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Chapter 7

Measurement of Pulmonary Function

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For well over a century, systematic anatomical observations of the lung, both gross and microscopic, have formed the main basis for attempts to understand the mechanism of altered function consequent to diseases of this organ. During most of this time, the tools of the pathologist were superior to those of the clinician and the physiologist, but there was often an unsatisfactory correlation between that which the pathologist could see or feel and the evidences of altered function of the lung. The discrepancies were both quantitative and qualitative, the clinical manifestations often seeming too minor for the obvious tissue changes and vice versa. In the first half of the century, and particularly during the past 25 years, physiologists, physicists and biochemists, as well as anatomists and electron microscopists, have provided us not only with a better understanding of the way in which the normal lung functions, but also have given us practical methods for measuring these functions during life, and to some degree even after death. As a consequence, the correlations between alteration of tissue and function now seem more rational, although some mystery still remains. I have been assigned the task of discussing methods for measuring pulmonary function, presumably from the point of view of those things that would be most appropriate for the pathologists to be aware of. The sheer bulk of this sort of information precludes an attempt at a detailed discussion of technic. Some of this sort of information has already been presented in this Monograph and additional will follow.

Several detailed discussions of methods for estimating the physical functions of the respiratory apparatus as a whole have been published in recent years. Alterations of function consequent to disease have been considered in depth in some of these publications. Since time is limited, I can mention only some of the ways in which important physical functions of the lung can be measured. Unfortunately, I must be arbitrary in my choice of material, and omissions should not be construed as being of lesser importance. The neuromuscular system of the respiratory apparatus and its nervous system control are not discussed, although these parts are as essential to normal function of the system as is the lung itself.

One can visualize the lungs as two conduits, through one of which flows a gas and the other a complex liquid, the blood, propelled by separate pumps. The gas

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and liquid phases meet on either side of a very thin barrier which, although strong enough to contain the blood, offers so little opposition to the diffusion of gases that their partial pressures are virtually equal in the two phases by the time that the blood is gathered in the postcapillary veins even under conditions of maximum metabolic demands and rate of capillary blood flow. The tubes are surrounded and bound together in an orderly and intimate fashion by connective tissue containing a third set of conduits, the lymphatics. About the lymphatics we know little as regards measurement of flow, and for this and other reasons of ignorance they are not discussed further.

The movement of gas and blood within their respective conduits is dependent chiefly upon the head of pressure impelling the fluid and upon the resistance to flow posed by the geometry of the conduits. It is important to recall that resistance to flow of these fluids varies by the 4th power of the radius of the conduits during laminar flow and is even more influenced by the radius during turbulent flow. Hence what may appear visually to be a minor change in the radius of a conduit may actually cause a large impediment to flow.

In normal persons at the end of expiration, the lungs contain a measurable volume of air and blood and the conduits are patent. It is easy to understand that the cartilage and thick walls of the larger bronchi and blood vessels prevent collapse of these tubes, but the smaller, distal conduits, having thin walls, will collapse by their own weight. Since at the end of expiration the intrathoracic pressure is atmospheric within the bronchial system, one can only conclude that the air tubes are held in their cylindrical shape and prevented from collapse either by a subatmospheric peribronchiolar pressure or by external supports acting as guy wires. Actually, both factors play a role. The same supporting forces apply to the vascular structures. The concept that the patency of these conduits is dependent in part on the tension of the supporting structure itself is of great and not always recognized importance since alteration of the supporting structures may have a profound influence on the radius of the conduits and therefore the resistance to fluid flow within them.

There are a number of ways in which one can group the various methods for measuring pulmonary function. Since the purpose of external respiration is to modify or "ventilate" the venous blood so as to produce an optimal partial pressure of oxygen (pO_2) and carbon dioxide (pCO_2) in the blood leaving the lungs, one can evaluate the integrity of the lung in terms of how well the optimum concentration of these gases is maintained at the rate of transpulmonary blood flow required to satisfy metabolic conditions in the resting and exercising state. For years, the common method for evaluating the degree of oxygenation of blood was to note the presence or absence of peripheral cyanosis and, for the proper removal of carbon dioxide, to measure the CO_2 combining power of venous blood. While it is true that in some kinds of lung disease abnormalities are revealed by these two methods, it has long been obvious that they are inadequate procedures. A more direct way to determine the effectiveness with which the blood is ventilated is to measure not only the hemoglobin saturation but also the pO_2 and pCO_2 (oxygen and carbon dioxide tensions) and hydrogen ion concentration of a sample of systemic arterial blood. These measurements some-

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times must be obtained not only during rest but also during the stress of exercise. Abnormalities of these measurements often suggest the nature of the alteration of function. For example, if the pO_2 is low and the pCO_2 is high, it is virtually certain that the lung is being underventilated with respect to perfusion, whereas, if the pO_2 is low and the pCO_2 is also low, a number of circumstances may exist, including not only regional ventilation-perfusion abnormality but also anatomical shunts or disturbed transtissue diffusion. When these measurements are within the limits of normal, it *cannot* be assumed that abnormalities of function within the lung are absent. That extensive disease which obliterates the pulmonary vascular bed in some regions of the lung may occur but produce no alterations of the peripheral blood gases is obvious.

A second group of measurements is aimed at elucidating the mechanisms underlying the cause of abnormal values of the peripheral arterial blood gases. Let us consider the methods utilized to discover the mechanism responsible for producing a subnormal pO_2 and hemoglobin oxygenation. When this occurs, it is obvious that some blood has passed from the right ventricle into the left ventricle without traversing an area where the pO_2 of the gas phase is adequate to produce a normal arterial pO_2. Such so-called venous admixture can occur in a number of ways.

Actual anatomical bypass, as, for example, in a direct pulmonary artery-pulmonary vein communication, is easy to understand as a cause of venous admixture. A number of methods are available to establish that such venous admixture is in fact caused by anatomical bypass. For example, under these circumstances, the inhalation of pure oxygen will have little or no influence on that moiety of blood which is bypassing the lung. Hence venous admixture or subnormal hemoglobin oxygenation of arterial blood will persist and be relatively little influenced during the inhalation of a pure or high oxygen mixture. The alveolar-arterial pO_2 gradient during high oxygen breathing will become much larger. In a manner dictated by the shape of the hemoglobin dissociation curve, the alveolar-arterial pO_2 difference will become smaller when a lower than atmospheric oxygen tension is breathed. If the bypass is discrete, such as in arteriovenous aneurysm, an angiogram will often reveal the mechanism of the venous admixture.

Low peripheral arterial pO_2 may also be caused by generalized alveolar hypoventilation with respect to metabolic activity. Methods are available to estimate the mixed alveolar pO_2 and under such circumstances it will be found low and there will not be an elevated alveolar-arterial pO_2 gradient. In these circumstances one will also always find an elevated arterial pCO_2, and it is rarely necessary to examine more than the peripheral arterial blood in order to recognize generalized alveolar hypoventilation as the cause of hypoxia.

Most commonly, however, only a portion of the total number of alveoli is hypoventilated. Under these circumstances arterial blood perfusing the hypoventilated alveoli emerges with a low pO_2 and a high pCO_2. It mixes with blood emerging from alveoli that are usually hyperventilated so that blood coming from these is normal with respect to pO_2 and subnormal with respect to pCO_2.

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The final mixture of arterial blood is likely, therefore, to have a subnormal arterial pO_2 and a normal arterial pCO_2. Other methods are available for the recognition of this condition which is generally spoken of as an alteration of the ventilation-perfusion (*Va:Qc*) relationship. Under these circumstances and in contrast to a direct shunt, inhalation of a higher than atmospheric oxygen tension mixture for a period of 10 to 15 min. will usually raise the hemoglobin saturation to normal. There are more direct but less easily quantitated measurements for demonstrating the presence of altered ventilation-perfusion relationships. I have reference here to the use of radioactive materials. With counters suitably arranged over the lungs, it is possible to demonstrate that gases introduced to the lung via the blood stream are removed at an uneven rate with respect to various areas of the lung and also that gases introduced via the air stream are absorbed at an uneven rate with respect to the various areas of the lung.

A third mechanism causing inadequate oxygenation of the blood occurs when the nature of the membrane separating the gas from the blood phase is altered and impedes the movement of gas across this boundary. Quite obviously, the membrane may impede diffusion consequent to a change in thickness of its components. Less obvious but equally real is the impairment caused by a reduction in the total surface area of the membrane. It is understandable that the speed with which capillary blood flow occurs may be an important factor in whether or not the blood emerging from the venous end of the alveolar capillary has been fully oxygenated. In general, the transit time in the capillaries is such that under normal circumstances no gradient persists between the alveolar and blood gases for oxygen or CO_2 by the time the blood reaches the end of the capillary. If, however, the total number of capillaries is greatly reduced by disease, it is conceivable that blood may rush so rapidly through the capillaries as to be oxygenated inadequately even though the alveolar oxygen tension is within the limits of normal. Methods are available for measuring diffusion, but it should be borne in mind that these methods are far from perfect and certain of them, as for example, the carbon monoxide methods, are subject to the influence of things other than the membrane itself, for example, the capillary blood volume and the nature of the red cell and the total hemoglobin. Because of the great difficulty in handling the technic for measuring the diffusion of oxygen, more measurements have been made using carbon monoxide as the diffusing gas. Although considerable reservation must be maintained as to the true quantitative interpretation of much of the diffusion data, a rather large body of important and useful information has been obtained.

With respect to arterial hypoxia, three generalizations seem appropriate. First, whereas at one time it was thought that diffusion impairment was the most common cause of arterial hypoxia, it is now recognized that alteration of the ventilation-perfusion ratio is the most common. Second, although pure examples of anatomical bypass, diffusion impairment and ventilation-perfusion abnormality undoubtedly do occur, it is common to find them coexisting. Third, it is oftentimes difficult with the methods at hand to be certain that one is dealing

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chiefly with one or the other of these types of impairment. This is so not only because of the fact that they tend to coexist, but also because of inadequate techniques.

Hypercapnia or an abnormally high pCO_2 is with rare exceptions assumed to be a manifestation of alveolar hypoventilation. A large number of alveoli must be involved for this to occur. It is possible, too, that alveoli are hypoventilated but also hypoperfused in a proportionate manner and therefore the $\dot{V}/\dot{Q}$ relationship remains proper, and from such a combination there is no consequent elevation of the arterial pCO_2.

Direct measurements of alveolar ventilation can be accomplished using either such foreign gases as helium or hydrogen or by breathing pure oxygen and measuring the rate at which nitrogen is rinsed out of the alveoli. These methods monitor the rate at which nitrogen or helium is rinsed into or out of the lung spaces without regard to whether or not blood is being properly ventilated. Such methods are aimed primarily at determining that certain portions of the lung are ventilated at a slower rate than are other portions. The radioactive gases can be used in a similar manner. It is apparent from the above that we have quite good methods for discovering the underlying mechanisms of inadequate ventilation of the blood as it traverses the alveolar system.

Something needs to be said about a slightly different circumstance, namely, those anatomical conditions which destroy the vascular bed or interrupt blood flow through the bed in alveoli which continue to be ventilated. Pulmonary embolization offers the striking examples of this phenomenon. Under these circumstances, we have ventilation without blood perfusion or what might be spoken of as "dead space" ventilation. Methods are available for detecting this. For example, one can determine whether or not there is a gradient such that the arterial pCO_2 is abnormally higher than the expired air pCO_2. It is apparent that the air which enters alveoli that are not perfused fails to pick up carbon dioxide and hence will dilute the alveolar gas from the perfused areas and cause the mixed expired air to be lower in pCO_2 than is the arterial blood. The same thing can be achieved utilizing discrete deep lung (alveolar?) samples obtained by catheters introduced into the nonperfused or markedly underperfused portions of the lung. Various radioactive techniques and cineangiographic techniques aim at elucidating the same pathologic mechanism.

Thus far we have concerned ourselves with whether or not the blood as it leaves the lung has been properly ventilated, and it is quite obvious that even in the presence of a considerable amount of tissue alteration the blood can be properly ventilated. The next group of measurements has to do with the fact that the ventilation of blood requires movement of a blood and gas stream. Motion of these two streams requires muscular effort and the expenditure of energy, and it is appropriate to ask whether or not disease alters the relationship between fluid motion and the energy that is required to accomplish it. It is obvious that as the metabolic rate is increased from the resting through various stages of exercise blood flow through the lung must also be augmented. If blood flow is augmented, ventilation must also be increased; otherwise, the blood will be underventilated and the pO_2 and pCO_2 of the peripheral blood will be ab-

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normal. Since in normal people pO_2 and pCO_2 change but little over a wide range of physical activity, it is apparent that there are large reserves both for blood and gas flow augmentation. It is equally obvious that, if disease produces an impediment either to blood or to gas flow, reserves are available that can be utilized in order to maintain a blood and gas flow proper for the existing metabolic state but it is achieved at a higher cost in terms of the energy used for pumping the fluids. Methods exist for exploring these situations.

The simplest is in reference to the blood circulation. Under normal circumstances one can double or perhaps even triple the transpulmonary blood flow with little or no elevation of pulmonary artery pressure by reason of the fact that there is recruitment of new vessels and, in addition, an increase in the radius of the vasculature at the point of highest resistance to flow. There are a number of disease states involving the lung which interfere with the capacity for vessel recruitment and for increase of the radius in the high resistance areas with the result that when metabolic demands are increased and cardiac output is increased the pulmonary artery pressure must be elevated and right ventricle work must increase in order to maintain the needed rate of transpulmonary blood flow. Because the pulmonary vascular system has such a tremendous ability to accept an increase of flow without an increase in pulmonary artery pressure, diseases which narrow or destroy blood vessels or interfere with the dilation of the arterioles can, depending upon the location, exist to a rather major degree before pulmonary artery hypertension develops. For this reason, measurement of the pulmonary artery pressure at rest and even during exercise is a tool which commonly will not show abnormalities until the volume of the total lung and vascular bed which is influenced by disease is great. It is of the greatest importance to point out that alveolar hypoxia consequent to underventilation causes a physiologic narrowing of the precapillary arterioles which will not be seen with ordinary autopsy technics. A small lesion obstructing a major bronchus will influence a large volume of lung tissue via the mechanism of alveolar hypoventilation and consequent vascular constriction in the hypoventilated area. Because of the ameliorating effect of the large reserve of the pulmonary vascular bed, it is important to know whether or not distal segments of the vascular bed have been obstructed without causing pulmonary artery hypertension. Numerous methods already mentioned exist for this purpose and include such things as angiography, mapping of distribution of radioactive materials and measurement of the expired air or regionally obtained air for gradients of CO_2.

Measurement of the interference with gas flow in the tracheobronchial system is somewhat more complex. Gas enters the tracheobronchial system by reason of the fact that it is enlarged during inspiration and leaves by reason of the fact that the system is diminished in volume during expiration. In addition to this mass movement of air into and out of the lung, there is diffusion of gases across a gradient or gas interface in the most distal portions of the lung. Contraction of the respiratory muscles during inspiration enlarges the thoracic cage and by reason of intimate contact through a liquid layer enlarges the surface of the boundaries which enclose the lung. As the lung surface moves peripherally in a centrifugal fashion, a pull is exerted upon all of those surfaces

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within the lung having direct connection with the outside air via the tracheobronchial tree, and these surfaces move *in an outward direction* also. Contraction of the inspiratory muscles, therefore, moves the chest wall, the lung surface and all of those surfaces lining the air conduit that are capable of motion at the pressures applied. In addition, the muscles must supply the energy needed to move air from the mouth down through the conducting system. We can therefore speak of muscular contraction overcoming the resistance to airflow and the resistance to stretch of those elements that have the capacity for elastic recoil in addition to overcoming the resistance of those viscous materials in the lung and chest wall that have no power of elastic recoil. The process is reversed during expiration, elastic recoil aiding rather than opposing the muscle force.

It is possible to measure airflow resistance and both the elastic and viscous resistances of the lung. The elastic resistance is spoken of as compliance and is of course measured under static conditions, whereas airflow and viscous resistance are measured under dynamic conditions. It can be readily appreciated that tissue alterations leading to the accumulation of secretions within the tracheobronchial lumen or thickening of the lining of this lumen or leading to narrowing of the lumen because of interference with supporting structures would lead to an increase in airway resistance. It is equally important to realize that the radius of the tracheobronchial tree is increased by the act of inspiration and that to some degree the narrowing of the lumen consequent to disease can be partially overcome by carrying out the act of breathing in a position of deeper inspiration. We have good methods for measuring airway resistance in the lung as a whole. Airway resistance can also occur locally so that the distal segment of lung is hypoventilated with respect to the remainder of lung where there is a normal resistance to flow. Methods for recognizing the presence of this condition exist, but the actual measurement of this sort of regional or localized resistance is difficult.

Methods also exist for measuring compliance. In this respect it must be recalled that compliance as ordinarily spoken of is a function not only of the elastic recoil of the distended tissue, but also of the volume of the tissue that is distended since the measurement conventionally is expressed in terms of cubic centimeters of enlargement per centimeter of transpulmonary pressure. Since disease often changes the volume of the lung, care must be exercised in interpreting compliance changes as of necessity representing alteration of the tissue components of the lung that is being distended.

While these methods for measuring airway resistance and compliance are being utilized more and more, especially by those interested in a better understanding of tissue alteration, they are somewhat cumbersome. Older methods designed to measure maximum volume change in the lung and maximum rates of flow which can be achieved during maximum contraction of either inspiratory or expiratory muscles are more commonly used. It is recognized that the result of such measurements is a function of the available muscle force and the resistance to that force, and that the result does not differentiate between these two factors. Nevertheless, such measurement as the total lung volume and its various

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components, the measurements of rate of airflow such as the maximum voluntary ventilation, maximum midexpiratory flow rate, the fast expiratory flow volume in 1 sec., etc., are commonly used in the study of people during life in an effort to recognize and determine quantitatively the impediment to the movement of air through the tracheobronchial system. Most of these same measurements can be carried out on the lung after it has been removed from the body.

Two other phenomena deserve study by measurement, and in both of these we have only the most rudimentary knowledge and understanding. The first of these has to do with the way in which the diseased lung accommodates to tissue alteration in an effort to maintain the proper ventilation of the blood. For example, in areas that are hypoventilated by reason of narrowing of the air conduit, there is a lessening of blood perfusion so that in some circumstances there is virtually no blood perfusing the hypoventilated segment, all of it going preferentially into the well ventilated areas. We know that this is related to alveolar oxygen tension. It is also known that areas that are underperfused tend rather rapidly to be less ventilated and this appears to be related to alveolar pCO_2. It is also known that, when some segments of lung are underventilated but maintain normal perfusion, other segments of the lung become hyperventilated both by the mechanism of the shunting of air from the badly ventilated area to the well ventilated area and also by an augmented total minute ventilation. Through this mechanism the arterial pCO_2 is maintained in a near normal state. We also know that in certain disease states the respiratory patterns both as to rate and depth and the total ventilation per minute are markedly altered. This is obviously a mechanism whereby controlling signals in some way reach the respiratory centers, and it is only reasonable to assume that they originate somewhere, at least in part, within lung tissue. This last phenomenon can be demonstrated and measured to some degree by relating minute ventilation to oxygen uptake. This ratio is the so called oxygen ventilation equivalent. It has other names and other modes of expression. Exercise studies have demonstrated that in the exercise state approximately 25 liters of air are respired when the oxygen uptake is at the rate of 1 liter per min., and this relationship is linear over a very wide range of augmented activity. In some disease states the ventilation may be as much as 3 times this high for every liter of oxygen uptake. When ventilation is disproportionately high relative to metabolic activity, the work of breathing is likewise disproportionately high and the sensations associated with breathing tend to be inappropriate.

The second poorly understood aspect needing study, particularly as to development of methods for measurement, has to do with a very important facet of respiration as a whole and it is commonly influenced by lung diseases. I have reference here to the comfort with which respiration is carried out. In the resting state, the general act of respiration occurs at a subconscious level, but, as the act is augmented during exercise, we finally reach a condition described as breathlessness. Breathlessness is a normal phenomenon about which we know little but which is likely to be a very complex matter. We know that it is related in some way to length tension phenomena and force of muscle contraction and also to activity of the respiratory center. It seems also to be influenced by the

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state of the cerebral cortex. Breathlessness is generally considered to be normal when it occurs under circumstances that seem appropriate or normal. When breathlessness occurs during inappropriate circumstances, as for example under ordinary conditions at rest or when doing very minor stints of exercise, it is then considered to be an abnormal sensation indicative of some abnormality of function. Abnormal breathlessness or dyspnea is one of the most common evidences of abnormality of the respiratory system and of disease of the lung. A start in the direction of measuring this phenomenon has been made along the lines of determining whether or not the *work of breathing* is appropriate at the time that abnormal breathlessness develops. This in turn, of course, is related to airway resistance and to compliance and viscous resistance of the lung and chest wall, as well as to whether or not the volume of air being breathed is appropriate for the circumstance. More in the way of measurements needs to be developed in this general field.

Before going on to examples, it is appropriate to indicate that the lung is a structure far more complex than its portrait as seen in terms of mechanics and optics would suggest. There is ample evidence that it is a considerable chemical factory. The biochemists and histochemists will doubtless have much more to tell us about this in the near future. In addition, it is an important part of the reticuloendothelial system and its precise functions in this respect are as yet poorly understood. Likewise, the lung contains within its substance the mechanism for keeping itself cleared of foreign materials and for responding in a defensive manner to irritating materials. It has a self-protective mechanism built in. Through measurements we have begun to arrive at a reasonable understanding of the mechanics and physics of the process of gas transfer and ventilation of the blood. The future holds a great challenge in terms of measurements of other important functions of the lung.

The following case presentations are illustrative of some of the relationships between measurement of pulmonary function and lung pathology.

CASE 1—PULMONARY ARTERY OBSTRUCTION

A 47-year-old male who as a young man was a cross country ski champion of international caliber began to experience unusual breathlessness on exertion 1 year before this study. The severity of symptoms progressed until he became so breathless on climbing one flight of stairs that he had to stop to rest. Ease of fatigue and substernal pain on exertion also developed during the past year. A chest roentgenogram (Fig. 36) shows normal lung parenchyma but large lung root shadows. The electrocardiogram indicated right ventricle hypertrophy. A lung biopsy (Fig. 37) shows marked thickening of the wall of virtually every medium and small sized artery seen. No abnormality is visible in the remainder of the lung parenchyma. Right heart catheterization during rest revealed marked pulmonary artery hypertension without elevation of the "wedge" pressures (Table 6) at a low normal cardiac output. The absence of interference with the mechanical action of the lung and with flow and distribution of air is revealed by the normal lung volumes, lung rinsing and maximum voluntary ventilation as noted in Table 7. The fact that the hemoglobin was subnormally saturated with

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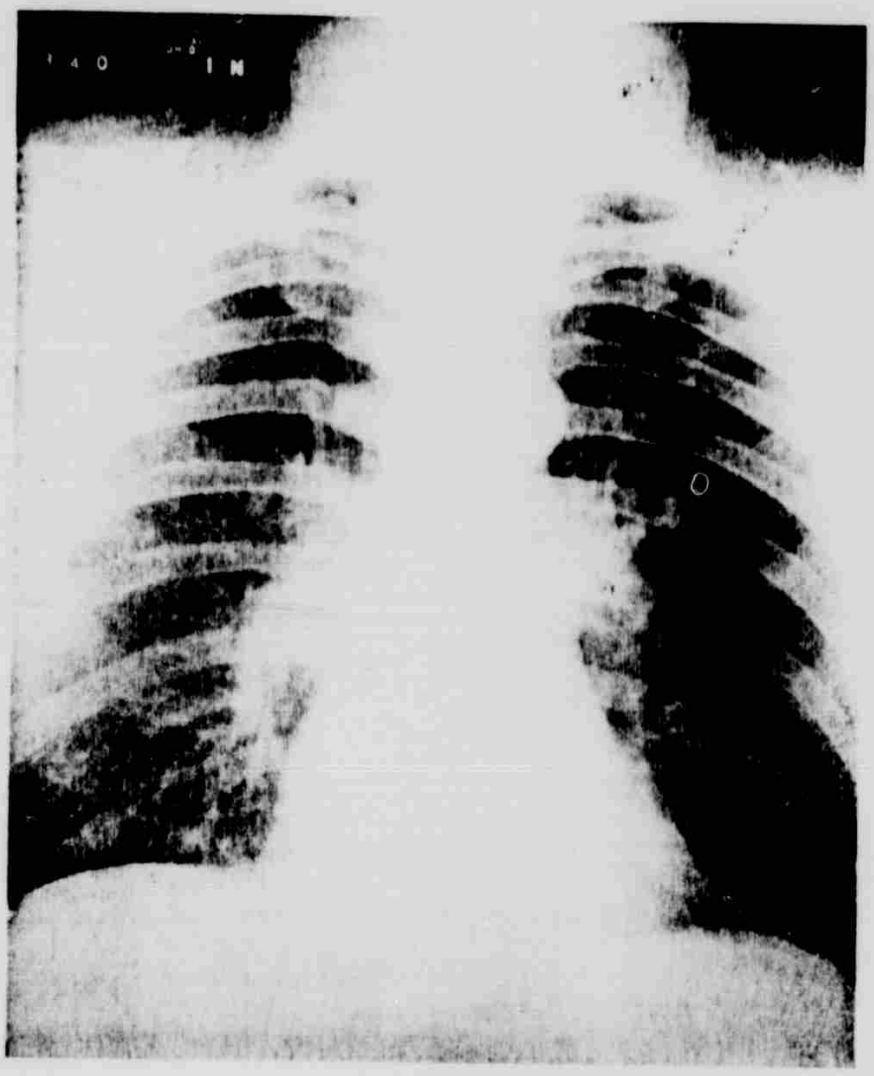


FIG. 36. Case I: pulmonary arterial obstruction. Roentgenogram of chest. Lung root shadows are large. The pulmonary parenchyma appears normal.

oxygen during its passage through the lungs is indicated by the low hemoglobin saturation of the arterial blood shown in Table 8. One can infer from the subnormal pCO_2 of the arterial blood and from the abnormally large alveolar-arterial oxygen gradient that the incomplete oxygenation of the hemoglobin arises either because of an actual anatomical bypass or a membrane defect. The fact that the unsaturation persists when a high oxygen (pO_2 of 300 mm. Hg) mixture is respired and the alveolar-arterial oxygen gradient decreases when a low oxygen mixture is respired (Table 8) indicates the cause of the hemoglobin unsaturation is not at the alveolar membrane level but is some kind of an ana-

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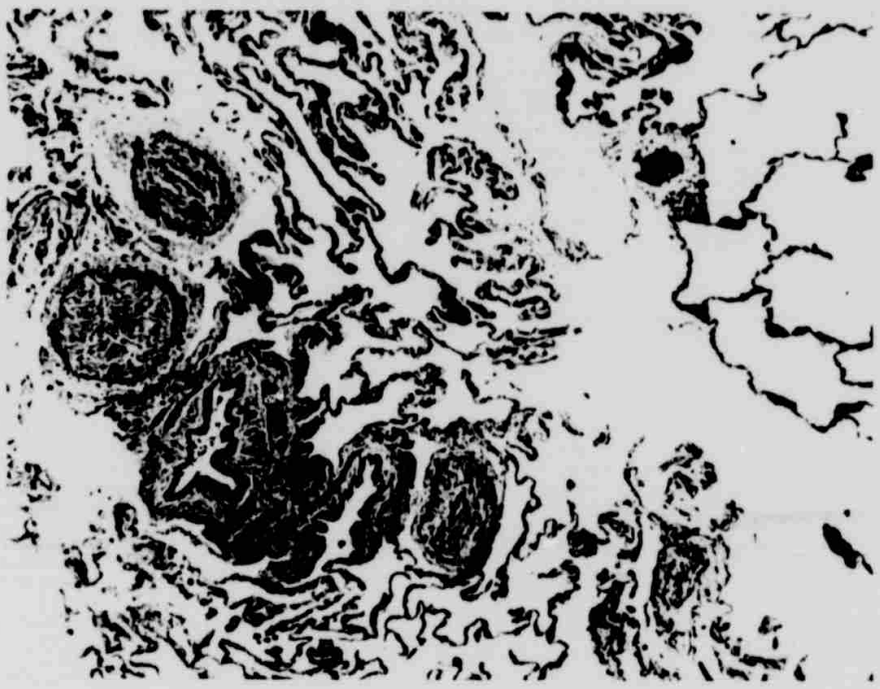


FIG. 37. Case I: biopsy specimen of lung tissue. Marked thickening of wall and narrowing of lumen in medium sized and small pulmonary arteries.

TABLE 6. CASE I. RIGHT HEART CATHETERIZATION DURING REST

Pulmonary artery	100/40 mm. Hg
Right ventricle	90/0-4 mm. Hg
Right atrium	2-4 mm. Hg
Pulmonary wedge	8 mm. Hg
Cardiac index	2.3 liters/min.

TABLE 7. CASE I. PULMONARY MEASUREMENTS

	Determined	Predicted
Total lung capacity	8.25 liters	7.03 liters
Vital capacity	5.70 liters	5.03 liters
Residual volume	2.55 liters	2.00 liters
N_2 rinsing curve	3 liters	<6 liters
Maximum voluntary ventilation	165 liters/min.	153 liters/min.

tomical bypass. This is a common finding in a number of pathologic conditions complicated by long standing pulmonary artery hypertension. The channels connecting the pulmonary artery to the pulmonary vein must exist, but are not identifiable in the conventionally prepared histologic material. While the me-

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TABLE 8. CASE I. PERIPHERAL ARTERIAL BLOOD AT REST

	pO₂ of Inspired Gas		
	147 mm. Hg	105 mm. Hg	300 mm. Hg
Hemoglobin O_2 saturation	87%		91%
pCO_2	25 mm. Hg	26 mm. Hg	
pO_2	57 mm. Hg	42 mm. Hg	
Alveolar-arterial pO_2 difference	58 mm. Hg	33 mm. Hg	

TABLE 9. CASE I. VENTILATION RESPONSE TO TREADMILL EXERCISE

	0°/2[b]/6[c]	4°/2[b]/6[c]
Ventilation (liters/min)	36.9	67
CO_2 output (cc./min.)	650	875
O_2 uptake (cc./min.)	810	980
Ratio of ventilation to O_2 uptake = $\dot{V}_E/\dot{V}_{O_2}$	45	67 (Normal, 25 ± 5)
Ratio of ventilation to maximum voluntary ventilation × 100	22	40
Breathlessness (on scale of 4)	0	3

[a] Grade.
[b] Miles per hour.
[c] Minutes.

chanical and ventilatory apparatus is not impaired, it is implicated in the major complaint of breathlessness during exertion. In Table 9 it can be seen that the ventilation during a walk at 2 miles per hr. on the level is inappropriately high and becomes markedly so with the slight increase of work caused by walking at the same speed on a 4 per cent grade. This is most strikingly expressed in the ventilation equivalent for oxygen, which is almost 3 times normal. The degree of breathlessness is appropriate for the intensity with which the breathing apparatus is being used as an air pump as indicated by the ratio between the minute ventilation and the maximum voluntary ventilation. Normal persons using 40 per cent or more of their maximum voluntary ventilation during sustained exercise are usually moderately to severely breathless. However, this degree of breathlessness is completely inappropriate when it develops while walking on a 4 per cent grade at 2 miles per hr. At such a slight intensity of work, no breathlessness would be experienced by the normal person. It is apparent that this man experienced severe dyspnea or inappropriate breathlessness not because of an impaired air pump but because of an inappropriate use of the pump. Whether the respiratory center is driven directly at a pathologic rate or is used at this rate to satisfy a pathologically developed respiratory desire (cortex or midbrain factor) or is a combination of the two is not known. Although varying as to degree, this type of respiratory response to exercise is common to all conditions leading to pulmonary artery hypertension. This case presentation exemplifies a severe impairment in the blood flow system of the lungs which in

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turn leads to an over-all impairment for physical exercise because of the way in which the pulmonary apparatus as a whole responds.

CASE II—DIFFUSE FIBROSIS

A 55-year-old housewife who had no known exposure to the inhalation of unusual materials developed as her initial symptom a most harassing and nonproductive cough, made worse in the recumbent position. A year later she developed unusual breathlessness on exertion. Both symptoms progressed slowly over the ensuing 5 years until she was unable to do more than self-care. Slight evidences of right side heart failure developed and she died suddenly with no

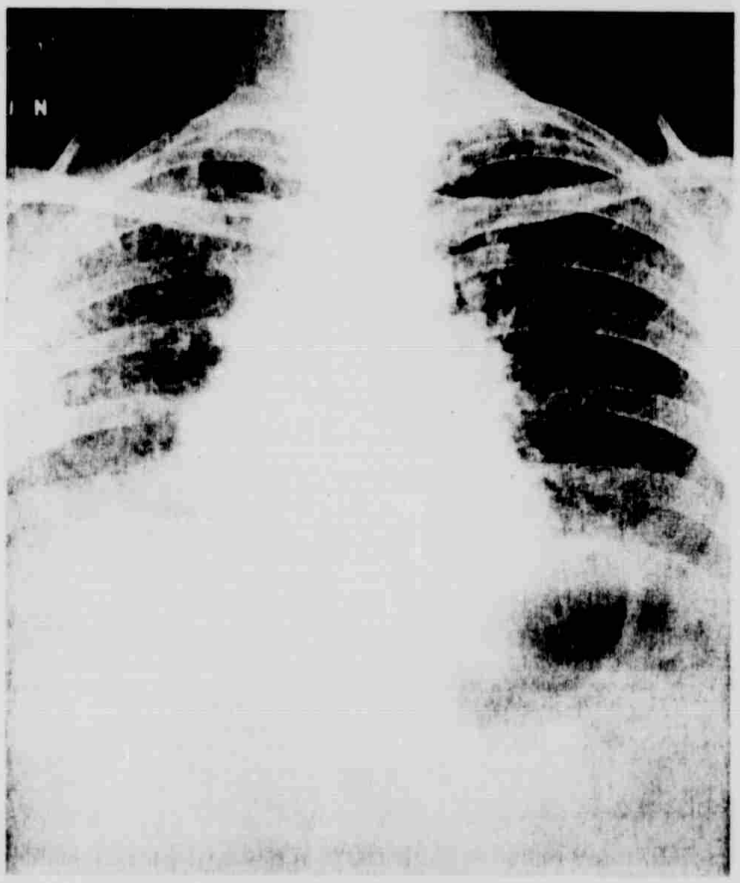


FIG. 38. Case II: diffuse pulmonary fibrosis. Roentgenogram of chest 1 year prior to death. Diffuse interlacing strandlike densities and irregular patchy and finely granular opacities scattered throughout both lungs.

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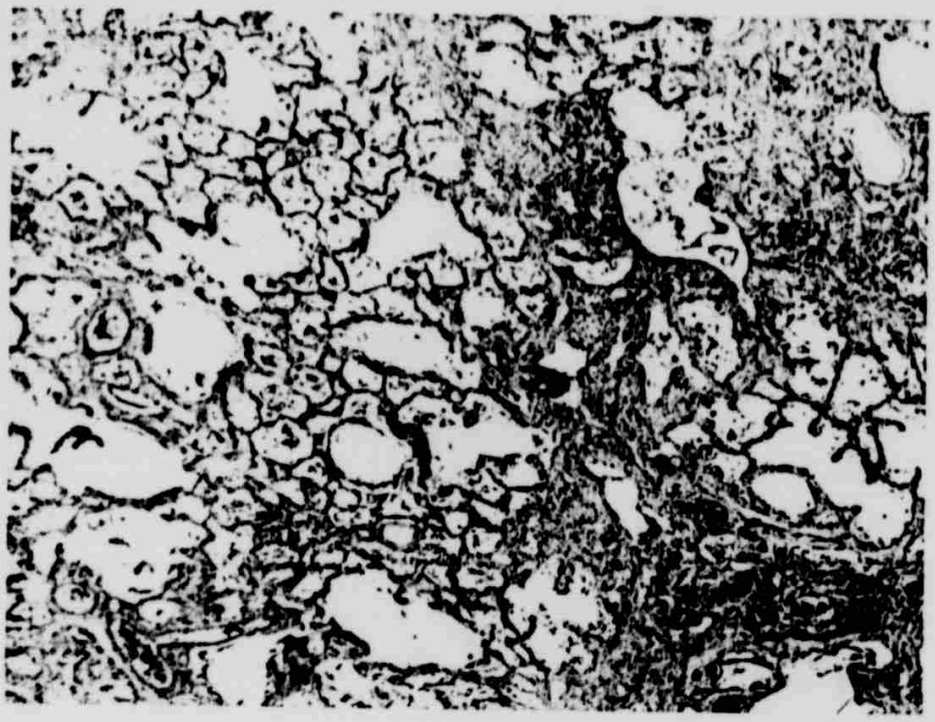


FIG. 39. Case H: representative histologic section of lung. Irregular streaky fibrosis, fibrous thickening and mononuclear infiltration of walls of distal air spaces. Scanty exudate, predominantly of mononuclear cells, in lumina of alveoli. Focal loss of alveoli.

particular precipitating cause. Over the course of the past few years she was totally refractory to several trials of prednisone. The chest roentgenogram shown in Figure 38 was taken 1 year prior to death and reveals a small lung with diffuse interlacing strands and irregular patchy, fine, granular densities scattered throughout both lungs. The entire mediastinum was quite wide and the lung roots could not be clearly differentiated. At autopsy, the cut surface of the lung had a meaty, granular appearance resembling a cirrhotic liver. There was a diffuse streaky fibrosis and sparse parenchyma, most severe in the lower half of each lung. The histologic appearance, representative of the severely involved areas, is shown in Figure 39. As one might expect from the roentgenogram and the appearance of the lung at autopsy, measurement of the various volumes of the lung was below normal in the manner characteristic of a "restrictive" defect as is shown in Table 10. The air spaces may have been somewhat unevenly ventilated since the nitrogen rinsing curve is slightly abnormal. In spite of the restriction imposed by the fibrosis, the maximum voluntary ventilation remains at a normal level, a characteristic finding in restrictive defects. The hemoglobin is not properly oxygenated during its passage through the lungs via the pulmonary artery, and this defect is augmented by exercise as shown in Table 11. The gradient between the alveolar and arterial pO_2 is abnormally high at rest, made

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TABLE 10. CASE II. PULMONARY MEASUREMENTS

	Determined	Predicted
Total capacity	2.08 liters	3.72 liters
Vital capacity	1.26 liters	2.50 liters
Residual volume	0.82 liters	1.22 liters
N$_2$ *rinsing curve*	II	<8
Maximum voluntary ventilation	91 liters/min	84 liters/min
D_LCO*	5.0 cc./mm./mm. Hg	11.0 cc./mm./mm. Hg

* Diffusion capacity of the lung for carbon monoxide.

TABLE 11. CASE II. PERIPHERAL ARTERIAL BLOOD

	pO_2 of inspired gas		
	147 mm. Hg	147 mm. Hg	105 mm. Hg
Activity	Rest	0.2 C*	Rest
Hemoglobin O_2 saturation	92%	78%	
pCO_2	42 mm. Hg	37 mm. Hg	40 mm. Hg
pO_2	70 mm. Hg	40 mm. Hg	36 mm. Hg
Alveolar *arterial* pO_2 *difference*	22 mm. Hg	63 mm. Hg	25 mm. Hg

* See footnotes *a*, *b* and *c*, Table 9.

TABLE 12. CASE II. VENTILATION RESPONSE TO TREADMILL EXERCISE

	0.2 C*
Ventilation per min.	23.7 liters
CO_2 output	425 cc.
O_2 uptake	490 cc.
Ratio of ventilation to O_2 uptake = O.I	48
Respirations per min.	(Normal, 25 ± 5)
Ratio of ventilation to maximum voluntary ventilation × 100	40
Breathlessness (on scale of 4)	26
	3

* See footnotes *a*, *b* and *c*, Table 9.

markedly worse by exercise and not affected by a low pO_2 in the inspired air. This is characteristic of a membrane defect rather than a pure bypass (shunt) as the mechanism for explaining the subnormal saturation of the hemoglobin obtained from the peripheral artery. The markedly subnormal D_LCO (Table 10) also implicates the membrane as the site of abnormal gas transfer. The histologic and gross autopsy *appearance of the lungs* suggests that the reason that the membrane has a subnormal oxygen transfer capacity is that the membrane *is not only thickened* but markedly reduced in total surface. In Table 12 is shown the ventilation response during exercise. The ventilation per minute, both with respect to volume and cycles, is abnormally high for this intensity of work. This inappropriate response is also indicated by the abnormally large O.I. *It is ap-*

parent that her complaint of abnormal or inappropriate breathlessness is related, in part at least, to the same mechanisms discussed in case I.

CASE III—CHRONIC BRONCHITIS WITH AIRWAY OBSTRUCTION

This is a 40-year-old bartender who has a history of daily cough "as far back as he can remember," accompanied by copious amounts of phlegm during most of this time. Many episodes of purulent sputum and three to four periods of house confinement each year because of lung congestion are recounted. Multiple admissions to hospitals in the past 3 years because of bronchopneumonia and congestive heart failure have occurred. He has had known cor pulmonale and polycythemia for the past 2 years. A smoking history of two or more packages daily for 20 years exists. Ultimately, he died a few hours after admission for "purulent bronchitis, bronchopneumonia and congestive heart failure." Autopsy showed extensive lobular pneumonia with purulent bronchitis, severe and ex-



Fig. 40. Case III: severe bronchitis with mucous gland hyperplasia. Plug of mucus in lumen.

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FIG. 41. Case III: large lung section demonstrating that the alveolated parenchyma is largely preserved, with only minimal emphysema.

tensive bronchial mucous gland hypertrophy, cor pulmonale, anasarca and polycythemia. The severe mucous gland hypertrophy is shown in Figure 40 and the minimal (virtually absent) anatomical emphysema is demonstrated in the large lung section shown in Figure 41. Throughout both lungs, many, but not all, small pulmonary arteries showed thickening of the wall and concentric narrowing as shown in Figure 42. The following data were obtained about 1 year before his death and at a time several months after recovery from an episode of bronchopneumonia and congestive heart failure. In Figure 43, three roentgenograms are shown. The one on the *left* was taken at full inspiration and shows a large

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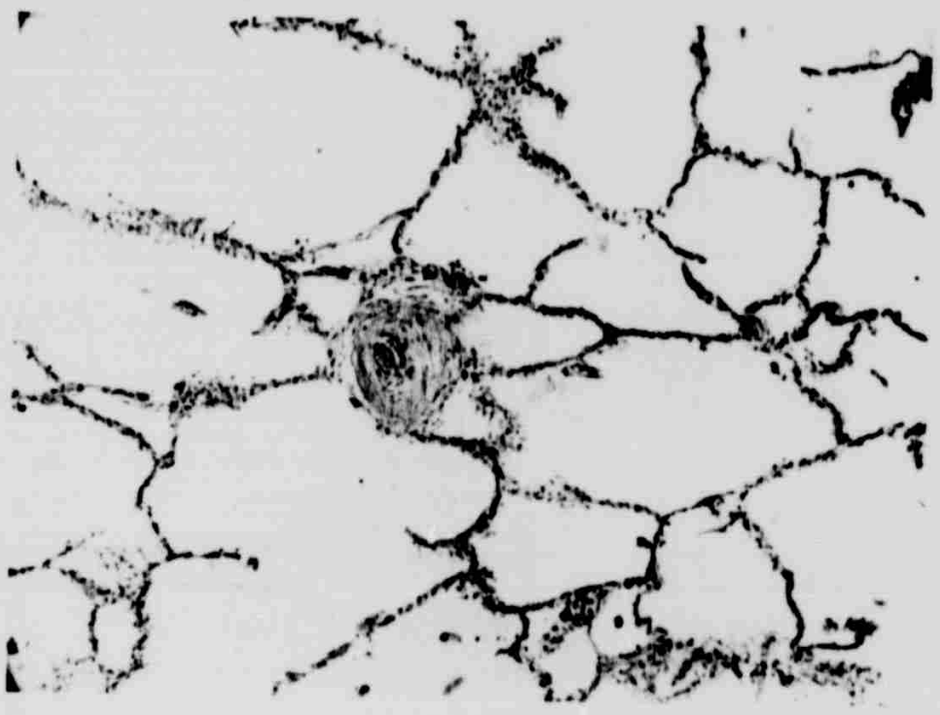


FIG. 42. Case III: narrowing of pulmonary artery by concentrically whorled fibromuscular tissue.

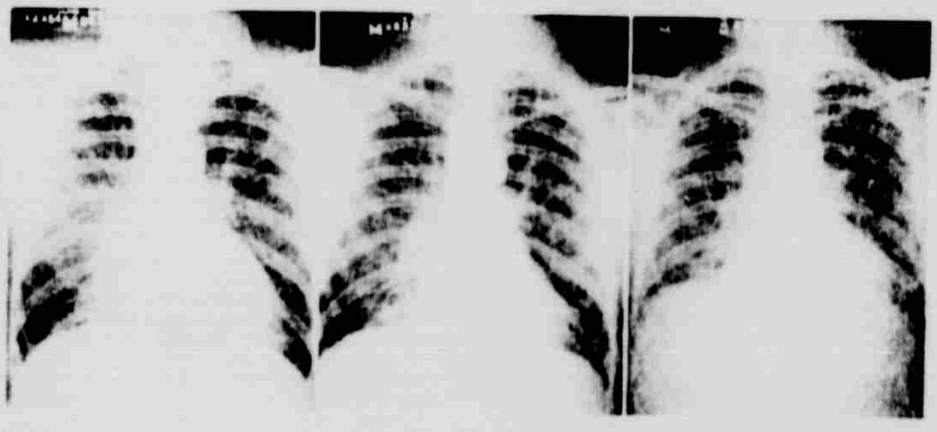


FIG. 43. Case III: evidence of obstruction of airways. Roentgenograms of chest. In the film at the *left*, in full inspiration, prominent lung roots, bronchovascular markings and cardiac enlargement are demonstrated. In the film at the *right*, taken after 20 sec. of forced expiration, is shown the degree to which the lungs could be emptied. The film at the *center*, taken 5 sec. after beginning of forced expiration, shows little reduction in lung volume, at a time when normally the lungs would have been emptied to a maximal degree.

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TABLE 13. CASE III. PULMONARY MEASUREMENTS

	Determined	Predicted
Total lung capacity	5.07 liters	5.58 liters
Vital capacity	2.24 liters	4.22 liters
Residual volume	2.84 liters	1.36 liters
N_2 rinsing curve	20+	<10
Terminal alveolar N_2	7.7%	<2.5%
Maximum voluntary ventilation	29 liters/min.	151 liters/min.
After bronchodilators	41 liters/min.	
D_LCO (rest)	16.0 cc./min./mm. Hg	18.5 cc.

* See Table 10.

TABLE 14. CASE III. PERIPHERAL ARTERIAL BLOOD OBTAINED AT REST

	pO_2 of Inspired Gas	
	147 mm. Hg	900 mm. Hg
Hemoglobin O_2 saturation	63%	100%
pCO_2	71 mm. Hg	
pO_2	24 mm. Hg	
pH	7.32	
Hematocrit	71%	

heart with large lung roots and prominent bronchovascular lung markings. The film on the *right* was taken after 20 sec. of forced expiration to demonstrate the degree to which the lung could be emptied. The *center* film was made 5 sec. after the onset of forced expiration and shows little reduction in lung volume at a time when normal persons will have emptied the lungs to a maximal degree. This sort of air trapping is characteristic of the obstructed lung. This same phenomenon is shown by the high residual volume and reduced vital capacity seen in Table 13. It is assumed that the persistently narrowed bronchi close or in some way cause closure distally while the lung still contains an unusually large air volume. Another evidence of air conduit narrowing is seen in the subnormal maximum voluntary ventilation noted in Table 13. Airflow resistance is not uniform throughout the lung and this leads to nonuniform deep lung space ventilation as shown by the high terminal alveolar nitrogen and the abnormal nitrogen rinsing curve indicated in Table 13. That much of the hypoventilated part of the lung is perfused by pulmonary artery blood thus leading to subnormal oxygenation of the peripheral arterial blood is shown in Table 14. That the mechanism leading to arterial hypoxia is not membrane defect or arteriovenous bypass is shown by the high arterial pCO_2 and the fact that the hemoglobin is 100 per cent saturated when respiring a high oxygen mixture. It is also shown by the normal D_LCO seen in Table 13. The low alveolar pO_2 consequent to alveolar hypoventilation is believed to cause pulmonary arteriolar spasm. The high alveolar pCO_2 may, by local pH changes, also influence this. The arteriolar

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TABLE 15. CASE III. CARDIAC CATHETERIZATION

	Resting	Mild Exercise
Pulmonary artery	60/30 mm. Hg	80/40 mm. Hg
Right ventricle	65/2 mm. Hg	90/6 mm. Hg
Wedge	6 mm. Hg	
Cardiac index	3.1 liters/min.	4.2 liters/min.
Hematocrit	70%	69%

TABLE 16. CASE III. VENTILATION RESPONSE TO TREADMILL EXERCISE

0/2/67	
Ventilation per min.	18.1 liters
CO_2 output	495 cc.
O_2 uptake	620 cc.
Ratio of ventilation to O_2 uptake = O_2V	29 (Normal, 25 ± 5)
Respirations per min.	20
Ratio of ventilation to maximum voluntary ventilation × 100	82
Breathlessness (on scale of 4)	4

[a] See footnotes *a*, *b* and *c*, Table 9.

narrowing plus the increase of blood viscosity caused by the polycythemia leads to pulmonary artery hypertension as shown in Table 15. This in turn leads to cor pulmonale. The long term pulmonary artery hypertension probably produced the changes seen in the wall of the small arteries of the lung, shown in Figure 42. This arterial wall reaction in turn makes the pulmonary vessels less compliant and augments the hypertension during exercise. The ventilation response to exercise is of special interest. The ventilation volume per minute, shown in Table 16, is only slightly higher than normal for this intensity of effort, as is also the O_2V. Even so, breathlessness is quite severe. The ratio of ventilation during exercise to the maximum voluntary ventilation for that day is 82 per cent. It is apparent from this that the entire muscular capacity for moving air is being utilized during exercise, but the resistance to airflow prevents inappropriate ventilatory response. In other words, excessive or inappropriate respiratory muscle activity is needed to overcome the high airway resistance, and hence the sensation of breathing (breathlessness) is totally inappropriate. If the airway resistance were somewhat less, an abnormally high oxygen ventilation equivalent doubtless would have developed as it does in many persons with less severe airway obstruction. This case demonstrates the kinds of physiologic impairment that occur consequent to persistent elevated resistance to airflow in the presence of a relatively intact peripheral pulmonary vascular system. Characteristically, there is an inappropriately high work of the respiratory muscles at all volumes of respiration and a reduction in the maximum capacity for ventilation. In addition, there is severe peripheral artery hypoxia and hypercapnia consequent to alveolar hypoventilation. This leads to polycythemia plus pul-

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monary artery hypertension and a train of events in the circulatory system consequent thereto. Inappropriate breathlessness, cor pulmonale and congestive heart failure arise from these impairments.

CASE IV—ANATOMICAL EMPHYSEMA

This man, 68 years old at the time of his death caused by acute myocardial infarction, was studied at intervals over an 8-year period. He was an executive who had no unusual exposure to airborne materials. Beginning at age 55, he first noted that because of breathlessness he was less able than others his age to wade trout streams and hunt in rugged country. By age 60 he had similar difficulty on golf courses and stair climbing. This difficulty progressed until at the time of the study reported here, 9 months before his death, he had given up all but such exercise as needed for self-care and getting to his office. During all of this period he had a minimal morning cough with a small amount of phlegm and none during the rest of 24 hr. He had never experienced pneumonia or admission to hospitals for lung or upper respiratory infection. Orthopnea, paroxysmal nocturnal dyspnea and peripheral edema were totally absent prior to the fatal episode. He had smoked a package of cigarettes a day for 45 years prior to age 60 but none after that. Physical examination showed an abnormally large anteroposterior diameter of the chest and faint to absent breath sounds, but no wheezing, rales or cyanosis. The chest roentgenograms, one at full inspiration and the other at maximal expiration, are shown in Figure 44, taken at age 60, and reveal his inability to empty his lungs properly. At autopsy the lungs were large and did not collapse by more than a slight degree when the thorax was opened. A large

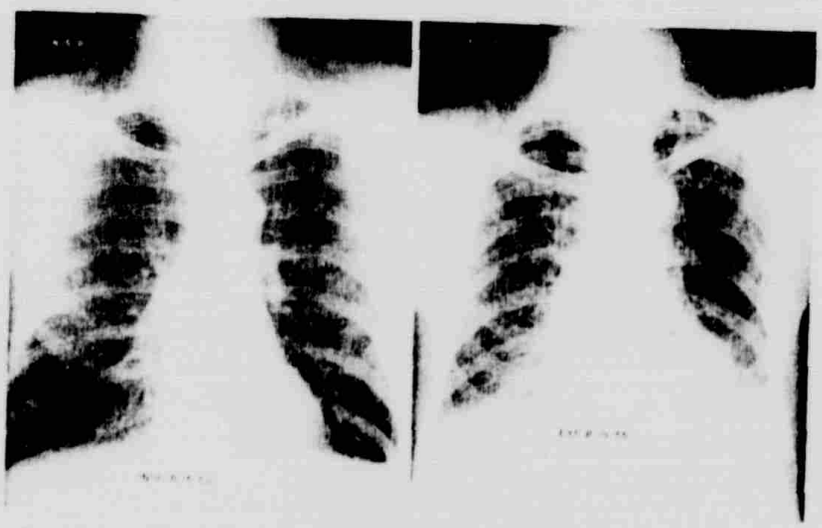


FIG. 44. Case IV: pulmonary emphysema. Roentgenograms of chest made at age 60, 8 years before death, at the *left* in full inspiration, and at the *right* in maximal expiration.

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FIG. 45. Case IV: large lung section demonstrating extensive emphysema. The loss of alveolar substance involves especially the upper lobe.

lung section is shown in Figure 45, revealing the characteristic appearance of anatomical emphysema. Histologic examination of the bronchi revealed normal mucous gland structures. There was moderate engorgement of the pulmonary vessels and the right ventricle measured 5 mm. at its thickest part. The evidences of the large lung and inability to empty it properly are shown by the large total

TABLE 17. CASE IV. PULMONARY MEASUREMENTS

	Determined	Predicted
Total lung capacity	7.80 liters	5.51 liters
Vital capacity	2.79 liters	1.16 liters
Residual volume	5.10 liters	1.35 liters
Terminal alveolar N_2	6%	<2.5%
Maximum voluntary ventilation	26 liters/min.	124 liters/min
FEV_1[a]	42%	75+%
FEV_1	1.17 liters	2.9 liters
Airflow resistance[b]	9	1 ± 0.5
D_LCO	6 cc/min./mm. Hg	17.0 cc

[a] Fast expiration, 1 sec. volume.
[b] Centimeters of H_2O per liter per second at flow rate of 0.5 liter per second.
[c] See Table 10.

TABLE 18. CASE IV. PERIPHERAL ARTERIAL BLOOD

	Resting	6 l/m[a]
pO_2 of inspired gas	147 mm. Hg	147 mm. Hg
Hemoglobin O_2 Saturation	93%	92%
pCO_2	31 mm. Hg	30 mm. Hg
pO_2	68 mm. Hg	72 mm. Hg
pH	7.50	7.49
Hematocrit	47%	49%

[a] See footnotes *a*, *b* and *c*, Table 9.

lung capacity and residual volume noted in Table 17. Evidence that the portion of lung taking part in ventilation was improperly ventilated is demonstrated by the high terminal alveolar nitrogen obtained at the end of 7 min. of oxygen breathing for purposes of measuring the residual volume. That resistance to airflow was severe is shown in Table 17 by the markedly subnormal maximum voluntary ventilation and fast expiration 1-sec. volume, and also by the high direct measurement of airway resistance using the body plethysmograph. In this condition, the elevated airway resistance is not due to a narrowing of the lumen by thickening of the bronchial wall. The cause of the narrowing is not readily seen in histologic preparations. Careful measurements of the diameters of large numbers of small bronchi have shown that, on the average, they are narrower in anatomical emphysema than in normal persons. This accounts in part for the elevated resistance, particularly when one recalls that the radius influences resistance by a power of 4. There is some evidence that there is also a dynamic distribution of air pressures about the most distal and unsupported air ducts such that these tubes become abnormally narrowed during forceful expiration. It seems likely that both of these kinds of narrowing stem from a loss of extramural support of the conduits as a result of the destruction of distal lung units. The importance of these distal structures as conduit wall supports was stressed early in this presentation. In striking contrast to case III, this man had mini-

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TABLE 19. CASE IV. VENTILATION RESPONSE TO TREADMILL EXERCISE

0.2.5*	
Ventilation per min.	19.2 liters
CO_2 output	585 cc.
O_2 uptake	620 cc.
Ratio of ventilation to O_2 uptake	30
Respirations per min.	(Normal, 25 ± 5)
Ratio of ventilation to maximum voluntary ventilation × 100	22
Breathlessness (on scale of 4)	76
	3

* See footnotes *a*, *b* and *c*, Table 9

nal peripheral artery hypoxia and no hypercapnia even during exercise as shown in Table 18. The nature of the anatomical lesion is such that the distal pulmonary artery vascular bed is destroyed in the poorly ventilated areas and such transpulmonary blood flow as does occur passes mainly through relatively well or even hyperventilated alveoli. The low pCO_2 suggests this. The reduction of capillary surface is indicated by the subnormal D_LCO shown in Table 17. The slight arterial hypoxia is probably due to a high transit time in the remaining alveolar capillaries, although some actual shunting has been demonstrated in this disease and may account for a portion of the hypoxia. The ventilation response to exercise is shown in Table 19. The comments made in this regard in case III apply here and need not be repeated. As is the fact in this case, cor pulmonale is less common and certainly less severe in anatomical emphysema than in chronic bronchitis of such a severity that it causes airway obstruction. Two factors may provide a partial explanation of this generally accepted observation. The location of the narrowing in all of the large bronchi in severe chronic bronchitis means that all parts of the distal lung are subject to alveolar hypoventilation and its consequences in terms of pulmonary artery hypertension. In contrast, anatomical emphysema is distributed unevenly and, although much of the vascular bed may be destroyed, that which remains has a better compliance and can be distended more readily. It seems probable that for comparable severities of airway obstruction the pulmonary vascular obstruction might be less in anatomical emphysema on this basis. That polycythemia is less severe in anatomical emphysema may be an important added factor. A second factor relates to the clinical observation that at comparable levels of airway obstruction the patient with anatomical emphysema becomes more breathless and is physically weaker during his general daily activities than is his counterpart with chronic bronchitis. Because of this, the average intensity of physical effort and hence the level of cardiac output is probably less in anatomical emphysema. This would be accompanied by lower average pulmonary artery pressure during the months preceding death from this disease and might account for the less severe cor pulmonale in emphysema. Admittedly, this is a most complex problem and other factors can be thought of but will not be considered here. Case IV, when taken in contrast to case III, demonstrates the striking difference that

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may be observed in the consequences of airway obstruction caused by two differing entities.

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Annotated references have not been appropriate for the style of presentation of this chapter; however, Dr. Wright has supplied the following general references which are relevant to his topic.—*Editor*

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