 admissions to the hospital were required during the final 8 years of his illness. Quite often, once pulmonary and cardiac failure appear together, the course of the patient is progressively and more rapidly deteriorating.

The evidences of heart disease require some comment. Atrial fibrillation is not a part of the picture of cor pulmonale, and is, I believe, a quite nonspecific complication in people, particularly in the older age group, dying from diverse unrelated causes. It is stated that his heart was not enlarged. His first x-rays showed, as is customary in such cases, a small “teardrop” heart with no evidence in the anteroposterior view of any enlargement, a lowered diaphragm that moved poorly, and evidence of cysts in the left lower pulmonary field. This lack of correlation between roentgenologic evidence of no cardiac enlargement and the finding of right ventricular hypertrophy at autopsy is common. It is difficult by x-ray to detect moderate right ventricular hypertrophy, although the oblique views are more helpful than the anteroposterior view. It is difficult even by electrocardiographic methods to detect lesser degrees of right ventricular hypertrophy. The presence of hepatic enlargement and edema together with the electrocardiographic changes justifies the diagnosis of cor pulmonale with cardiac failure secondary to chronic pulmonary disease. The improvement with digitalis also favors this, although it should be pointed out that digitalis is of rather limited value in cor pulmonale. As in this case, however, it may be helpful in controlling the ventricular rate in atrial fibrillation. His final illness was apparently that of bronchopulmonary infection superimposed on emphysema.

The terminal massive hemoptysis poses a problem. One can think of a large pulmonary infarct or rupture of a bronchial vessel or even associated left heart failure. The last of these seems unlikely in the absence of other evidences of disease involving the left side of the heart; the first 2 are most likely. Massive hemoptysis is not common in emphysema.

The differential diagnosis would appear to be readily dispensed with, since there is no history of bronchial asthma and it seems unlikely that congenital cystic disease of the lung could be important in an illness of this duration at this age. We have little evidence that pulmonary fibrosis existed in view of the x-ray findings of clear lungs and there is no good background or x-ray evidence of bronchiectasis, tuberculosi, Boeck’s sarcoïd, pneumoconiosis, berylliosis, etc. It would also appear that the element of chronic lung infection must have been relatively minor if the multiple admissions were as indicated almost solely for pulmonary failure without clinical signs of pneumonitis.

Finally, it would appear that this 76-year-old man’s worsening course can be explained by emphysema of unknown origin, perhaps related to persistent cough, secondary to prolonged use of tobacco and chronic bronchial infection with decreased pulmonary elasticity and impaired mixing of air in the lungs. I believe that some degree of cor pulmonale existed owing to a combination of pulmonary hypertension from a reduced capillary bed, perhaps with thrombi, and to secondary pulmonary arteriolar sclerosis with narrowing of the pulmonary arteriolar bed. Doubtless a further factor contributing to this was hypoxia, which may lead to pulmonary vascular constriction. Was oxygen given?

**Dr. Taylor:** Yes. The patient was in an oxygen tent almost continuously during his final stay in the hospital.

**Dr. Paul:** The continuous use of oxygen in treating such patients may be harmful because of the appearance of a carbon dioxide narcosis. It is necessary to give oxygen intermittently in order to avoid elevation of the plasma carbon dioxide and a reduction in the pH of the blood. There is a degree of carbon dioxide
elevation that acts as a stimulant and beyond that there is depression of the respiratory center.

Dr. George M. Hass: Do you have any proof that a chronic mild cough due to any cause is productive of pulmonary emphysema? In other words, do you anticipate the development of generalized pulmonary emphysema when a patient with a chronic cough has localized pulmonary lesions such as bronchiectasis or tuberculous?

Dr. Paul: It is my impression that patients who have had a chronic cough associated with excessive use of tobacco have a tendency over the course of years to develop chronic pulmonary disease with 2 components. One is the presence of chronic bronchitis and often pharyngitis and laryngitis, and the second is pulmonary emphysema. This impression is further supported by recent studies that also indicate that not only is carcinoma of the lung related to the use of tobacco, but also that other types of pulmonary disease, not neoplastic in nature, may be related to the use of tobacco.1 What do you think?

Dr. Hass: I have no strong opinion. My impression is that in patients with localized pulmonary disease characterized by mild chronic cough over a period of years, the pathologist seldom finds uniformly distributed pulmonary emphysema of the type found in patients in whom a diagnosis of senile emphysema is made. Furthermore, pathologists often find little pulmonary emphysema in young patients who have had chronic cough with severe bronchial asthma for many years. Something more than chronic cough is required to produce emphysema.

Dr. Paul: I am not suggesting that all chronic emphysema is due to tobacco and the often associated chronic cough. How do you account for the fact that so many heavy smokers end with the clinical picture this patient possessed?

Dr. Hass: To this end, it is generally conceded that further study of harmful effects of inhaled products arising from combustion of tobacco and other materials is indicated. At least some of these products are certainly irritating to the respiratory mucosa.

Dr. Schweitzer: I would like to ask Dr. Paul whether the clinical diagnosis of emphysema has any particular meaning in terms of the pathologic anatomy of the disease. When you say the patient has emphysema, what is your idea of the pathologic anatomy of the disease? Is it a uniform process and is it always the same from patient to patient? I refer especially to clinical conditions loosely designated as generalized arteriosclerosis, senile emphysema, and other similar diagnoses that have no specific meaning, physiologically or anatomic.

Dr. Paul: The term chronic senile emphysema implies that it is a generalized disease. Where emphysema is limited to an area distal to local bronchial obstruction, one would expect focal emphysema unless so-called compensatory emphysema in the remaining unobstructed parts of the lungs complicates the picture. In the present case where there is clinical evidence of bilateral pulmonary disease with diminished alveolar mixing and a typical "barrel chest" with auscultatory findings characteristic of a diminished respiratory exchange, I think it is fair to say that this is a generalized disease. To the clinician the word "emphysema" denotes a disease in which there is a reduction of functioning alveolar units associated with rupture of alveoli and an increase in size of alveolar spaces. Also, there is usually a reduction in the over-all volume of the capillary bed and probably a reduction in elasticity of the lung as a whole.

Question to Dr. Paul: What did you mean by speaking of bleeding from a bronchial vessel?

Dr. Paul: This man evidently had a massive hemoptysis. It is possible that this might have resulted from rupture or erosion of a bronchial vein. This has been described in mitral stenosis and it is conceivable to me that it might occur in cases of emphysema in which the bronchial circulation may be increased.2

Dr. Taylor: Liebow3 has recently described injection studies of bronchial and pulmonary veins in a large series of normal and diseased
human lungs as well as lungs from cases with congenital cardiac disease and canine lungs with experimentally altered pulmonary circulations. He found striking increases in bronchial venous channels and their collateral branches in all cases of advanced pulmonary emphysema, whereas, in other diseases such as mitral stenosis, chronic bronchiectasis, and tuberculosis, these changes were relatively infrequent and, when present, were less pronounced. Normally, the proximal “true” bronchial veins drain venous blood from major and second order bronchi into the azygos system. There are capillary anastomoses between the pulmonary veins and these proximal “true” bronchial veins; they may have little function in normal lungs. The more peripheral bronchial veins, including all bronchial veins from third order bronchi outward, drain into pulmonary veins through demonstrable anastomoses and this blood returns to the left atrium. It appears that in emphysema there may be stasis or partial obstruction of pulmonary venous channels with a resultant dilatation and enlargement of the pre-existing small venous channels anastomosing bronchial with pulmonary veins and a concomitant enlargement of both proximal and peripheral bronchial veins.

DR. TRUEHEART: Could not these new venous routes alter normal cardiac physiology?

DR. TAYLOR: It is probable that these dilated bronchial veins with their anastomoses may carry oxygenated pulmonary venous blood back to the azygos veins and right heart, causing a left-to-right shunt. The emptying of this already oxygenated blood into the right heart would increase its work load.

DR. BROWN: Has anyone implicated these bronchial venous changes in the genesis of cyanosis, seen so frequently in advanced pulmonary emphysema?

DR. TAYLOR: Yes. Liebow has suggested that, in far-advanced pulmonary emphysema with cor pulmonale, systemic venous pressure may exceed left atrial pressure, resulting in a right-to-left shunt through engorged bronchial veins and their anastomoses to pulmonary veins. This right-to-left shunt might be a factor in the systemic arterial oxygen desaturation and hypercapnia frequently observed in these cases. I would also like to point out that Liebow observed no correlation of overdevelopment of the bronchial arterial system with an expanded bronchial venous system.

DR. ARMIN F. SCHICK: How accurate are methods for diagnosing emphysema, especially in its earlier and locally distributed phases?

DR. TAYLOR: During the past 15 years a number of ingenious methods and instruments for evaluation of pulmonary function have been developed. Comroe has reviewed these advances. It is my impression that with newer equipment and methods one can get a more definite picture concerning pulmonary function in any one case and that more objective criteria for separate evaluation of pulmonary ventilation, diffusion, and circulation have been established. These function tests are very useful for verifying and studying in a more quantitative way the earlier cases of pulmonary emphysema that on the basis of x-ray and clinical findings are presumed to have the disease. I do not believe that these new techniques have been sufficiently developed to aid significantly in detection of cases earlier than with the usual clinical and x-ray findings. Comroe and Fowler have developed an excellent rapid test in which expired air, following inhalation of a single breath of oxygen, is analyzed by a Lilly nitrogen meter and believe it is as suitable as x-ray studies for mass screening purposes. Bronchospirometric studies are now being done on individual lungs and lobes of lungs. Studies of this nature should prove to be of value in the study and detection of local disease.

DR. PAUL: Our respiratory physiologists tell me that a clinical diagnosis of emphysema can be confirmed by pulmonary function tests that indicate a sizable reduction in the maximum breathing capacity, a less striking reduction in vital capacity, prolongation of expiration, an increase in the residual volume, and increased nitrogen in the alveolar sample after 7 minutes of oxygen inhalation or by the “single-breath” method mentioned above. The more severe cases will show a lowering of the systemic arterial oxygen level and an increased carbon dioxide content. These studies can be done in most hospitals and are decidedly helpful. In
most instances they simply confirm an impression obtained clinically.

**DR. TAYLOR:** Dr. Paul, I wonder if you would make a few comments about the efficacy of treatment in prevention of progression of early cases of this disease?

**DR. PAUL:** This is a disease of unknown origin. I do not believe there is any specific treatment. However, one can relieve the symptoms and perhaps slow the progress of the disease by prevention and treatment of infection, avoidance of tobacco, administration of drugs that produce bronchodilatation, promotion of drainage of secretions, and use of breathing exercises to encourage the optimal exchange of air. The last of these has limited value, as does the use of abdominal supports; but both may in some instances result in better diaphragmatic excursions. The use of steroids, such as cortisone, has not been consistently beneficial although some reports are enthusiastic. The use of carbonic anhydrase inhibitors is most helpful in patients with chronic carbon dioxide retention and cor pulmonale who require diuresis.

**DR. SCHWEITZER:** If diminution in elasticity of the lungs is a primary factor in progression of the disease, I do not see how any of the stated measures, except those concerned with eliminating inflammation could have much value.

**DR. HASS:** There was obliteration of both pleural cavities by adhesions in this case, so that pulmonary elastic recoil would seem to be limited, anyway. Dr. Taylor, where is the effective locus of pulmonary elastic recoil? There are many cases with excellent pulmonary function despite complete fusion of the visceral and parietal layers of the pleura of both lungs.

**DR. TAYLOR:** Effective pulmonary elastic recoil is mainly dependent upon a well-functioning total pulmonary elastic network with continuity of all elastic fibers; smooth muscle of bronchi and bronchioles has a lesser role. I do not believe that obliteration of pleural cavities plays a role in the development of diffuse pulmonary emphysema. Normally these cavities are only potential spaces. After a chest cage relaxes during expiration, pulmonary elastic recoil may occur as well with adherent pleural surfaces as when they are not adherent. With inspiration and expiration the visceral pleural surfaces slide over the parietal pleural surfaces. With pleural adhesions or obliteration of pleural cavities, this loss of mobility of the visceral pleura might result in some local abnormal tensions leading to focal emphysematous lesions but I would not expect it to be of any significance in the development of diffuse pulmonary emphysema.

**AUTOPSY FINDINGS**

**DR. TAYLOR:** The anatomic lesions were almost classical. I shall outline them briefly so that we may devote more time to a consideration of 2 fundamental problems illustrated by this case: 1. What is known about the pathogenesis of pulmonary emphysema? 2. What is our present knowledge concerning pulmonary hypertension, pulmonary arteriosclerosis, and cor pulmonale?

On gross examination, both lungs showed marked diffuse emphysema with numerous subpleural blebs. The emphysema was symmetrically distributed and affected all lobes equally. There was slight uniform dilatation of all bronchi. The pleural spaces were obliterated by fibrous adhesions.

The source of the massive hemorrhage was a saccular arteriosclerotic aneurysm of the aortic arch that ruptured into one of the emphysematous blebs and filled part of the lungs and tracheobronchial tree with blood. This was an unexpected finding and evidently unrelated to the cardiac and pulmonary disease.

The heart weighed 510 Gm. and showed conspicuous right ventricular hypertrophy and dilatation. There was moderate left ventricular hypertrophy. Severe arteriosclerotic and atheromatous changes were present throughout the pulmonary arterial system. Stigmata of chronic pulmonary as well as chronic systemic venous congestion were observed.

Microscopic examination of the lungs showed a tubular form of mild bronchiectasis with conspicuous hyaline thickening of the basement membranes of bronchi. There was mild active chronic inflammation of the mucosa of the large and medium sized bronchi. A great deal of dark granular pigment was scattered throughout the interalveolar and interlobular interstitial tissues. Considerable fibrosis accompanied the pigmented deposits but there was no specific relation between the increase in fibrous tissue and the dilatation of alveoli, many of which had defective walls that led to the formation of large saccular blebs consisting of intercommunicating alveolar spaces. The accumulation of nonsilicate pigment of the type found here probably represents a result rather than a cause of the primary disease.
process. In addition, there were very severe arteriosclerotic changes in the small and medium-sized arteries. The lumina of these vessels were rather uniformly reduced in caliber by conspicuous concentric fibroelastic thickening of the intima with occasional small atheromatous plaques. The findings are consistent with the diagnosis of senile emphysema, chronic bronchitis, bronchiectasis, pulmonary fibrosis, anthracosis, and pulmonary arteriosclerosis associated with pulmonary hypertension and cor pulmonale.

**DISCUSSION**

**Dr. Schick:** What is the current idea as to the pathogenesis of diffuse pulmonary emphysema of this type?

**Dr. Taylor:** There is an extensive literature concerning altered pulmonary function in emphysema and the application of various complex tests of pulmonary function for diagnosis of pulmonary emphysema. Unfortunately, there has not been a concomitant series of studies related to the pathogenesis of the disease. Consequently, we now have many complex methods for diagnosing a condition that is poorly understood in terms of etiology and pathogenesis.

I believe that the structural and functional integrity of pulmonary elastic tissue should receive more consideration. There are many conflicting opinions concerning elastic tissue in pulmonary emphysema. I would like to spend a few moments illustrating a probable explanation for these conflicting opinions. The central drawing in figure 1 illustrates the relatively large ovoid 3-dimensional structure of a sacculus alveolaris. This drawing is based upon material described by Miller who studied reconstructions of serial sections of air spaces from 2 normal lungs (1 infant and 1 adult). The studies of the 2 normal lungs by Miller are the only reported studies of pulmonary elastic tissue that I think are adequate. As seen in the drawing, delicate elastic fibers surround and enclose the spheroid alveoli and adjacent structures in a loose meshwork of elastic tissue. Continuity of elastic fibers and fixation at points of termination are mandatory for proper function of these meshworks. A conventional (5 μ) microscopic section is illustrated in the upper photomicrograph of figure 1. It has been stained to show elastic tissue. The elastic tissue in this section appears as small black dots or short, “rod-like,” cross or diagonal sections through elastic fibers. The zone between the 2-horizontal lines in the central drawing represents the small amount of tissue sampled by a conventional microscopic section such as that shown in the upper photomicrograph.

**Dr. Paul:** Have not many pathologists been satisfied with this method of studying elastic tissue?

**Dr. Taylor:** We do not believe it is possible
to evaluate the structural integrity of a pulmonary elastic network by taking random standard microscopic sections through its 3-dimensional network of interconnected and functionally integrated elastic fibers. All one has in conventional microscopic sections are several cross sections through elastic fibers that actually make up an ovoid meshwork like a small, loosely woven basket. There could be many breaks in continuity in the elastic meshwork and none might be apparent in a conventional microscopic section, even though it is specially stained for elastic tissue. Attempts at evaluation of elastic tissue by study of random 5–10 μm sections seem useless to me.

**Dr. Schick:** Do you have any better suggestions?

**Dr. Taylor:** I think so. The lower photomicrograph illustrates pulmonary elastic tissue isolated by a method that Dr. Hass described in 1942. He originally employed it for chemical isolation of arterial elastic tissue in its structurally unaltered state, and used it to study the changes in aortic elastic tissue associated with increasing age. We are currently applying this technic in a study of elastic tissue in normal and emphysematous lungs. The section illustrated in the lower photomicrograph of figure 1 has a thickness of 2 mm, and gives an excellent 3-dimensional picture of connecting functionally integrated elastic fibers and fibrils that make up the elastic meshwork or basket-like structure of alveoli, bronchi, bronchioles, and intrinsic vessels. Laborious reconstruction of serial sections may represent a better method than the chemical method mentioned above, but in the past 60 years there have been only 2 reconstruction studies. Certainly Dr. Hass' chemical method for isolation and study of elastic tissue is a practical method for 3-dimensional evaluation of thick segments of pulmonary tissue. We should be able to study a good series of normal and diseased lungs in a relatively short period of time and determine whether pulmonary emphysema results from a change in the quality, quantity, continuity, or tensile strength of elastic tissue. It may even be possible to demonstrate limitation of its function due to splinting of the elastic networks by inelastic collagenous scar tissue.

**Dr. Paul:** Does this approach imply that all forms of emphysema have the same pathogenesis?

**Dr. Hass:** No, Dr. Paul, there are several types of emphysema, some with well-established causes but I am assuming that our interest centers about the type known as senile emphysema that is present to some degree in every aged person. It tends to be more severe when complicated by an indolent chronic bronchitis of the type found in this case. Relaxation of pulmonary structure and loss of its capacity to return in the elastic sense to its normal volume seem to be important in the pathogenesis. These changes may be attributed to a decrease of elasticity of the elastic tissue of the lungs, to a relaxation of elastic tissue, or to the imposition of new fibrous splinting elements that prevent elastic recoil or its proper integration. Chronic inflammation of bronchopulmonary structure certainly favors the progression of these changes and actually may occur secondarily after some emphysematous changes have developed.

**Dr. Paul:** We are willing to admit these possibilities, but wherein are they related to a process of aging—a process of senility?

**Dr. Hass:** Certain parallelisms may be drawn between changes that might be occurring in the lungs and changes that occur elsewhere in elastic and fibroelastic tissues during advancing age. We are familiar with the increasing elongation and tortuosity of arteries in the aging person. Actually, senile arteriosclerosis is characterized not only by atheromatosis but also by the deformation of walls of arteries due to irregular dilatation, elongation, and tortuosity. An analysis of this effect of age was made some time ago to determine whether the changes were due to a loss of elasticity of elastic tissue. When aged arteries that were abnormally tortuous and dilated were subjected to procedures that extracted all components of the arterial wall, except elastic tissue, some interesting observations were made. The first observation was that as soon as all nonelastic components were dissolved away during extraction, the artery retracted to its youthful length and caliber.

**Dr. Schick:** Do you mean that the elastic
tissue of the rigid arteriosclerotic senile aorta still is elastic when it is freed from other tissues?

Dr. Hass: Elasticity of an artery or aorta, so far as elastic recoil of its elastic tissue is concerned, is as good in an aged person as in a child. Furthermore, if isolated elastic tissue of an artery or aorta is extended and its capacity to retract to its resting dimension is measured, aged elastic tissue exhibits essentially the same elasticity as elastic tissue of the newborn child. Elasticity of pure elastic tissue of an aged artery, therefore, is identical with that of a youthful artery.

Dr. Schweitzer: Does this mean that the senile changes in the aorta occur primarily in the extraelastic tissues?

Dr. Hass: No, Dr. Schweitzer. Further study of isolated elastic tissue from aged arteries indicated that there was a difference between this tissue and the elastic tissue of youthful vascular walls. The principal difference was that elastic tissue of aged arteries did not have, per unit cross-sectional area, as much tolerance to a breaking load as elastic tissue isolated from young arteries. This seemed referable to 2 changes. One was the formation of discontinuities in aging elastic membranes and networks. The other change was due to imperfections often with calcification in aging elastic networks that preceded formation of discontinuities. Thus, when tension was placed upon an aged network of arterial elastica, it had to be supported by less functionally intact elastic tissue than in the young network because of discontinuity of structure among the various membranes and fibers. This indicated that elongation of arterial walls and their distention with increasing age were probably secondary to deteriorative factors that led to the formation of discontinuities in elastic tissue. A careful study of these foci of real and impending discontinuity showed that an increase in the amount of fibrous tissue occurred around them. The increase in fibrous tissue was in the nature of splints composed of collagenous fibers and the amount of splinting of the foci of discontinuity increased with increasing distention and elongation of the vessel. This seemed to be a reaction on the part of cells of the arterial wall to form enough fibrous tissue to make up for the deficiency of elastic tissue. This increase in fibrous tissue led to a fixation in extension of the weakened elastic network. Therefore, the decrease in elasticity of the aged arterial wall was due to imposition of fibrous restraints on the elastic tissue and not to any loss of elasticity of elastic tissue or any appreciable decrease in its quantity.¹⁰

Dr. Schick: Are you suggesting that something similar to this may not only reduce the elasticity of the lungs but also lead to loss of tone, relaxation, and fibrosis of alveolar walls in senile emphysema?

Dr. Hass: We have adopted the view that loss of elasticity in the lung in the senile form of emphysema may be referable to changes similar to those that affect the elasticity of the aging arterial wall. In the lung, however, elastic tissue is not restricted to vascular walls but is spread throughout the interstitial tissues in alveolar walls, around bronchial walls, and in the walls of bronchi. We assume that any quantitative study of elastic tissue would not be useful because it has been of little value in the analysis of changes in senile arterial walls. A study designed to remove all tissue except elastic networks from pulmonary structure with subsequent analysis of the isolated elastic tissue in 3 dimensions by carefully selected physicochemical methods would doubtless furnish some information of value that could be correlated with symptomatology of patients. Methods for making such a study are available.³ Some modifications may be necessary in applying them to pulmonary tissue.

Dr. Taylor: Do you believe that one aspect of the pathogenesis of loss of elasticity might be related to the influence of hypercholesterolemia on the processes of regeneration and repair of fibroelastic tissues?

Dr. Hass: A word may be said about the possibility. There is a fibroelastic intimal repair following injury to the media of arteries. The repair of fibroelastic tissue in the hypercholesterolemic rabbit is sluggish in comparison with that which occurs following identical medial damage in normocholesterolemic animals.¹¹ Therefore, the hypercholesterolemic animal is less able than a normal animal to
repair arterial injury by formation of fibroelastic tissue. The regulation of formation, repair, and regeneration of elastic tissue under any condition is unknown. Furthermore, factors that lead to deterioration of elastic tissue in various diseases are poorly understood. Perhaps experiments designed for the specific purpose of defining relations between hypercholesterolemia, calcification, and degeneration of elastic tissue should be done.

**Dr. Paul:** What about the relation between the structural changes that you described and the circulation in the lungs?

**Dr. Hass:** There is a speculative matter seldom referred to in discussions of this kind. That is the possible interference in the exchange and diffusion of gases as a result of deteriorative and secondary sclerosing changes in the supporting tissues of the alveolar wall. Changes in the interstitial tissues may greatly influence the movement of gases. This might be a much more important factor in pulmonary emphysema and pulmonary hypertension than is generally recognized. There can be no question that the circulation of the blood and lymph suffers from the interstitial changes occurring in senile emphysema.

**Dr. Paul:** Are you referring to the reduced size of the capillary bed available to pick up oxygen?

**Dr. Hass:** I am referring to the modification in anatomic structure as a result of deformation and rupture of elastic tissue with secondary interstitial fibrosis. I am assuming that normally there is a perfect relationship between capillary, alveolar wall, and the flow of gases in the alveolar space. At least, a perfect relationship would be necessary for optimal gaseous exchange. If the alveolar wall happened to be modified by an increment of collagenous tissue secondary to defective elastic tissue and restricted elasticity, the mobility of blood and exchange of gases might be seriously impaired even though anatomic changes seemed insignificant.

**Dr. Paul:** You do not then believe that the size of the capillary bed may be critically reduced?

**Dr. Hass:** I am not certain that a limited reduction in the volume of the capillary bed would be important. An entire lung can often be removed without incapacitating the patient appreciably. I have never been able to correlate the so-called overdistention of alveolar spaces or reduced elasticity of the lung with the variable and often severe symptomatology of patients with senile emphysema. There is doubt in my mind that the difficulty is entirely mechanical. It is certainly not quantitatively related to the reduction of the number of capillaries, as judged microscopically.

**Dr. Paul:** Is not a fundamental difficulty the lack of ability to ventilate the alveoli?

**Dr. Hass:** There must be some reason, however, for the difficulty that you propose. The difficulty might lie within tissues of the alveolar wall and alveolar ducts. In other words, for a proper exchange of gas to occur there should be a proper anatomic and functional relationship of all participating elements. The changes in pulmonary structure associated with emphysema in the elastic and structural sense may create inefficient arrangements in the alveolar wall. There is, at least in some cases, a change in the collagenous content with an increased rigidity, relaxation, and discontinuity of the walls of alveoli. This often is associated with a change in the relation between the capillaries in the wall and the gases in alveolar spaces. Whether this is primary and significant or secondary and insignificant is unknown.

**Dr. Taylor:** Respiratory physiologists do employ methods for separate evaluation of pulmonary ventilation, diffusion, and circulation. The mixing of practically insoluble gases, such as nitrogen and helium, is employed for ventilation studies. Carbon monoxide is used for evaluating diffusion and nitrous oxide for measurements of circulation.\(^6\)

**Dr. Schweitzer:** Do you believe that the function of the capillary bed of the lungs is closely related to the composition and function of the fibroelastic tissues that surround the capillaries?

**Dr. Hass:** It is not reasonable to take any other view. The importance of the structure that supports vascular endothelium is becoming more significant in analysis of capillary function. The opinion is often expressed that all capillaries are alike. This is not true. All capil-
laries may look alike but all capillaries are far from being alike.

**Dr. Paul:** In what sense, anatomically, physiologically, or histologically?

**Dr. Hass:** Current views with respect to capillary beds differ from older views that were rigidly mechanistic even to the point of allocating a standard bore size and permeability to all. Actually, permeability of all capillary beds is not the same. Functions of capillaries are not only governed by capillary endothelium but also by the environment in which the capillary endothelium finds itself. This environment is a very complex and integrated one in most organs, so that it would seem unwise to look upon all capillary beds as having identical properties or even responding to the same stimuli. Hence, in a consideration of the syndrome of senile emphysema with pulmonary hypertension and cor pulmonale, strict attention should be paid to changes in the tissues around the capillaries rather than to reduction in the number of capillaries alone.

**Dr. Schick:** I gather that you would prefer that more work be directed toward an analysis of pathogenesis of emphysema rather than the results of emphysema as defined by study of the flow of blood and gases.

**Dr. Hass:** The problem of senile pulmonary emphysema can be approached by other means than studying the composition and flow of gases and blood. These matters would seem to be secondary and unrelated to the pathogenesis. If the pathogenesis lies in a primary bronchitis with secondary changes in the alveolar structure, as implied by Dr. Paul, the problem of prevention of the disorder and its progression is well defined at once. If the pathogenesis lies in a primary modification of interstitial tissue of the lung with secondary bronchial, vascular, and cardiac changes, further study can be directed to determine the cause of the modification and reasons why it does not follow the same quantitative pattern in all aging people. A study of the latter type should not require elaborate respiratory laboratories, at least in the initial stages of the investigation. Dr. Taylor is not entirely in agreement with me on this area. Perhaps he could prove his point by a little discussion of the pulmonary circulation.

**Dr. Taylor:** Figure 2 diagrammatically illustrates the dual circulation of the lungs. In normal lungs about 99 per cent of blood passing through the lungs is from the right side of the heart and flows through the pulmonary arteries at a mean pressure of 13 mm. of Hg; the remaining 1 per cent is from the left side and flows through the bronchial arteries at a mean pressure of 100 mm. Hg. Note that most of the bronchial arterial bed fuses with the pulmonary arteriolar and capillary bed and that in the lung these 2 arterial systems have a common venous return. Both the lungs and the liver have dual blood supplies. Normally both organs have well balanced, high flow with low pressure and low flow with high pressure inflow vascular beds that fuse at a capillary and precapillary level. In chronic diseases with scarring, both organs have a propensity to develop hypertension in the high flow, low pressure vascular bed.

**Dr. Paul:** Are we to believe that involvement of the vascular bed of the lung by scar tissue is the cause of pulmonary hypertension in senile emphysema?
Dr. Taylor: I will answer this question by bringing out a few points concerning our present knowledge of changes in the pulmonary circulation accompanying some chronic pulmonary diseases. This subject has been discussed more extensively previously. The 2 arterial systems in the lung with widely divergent pressure and flow characteristics are interconnected arterial systems. Capillary anastomoses as well as small arteriolar anastomoses between them have been demonstrated in normal lungs. Anastomoses as large as 500 μ in diameter between pulmonary arteries and veins and large anastomoses between bronchial and pulmonary veins have also been demonstrated. There are several teleologic reasons for these various vascular anastomoses and there may be a number of unknown important reasons for their presence. In chronic pulmonary disease, however, the overdevelopment of the anastomoses between the bronchial and pulmonary arteries into large vascular fistulae appears to alter seriously the pulmonary circulatory dynamics. It appears that, as obliteration or constriction of small arteries, arterioles, and capillaries develops in chronic pulmonary disease, these shortcircuiting vascular fistulae enlarge. It has been suggested, and there is good evidence to support it, that pulmonary hypertension is due to a markedly increased bronchial arterial flow (with a mean pressure of 100 mm. Hg) that enters the pulmonary arterial bed (mean pressure, 13 mm. Hg) through enlarged anastomotic channels and elevates its pressure.

Dr. Edwards: Do you think that the overdevelopment of the bronchial arteries and their collateral anastomoses serves any useful purpose?

Dr. Taylor: Collateral blood channels are of value when they supply a new route for delivery of blood to a capillary bed. When they, as in the enlarged bronchial-pulmonary arterial anastomoses, act only as vascular fistulae through which previously oxygenated systemic arterial blood flows in a circle and returns to the left heart and also leads to an elevation of the pressure in pulmonary arteries, they are not useful collateral blood channels. I have not been able to appreciate the value of the development of these shortcircuiting vascular fistulae and have raised the question as to whether man would not be better off if the bronchial arteries were separated from the systemic circulation.

Dr. Trueheart: Are not the mechanisms concerned in the pathogenesis of pulmonary hypertension known and, if not, do you have any views on this subject?

Dr. Taylor: Although there is not yet no experimental evidence to support it, it is tempting to implicate the vasoconstrictive response of the pulmonary arteriolar and capillary bed to hypoxia and the diametrically opposite (vasodilatory) response of the bronchial arteries to hypoxia in the genesis of pulmonary hypertension. The above physiologic responses have been well documented in several animals and in man; they have been reviewed elsewhere. As an example, in pulmonary emphysema, occlusive and constrictive lesions in small peripheral arteries and arterioles may result from the combined effects of spasm from hypoxia and superimposed vasculitis and thrombosis from infection or other causes. Periods of spasm of the pulmonary vascular bed may cause sufficient ischemia to result in decreased resistance to infection and vasculitis with subsequent thrombosis and vascular scarring. It is likely that, if pulmonary arteriolar walls are not subjected to bouts of hypoxia and spasm, they are much less susceptible to development of vasculitis and thrombosis. For obstructive vascular disease to occur, periods of vascular spasm and chronic infection probably both have to be present. The bronchial arterial system dilates during hypoxia and with this type of response the bronchial arterial system appears to be protected from ischemia of the wall, vasculitis, and thrombosis. The many-fold increase in the size of bronchial arteries and the rate of flow of blood through them in emphysema and other chronic pulmonary diseases imply that this arterial system thrives in the presence of hypoxia and chronic infection.

Dr. Edwards: Is there a definitive treatment for pulmonary hypertension?

Dr. Taylor: If pulmonary hypertension is due to chronic disease in one lobe or one lung,
with vascular changes in the diseased tissue causing hypertension in the entire pulmonary arterial bed, resection of the diseased tissue might correct pulmonary hypertension if it has not been present too long and caused diffuse irreversible arterial changes. There are some very interesting studies on a case surgically treated for unilateral bronchiectasis.\textsuperscript{12}

\textbf{Dr. Edwards:} How about patients with diffuse pulmonary disease such as this case? Is there any definitive treatment for cor pulmonale in cases of this type?

\textbf{Dr. Taylor:} There is no definitive treatment at present but I believe that, sometime in the future, cases with diffuse pulmonary disease and cor pulmonale may be treated by separation of the bronchial arteries from the systemic circulation. The bronchial arteries would not become obliterated but would continue to supply blood that entered them from pulmonary arteries through their anastomoses. Several years ago it was demonstrated in this laboratory that lungs and bronchi of both dogs and man survive and function normally after bronchial arteries have been completely severed from the systemic circulation.\textsuperscript{16} Since anastomoses between bronchial and pulmonary arterial systems are much larger in diseased lungs, there should be an abundance of blood entering the bronchial arteries from the pulmonary arteries for the nutrition of bronchi.

\textbf{Dr. Brown:} Do you think that severance of the bronchial arteries from the aorta would be well tolerated by patients?

\textbf{Dr. Taylor:} I have pointed out that in both dogs and man, with normal bronchopulmonary vascular beds, severance of the bronchial artery from the aorta was accomplished without moment. However, I think that more experimental work is indicated. Unfortunately, we as yet have not studied experimental animals with chronic pulmonary disease and cor pulmonale for evaluation of this problem.

\textbf{Dr. Clasen:} Would the pulmonary hypertension and the strain on the right heart be corrected?

\textbf{Dr. Taylor:} We will have to wait for a definite answer but it seems probable that separation of enlarged bronchial arteries from the aorta should reduce the elevated pulmonary arterial pressure. Not only would the strain on the right ventricle be reduced, but also a rather large burden on the left side of the heart would be eliminated. The large volume of already oxygenated blood flowing through the bronchial arteries then through the smaller pulmonary arteries and the pulmonary veins back to the left atrium would no longer be able to traverse this apparently useless circular flow pattern.

\textbf{Dr. Clasen:} Do you think that separation of bronchial arteries from the aorta might influence the rate of development of pulmonary arteriosclerosis?

\textbf{Dr. Taylor:} If separation of the bronchial arteries from the aorta resulted in a significant decrease in the mean pulmonary arterial pressure, this procedure might very well have a favorable influence upon the obliterative arterio-atherosclerotic changes that affect the pulmonary arteries and arterioles in emphysema. In all cases of long standing pulmonary hypertension, regardless of the causative mechanism, we find considerably more pulmonary arteriosclerosis and atherosclerosis than is found in comparable cases without pulmonary hypertension. Undoubtedly at least some of the pulmonary arteriosclerotic changes are due to the pulmonary hypertension.

In summary, we have presented and discussed a case demonstrating chronic pulmonary disease with senile emphysema, chronic bronchial disease, cor pulmonale, and terminal rupture of an arteriosclerotic aneurysm of the aorta. Some of the clinical and physiologic implications suggested by this case have been presented.

\textbf{REFERENCES}


Since the demonstration of the pulmonary hypertensive effect of an acute and temporary period of anoxia in animals and in man, considerable interest has been focused upon the influence of anoxia when it is constant in nature. Persons living at an altitude of 14,900 feet had a moderate degree of pulmonary hypertension, which was more accentuated in permanent than in temporary residents. Since the cardiac output was normal, it could be eliminated as a cause for the hypertension. Pulmonary vasoconstriction was unlikely because autopsies performed on healthy men killed accidentally revealed marked dilatation of the vascular bed of the lungs. Prolonged anoxia caused polycythemia with an increase in pulmonary blood volume. An elevation in the blood viscosity was believed to be the ultimate cause of the increased pulmonary vascular resistance.
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Circulation. 1957;15:757-769
doi: 10.1161/01.CIR.15.5.757

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