The Interdependence of Pulmonary Structure and Function

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In classical Greece the function of the lung was argued chiefly from the observed gross anatomy. Unfortunately, the method of strangulation introduced by Aristotle for killing animals caused most of the circulating blood to pool in the venous system. The finding of empty arteries led Erasistratus to the conclusion that the arteries in life must contain pneumonia, a substance derived from air in the lungs which entered into the left side of the heart via the pulmonary veins. According to Wilson,121 Galen in the second century A.D. successfully refuted this view. However, he had his own philosophical notions about cardiopulmonary function, and when these ideas ran counter to experiment he tended to ignore or challenge the data rather than change his beliefs. Although he had available to him all the necessary facts, he failed to discover either the proper function of the lungs or the circulation of the blood.

There is some similarity between these ancient events and views of pulmonary physiology today. Too many workers are content with an unrealistic image of lung structure derived from functional experiments often conducted under unphysiologic conditions in a single species of animal and freely interpreted to be similar to intact unanesthetized human lungs.

Simplified lung models have been set up to illustrate certain functional points (fig. 1), and because of their usefulness in developing elementary concepts of whole lung function a generation of students has grown up to regard the model as the real lung. When actual pulmonary structure is discussed, senior workers still invoke Miller22 as the final authority. Misconceptions have grown until the picture of the lung based on extrapolations from gross function is as misleading as the classical view of function based on morbid anatomy.

Recently there has been a renewal of interest in pulmonary structure-function relations. The impetus came mainly from pathologists trying to envision the lung as it was in life.8, 26, 12, 11 Many anatomists and physiologists have recognized the fact that their isolated positions are inadequate and that a coordinated approach is needed. 21, 110 We may expect to see increasing emphasis on "true" lung structure as it relates to function. 105, 21

This review is an attempt to show a more or less coordinated view of the remarkable interdependence of lung physiology and morphology. I will examine three problems of current interest in which the final solutions will depend on thorough understanding of structure and function.

Relation of Airways and Blood Vessels to Other Lung Tissue

A central feature of the structure-function relations of the airways lies in the relations of these conduits to the whole lung.

Airways

In table 1 I have classified the airways so that the terms used by various authors may be equated. The following section will be more meaningful if the table is examined first.
the living preparations as possible with present technology.165

Figure 2–1 shows a lobar bronchus. Bronchi of this type in man have more or less complete cartilaginous rings or plates (mostly plates beyond the main stem bronchi). They also contain elastic and collagen connective tissue fibers, smooth muscle and their own blood supply via the bronchial circulation.45,59

This type of airway continues down to about 0.1 cm. diameter (table 1), although the cartilage gradually disappears before the airways become that small. Wright122 in a post-mortem study showed that excised bronchi from normal lungs are able to maintain their shape down to about 0.2 cm. diameter. This supports the view of Dayman36 that one function of the cartilage is to maintain the patency of these larger airways without benefit of lung tissue support.

Figure 2–1 also shows that in the relaxed or nearly relaxed state the airway lumen is smooth except for undulations due to the slight outward bulging of the membranous walls between the cartilage rings. As can be seen from the whiteness of the mucosa against the pink of the lung tissue the capillary bed of the airways is relatively poor compared to the alveolar septae. In the figure at least two bronchial vessels can be seen. These vessels supply the nutrition of the airway down to the terminal bronchioles.

Figure 2–2 shows a smaller segmental cartilaginous airway in an animal with acute pulmonary edema. The important feature is the space around the airways and vessels filled with fluid. This demonstrates graphically that there is a potential space around these airways and that they are not connected tightly to the lung parenchyma.31 Hayek13 in his study of the human lung emphasized that the alveolar tissue is separated from the main airways by a strong elastic limiting membrane tending to pull the lung away from the airways. This suggested to him that the peribronchial pressure is subatmospheric, although not necessarily as low as the intrapleural pressure. He stated that the limiting membrane fuses with the bronchial walls at approximately the point where the cartilage ends. These facts are consistent with the hypothesis that the cartilage-containing airways are af-
fected more by transpulmonary pressure than by lung volume. One cannot say that lung volume has no effect; Marshall has presented preliminary evidence that it does, although the relation is not a simple one.

Figure 3(A) is a lung model designed to show the relations of the airways at various levels to the lung proper. The large central tube represents the cartilaginous airways. In the figure the potential space between the surrounding lobules and the airways is exaggerated. Figure 3(B) is a cross section showing how the lobular limiting membranes enclose the cartilaginous airways without attaching directly to them except for some loose connective tissue.

The effects of coughing provide interesting evidence about the support of the large airways. Dayman stated that during coughing the trachea can be completely occluded by invagination of the membranous portion. Di Rienzo showed by careful bronchography that various portions of the larger lobar and segmental bronchi can narrow markedly during a cough at a time when lung volume has not changed much, but when transmural airway pressure is positive inward. It was Dayman's view that the cartilages help to hold the airways open at low transmural pressure (expiration) and to prevent overdistalation at large outward pressures (deep inspiration). Wright added to this view by showing in emphysematous lungs that the cartilage of the medium and larger bronchi may be so atrophic that they collapse when dissected away from the lung. On the basis of his evi-

### Table 1. Classification of Airways by Order of Branching, Common Name and Description

<table>
<thead>
<tr>
<th>Numerical Order (10)</th>
<th>Average Diameter (about 75% TLC)</th>
<th>Common Name (10, 30, 52, 108, 31)</th>
<th>Description and Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.3–2.2 cm.</td>
<td>Trachea</td>
<td>Main cartilaginous airway; partly in thorax.</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Main bronchus</td>
<td>First branching of airway; one to each lung; in lung root; cartilage.</td>
</tr>
<tr>
<td>2</td>
<td>0.7</td>
<td>Lobular bronchus</td>
<td>Named for each lobe; cartilage.</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>Segmental bronchus</td>
<td>Named for radiographic and surgical anatomy; cartilage.</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>Subsegmental bronchus</td>
<td>Last generally named bronchi; may be referred to as medium-sized bronchi; cartilage.</td>
</tr>
<tr>
<td>5-10</td>
<td>0.4–0.1</td>
<td>Small bronchi</td>
<td>Not generally named, contain decreasing amounts of cartilage. Tenth order is about 0.1 cm, diameter. Beyond this level airways enter the lobules as defined by a strong elastic lobular limiting membrane.</td>
</tr>
<tr>
<td>11-13</td>
<td>0.4–0.05</td>
<td>Bronchioles</td>
<td>Not named. Major distinction is not size but absence of cartilage, mucus secreting elements and cilia. Tightly embedded in lung tissue.</td>
</tr>
<tr>
<td>14-15</td>
<td>0.05</td>
<td>Terminal bronchioles</td>
<td>Question of how many orders of bronchioles ought to be called terminal; generally 2 or 3 so designated; morphology not significantly different from orders 11-13.</td>
</tr>
<tr>
<td>16-18</td>
<td>0.05</td>
<td>Respiratory bronchioles</td>
<td>Definite class; bronchiolar ciliated epithelium present but scattered alveoli are present giving these airways a gas exchange function. In some part of text order 16 will be called first order respiratory bronchiole, 17 will be second order and 18 will be third order.</td>
</tr>
<tr>
<td>19-22</td>
<td>0.04</td>
<td>Alveolar ducts</td>
<td>No bronchiolar epithelium; have no surface except connective tissue framework; open into alveoli.</td>
</tr>
<tr>
<td>23</td>
<td>0.04</td>
<td>Alveolar sacs</td>
<td>Usually named although 1 see no reason to assign a special name; they are considered short alveolar ducts in this paper.</td>
</tr>
<tr>
<td>24</td>
<td>0.02</td>
<td>Alveoli</td>
<td>Macklin's description (second section in text) is unsurpassed. Pulmonary capillaries are in the septae that form the alveoli.</td>
</tr>
</tbody>
</table>
dence it may be that more of the expiratory obstruction in severe emphysema is in the larger airways than is generally believed.

Membranous Airways. There is no cartilage in the airways within the elastic limiting membrane of the lobule (table 1); and these airways are truly in the lung, that is, the pressure outside their walls is alveolar pressure rather than intrapleural. Since airway pressure is the same as alveolar pressure when no gas flow is occurring, the transmural pressure (the pressure between the inside and outside of the airway) is zero at end-inspiration and expiration. Since the elastic and muscle elements of the bronchioles tend to collapse them (as happens when they are dissected free from the lung), stability of these small passages must depend upon the interconnections of their elastic skeleton and that of the alveolar tissue. This implies that their size is dependent directly on lung volume. Figure 3(C) shows how they are held open by the pull of the adjacent alveolar septae. The actual force of the transpulmonary pressure across the lobular limiting membrane is acting via the interposed alveolar septae.

In figure 2–(3 and 4) we see the small airways very much as they appear in life. Figure 2–3 shows a terminal bronchiol and some of its branches. The mucosa is white and glistening. Generally, the lining of these airways is quite smooth since there is no cartilage. Sometimes there is longitudinal furrowing of the mucosa indicating that there is either active constriction or a reduced distending force. No one has determined the

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Fig. 2. (1) Frozen specimen showing a lobar bronchus, adjacent pulmonary artery (venous blood) and two pulmonary veins (arterial blood). On the cut surface of the bronchus you may be able to see the cartilages (white). There are at least two bronchial vessels (arrows). Around the pulmonary artery is a ring of perivascular fluid and one distended lymph vessel. Dog, acute pulmonary edema, frozen, unfixed, from 4×.

(2) Segmental and subsegmental bronchi, full of edema foam. Adjacent to each airway is a pulmonary artery. Perivascular fluid around vessels and airways. Most of the fluid is not in organized lymph vessels but is in the connective tissue spaces that surround the conducting tubes. Human lung has more connective tissue and would show even larger spaces. Dog, acute pulmonary edema, frozen, unfixed, from 12×.

(3) Membranous bronchioles and vascular relations. Large bronchiole with adjacent pulmonary artery. Lateral branch of bronchiole is mostly cut away, but it branches again and the upper branch accompanied by an artery (arrow) turns into the specimen. The pulmonary vein seen at the top with its bright red arterialized blood is as far from the airway and artery as possible. Cat, frozen, unfixed, from 8×.

(4) Respiratory bronchiole with lateral and distal formation of alveolar duct systems. Each branch is accompanied by a pulmonary arteriole (arrows). The first order respiratory bronchiole containing only scattered alveoli has risen from a terminal bronchiole off to the right and deeper in the specimen. Successive orders of respiratory bronchioles have more and larger alveoli. The cat does not have very well developed respiratory bronchioles except in the long thin upper lobes from which this specimen is taken. This lobe would be excellent for the experimental study of airways because they are long, well developed and the lobe is flat and thin. Cat, frozen, unfixed, from 8×.

(5) Alveolar duct system arising via a short duct from a terminal bronchiole. This grouping shows a ventilation/perfusion unit in one plane. Note the arrangement of alveoli along the duct branches and the intimate relation of the small vessels to the air spaces. Guinea pig, frozen, fixed, thin section, from 30×.

(6) Portion of an alveolar duct and its alveoli. Note relation of small vessels. For comparative purposes this bit of alveolar duct from a human is as large as the entire duct system in the guinea pig (5). The lungs in 5 and 6 were frozen at about 10 cm. of water inflation pressure after a previous full inflation. Thus the unit, duct and alveolar size differences are real. Human surgical specimen, frozen within 60 seconds of clamping lobe tip during manual inflation to 10 cm. of water and with blood flowing, fixed, thin section, from 30×.

Fig. 3. Lung model designed to show only the relation of the various airways to the lung gas exchange tissue. (A) Cartilaginous airway surrounded by lobular limiting membranes. Potential space between lobules has been exaggerated. Membranous airways branch from cartilaginous airway and enter lobules. Respiratory bronchioles and alveolar ducts are shown as dashed tubes. (B) Cross section of cartilaginous airway showing how limiting membranes enclose it without being tightly attached to it. (C) Cross section of membranous airway within lobule showing how alveolar wall traction holds it open.

precise effect of the furrowing on airflow; some jet airliners have similar furrowings on their noise suppressors presumably to prevent turbulence.

Although the diameter of the airways decreases steadily from the trachea downward (table 1), the total cross section area increases. Miller stated that the area increased about 20 per cent at each branching. Hayek accepted Miller's rule, but notes that Stutz did not confirm it in his bronchographic studies. In the membranous bronchioles the diameter does not decrease much further so that with each branching the total area nearly doubles. Weibel and Gomez in a study of five human lungs reported little decrease in size after the fourteenth to fifteenth order of branching, that is, at the terminal bronchiole level. The sharp increase in total cross sectional area means that air flow velocity is much reduced in each tube. Mead and Hayek calculated that air flow and cross sectional area at the respiratory bronchiole level are about 0.1 and 10 times the tracheal flow and tracheal area, respectively. But calculations based on Weibel and Gomez's data (table 1) show that the cross sectional area of all the respiratory bronchioles (eighteenth order) is more than 100 times that of the trachea. The point here is not so much the actual numbers (all methods used are subject to criticism) but the fact that the total cross sectional area of the membranous airways increases far more rapidly than in the cartilaginous airways. This leads to interesting calculations concerning the distribution of flow resistance in the normal lung (see Discussion).

Although figure 2-4 shows membranous airways, these are different from figure 2-3 because they are also part of the gas exchange portion of the lung (see section Ventilation/Perfusion Units). The photograph shows the transition from a smooth airway to the respiratory bronchioles with patches of small alveoli and finally to the alveolar ducts where there is no mucosa but only openings into alveoli. Wright has analyzed the connective tissue skeleton of these units and shown that the elastic and collagen fibers are arranged helically. The alveolar ducts also contain smooth muscle in rings and spirals that loop around the mouths of the alveoli.

The respiratory bronchioles and alveolar ducts form a distinct subdivision of the membranous airways based on their blood supply. Down to the terminal bronchiole in man and the airway receives its metabolic support from the bronchial circulation. The respiratory bronchioles and ducts, however, are nourished by the pulmonary artery. This opens the possibility of independent function of these terminal units. Hayek shows an example of alveolar duct contraction. Recently, Halmagyi and Colebatch published data compatible with alveolar duct contraction. Nadel, Colebatch, and Olsen also found evidence of terminal airway closure which followed injection of microemboli or histamine into the pulmonary artery. They reasoned that only the alveolar ducts and respiratory bronchioles are supplied by the pulmonary arterioles and therefore independent contraction of these units was occurring. They have now confirmed this anatomically using the rapid freezing process of Staub and Storey in the lungs of cats (figure 2-7a, b, c). In these experiments the
larger airways did not appear to be involved, but there was some decrease in the diameter of terminal bronchioles. This is to be expected because the decrease in lung size caused by contraction of alveolar ducts would decrease the elastic distending force on the membranous airways; however, for the same transmural airway pressure little effect would be expected in the cartilaginous airways.

Discussion. One may argue that the space around the bronchi is only a potential one and that in normal lungs the large bronchi expand and contract with increasing and decreasing lung volume as if the bronchi were directly attached to the alveolar septae. "As if" arguments are functionally useful, but we should use them only when the true relation is unknown. After all, the lungs behave "as if" they were attached directly to the chest wall but we know they are not. If our view becomes fixed on the anatomical oneness of the airways, important clues to altered function may be missed. This fixation has led Widdicomb to state "... provided alveolar collapse does not occur, smooth muscle contraction does not 'constrict' the lung." This neglects the fact that the alveolar ducts, which function both as airways and gas exchange units, occupy about 30 per cent of the human lung volume. Figure 2-7 shows that this 30 per cent can be markedly reduced with additional decreases in volume due to passive decreases of alveolar volume.

This problem affects the interpretation of the experiments of Caro, Butler and DeBois. They showed that chest strapping can alter markedly the relations of lung volume to transpulmonary elastic pressure. In ten normal subjects during strapping, airway conductance (the reciprocal of resistance) was more than doubled at the same lung volume but at larger transpulmonary pressure than in the control period. They attributed their results to increased elastic lung traction on the small airways. But the anatomical relations as already outlined make it just as likely that the increased negative intrapleural pressure was increasing the transmural distending pressure across the larger airways.

We have been living for a long time with the belief that the major site of airway resistance is in the very small airways, that is, the membranous airways. Mead traces the concept back to Rohrer who made a dimensional analysis on excised human airways and calculated that more than 70 per cent of the subglottal airway resistance is in tubes less than 0.1 cm. in diameter. Mead believes this may be in error because Martin and Proctor found the smaller bronchi to be more distensible, so that in life they may be larger than in Rohrer's dead lungs. We have already mentioned the measurements of Weibel and Gomez (table 1) which indicate a much greater cross sectional area in the membranous airways than formerly thought. This would also tend to lower the portion of resistance attributed to the smallest airways.

In summary, there is good anatomical evidence for considering two major subdivisions of the airways (cartilaginous and membranous), with a further subdivision of the membranous airways into conducting airways supplied by the bronchial artery and conducting and gas exchange airways supplied by the pulmonary artery. The functional evidence to support this classification is only fragmentary, but it is consistent. The elucidation of further details of anatomical relations may be expected to speed up the resolution of many vexing problems concerning the airways.

Blood Vessels

Much of what I have discussed about the airways applies to the blood vessels. For example, the large vessels like the cartilaginous airways are in the connective tissue spaces outside the lobular limiting membranes, while the small muscular vessels and capillaries are embedded in the alveolar tissue.

Large Vessels. Whereas the air moves in and out through the same airways and alveolar ventilation is therefore discontinuous, the pulmonary vascular bed is a continuous flow-through system with no dead space. It is well known anatomically that the pulmonary arteries run parallel and close to the airways (figures 2 (1 and 2)). The pulmonary veins, however, are located between the lobules as far from the airway and artery as possible. Surely this arrangement is more than chance. It suggests that the pulmonary artery and airways are functionally related in a more intimate way than mere use as con-
ducting tubes requires. We will see in the next section the intrapulmonary regulation of ventilation to perfusion is consistent with this arrangement. The separate course of the pulmonary vein indicates that it acts more like a simple drainage tube. * 

Figure 2–3 shows the relation of the pulmonary vessels to the airway in the main respiratory portion of the lung. The artery and vein are easily distinguished by color in the frozen unfixed specimen. At the hilum (fig. 2–1) the large veins do approach the other conducting tubes. This may be a matter of space economy and the mobility of the lung root.

The larger pulmonary arteries are very distensible structures and are able to hold a large fraction (over one-third) of the right ventricular systolic ejection volume at normal pulmonary artery pressures. 52 54

Since the arteries are in the same connective tissue space as the bronchi, they are subjected to the same external forces. Thus, normally they are surrounded by a subatmospheric pressure. During inspiration the trans-

* The pulmonary veins have an additional function as a blood reservoir for the left heart which is not, however, related to primary lung function. 10
mural pressure becomes more positive outward tending to enlarge them, and Riley and Howell, Permutt, Proctor and Riley who seem to have been unaware of Hayek’s and Altmann’s work came to similar conclusions; but, in addition, they believed the pressure around the “larger” vessels was even more negative than intrapleural pressure due to the radial traction exerted by alveolar structures. Actually, the larger arteries are not attached directly to the lung parenchyma. Figure 2–2 shows that, if anything, the arteries are more independent of the pull of lung tissue traction than the airways because the arteries develop a much larger and more complete perivascular fluid space in the presence of edema than do the bronchi. The model illustrating the effect of lung expansion on the vessels proposed by Altmann and, later, by Riley (which was based on the proposition that the space between spheres becomes larger as the spheres get larger) corresponds very well to the relation of the larger elastic arteries and cartilaginous bronchi to the lobules. According to Altmann, the actual volume changes with breathing will depend on the relative compliances of the vessels, airways and the lobules. The veins are outside the lobular limiting membranes in the same sense as the arteries and airways and are subject to similar forces as far as lung expansion effects are concerned.

Small Vessels. Let us look at the vessels in the lung that lie within the limiting membrane of the lobules. These include the so-called muscular arteries, arterioles, capillaries and small veins.

Arteries and Veins. These vessels, especially the arteries, are not really muscular in the sense that they are like the thick-walled muscular arteries in the systemic circulation. Rather, there is a gradual transition to relatively more muscle and less elastic tissue. The veins also have very little muscle and so we identify them mainly by their location rather than by histological structure. As figure 2–(5 and 6) and figure 4–(10 and 14) show, these vessels are located in the alveolar septae usually where the septae join. The forces operating here are similar to those acting on the intralobular membranous airways. There is no direct effect of intrapleural pressure, but rather the effect of traction of the lung tissue when volume changes. These vessels are among those whose diameter (volume) increases as lung volume increases.

Some of the vessels are too large for the space available and consequently bulge into the air spaces (fig. 2–(5 and 6)). As lung volume increases these vessels may be distorted in cross section from oval to triangular and they may be partially compressed.

The vessels within the lobular limiting membrane, like the respiratory bronchioles, alveolar ducts and alveoli, receive their nutrition from the pulmonary artery. The vasa vasorum from the bronchial artery do not extend this far.

Capillaries. In this section I will emphasize only the location of the capillaries in the alveolar septae so that we may deal with the effect of changes in lung volume. In section Alveolar-Capillary Gas Exchange other features are discussed.

Many, if not most, of the capillaries arise very abruptly (fig. 4–10) from much larger vessels. Kriisey and Kriisey attributed the success of the lung as a filtration device to this arrangement: microemboli can plug the distal end of arterioles without blocking the capillaries that arise proximally. Capillaries may travel over the surface of more than one alveolar wall before entering a drainage vessel (fig. 4–10). This is important in considering the red cell transit time through the capillary bed.

Since the capillaries have a small diameter and a small radius of curvature they can withstand high internal pressure; however, they have almost no external support so that they are subject to any compressing forces that are present (alveolar-capillary luminal pressure gradient). In theory their size and cross sectional shape are influenced by changes in lung volume due to stretching and compression, but there is no agreement as to what actually happens. Altmann stated they were dilated by increasing the lung volume; however, the majority of other workers believe they are compressed. Olkon and Joannides and Ramos used direct microscopic examination of the living lung surface and found that the capillaries were flattened during inspiration. They used open chest preparations.
with positive pressure breathing so their results are not conclusive. Riley and his co-workers presented evidence consistent with capillary compression with increasing lung volume, and Banister and Torrance introduced the term "sluice effect" by which they meant that the main pulmonary vascular resistance lies in the compressed capillaries when pulmonary venous pressure is less than alveolar pressure (both pressures measured relative to intrapleural pressure).

Recent measurements of capillary blood volume by diffusing capacity methods have not clarified the situation. Apthorp and Marshall and Caughan, Marks, Elliott, Jones and Gaensler postulated that the increase in diffusing capacity with increasing lung volume was mainly due to increased capillary volume (Vc). Staub, Bruderlen, Quock and Young confirmed this prediction by finding in seven of eight experiments that Vc increased with increasing lung volume. These data support Altman's view. However, Hamer has found just the opposite, that is, Vc decreased with increasing lung volume.

We are left then with no agreement on the effect of changes in lung volume on the capillaries in normal man. Until we know what alveolar shape really is under normal conditions (next section), the exact relations of some of the small vessels to the air spaces will remain cloudy.

Discussion. What does all this imply about the effect of normal lung inflation on pulmonary vascular resistance? Several concepts have been proposed. Altman felt that pressure-flow data obtained at cardiac catheterization required acceptance of the concept that pulmonary vascular resistance decreased during lung inflation. He obtained evidence in models and in experiments on isolated lungs that supported his hypothesis. Permatt, Howell, Proctor and Riley felt that vascular resistance increased with increasing lung volume owing to capillary compression. Patel and Burton found in rabbits that resistance was high both at low and high lung volumes but was low at intermediate volumes. Roos, Thomas, Nagel and Prommas believe that resistance is little affected by spontaneous breathing. DuBois and Marshall showed that pulmonary capillary blood flow in man was not altered by normal breathing. It is clear that no final solution has been reached, but I will attempt to synthesize the many diverse views into the following picture.

In a spontaneously breathing animal with open glottis and a well-inflated normal lung-thorax system the pulmonary vascular resistance at end-expiration lies mainly in vessels other than the alveolar septal capillaries. As the lung expands in the range of useful activity and without breathing, the increasing transmural pressure distends the larger vessels, lung traction distends most of the smaller intralobular vessels, and the alveolar septal capillaries are somewhat compressed. The location of the major pulmonary vascular resistance shifts from the larger vessels to the capillaries but the total resistance of the system is not necessarily altered.

It may seem strange considering the hundreds of investigations on the pulmonary circulation that no completely consistent analysis is possible. I believe much of the data cannot be applied to solution of the problems. To achieve this we must devise experiments in intact, normally breathing animals in which simultaneous functional and anatomical analysis of the vascular bed can be achieved.

Ventilation/Perfusion Units

Air and blood entering the lungs via separate conducting tubes come into intimate relation at the terminal respiratory units. The efficiency of gas exchange for any level of ventilation and perfusion depends upon the matching of ventilation to perfusion (V/Q) in each unit. Rahn and his co-workers have contributed greatly to our understanding of the overall physiological picture. Recently, several new approaches to the analysis of V/Q problems in health and disease have been reported. In this section we shall consider what these terminal respiratory (V/Q) units actually are and how local regulation may occur.

No major anatomist considers the alveolus as the structural unit of the lung. On the other hand, most respiratory physiologists and, I presume, anesthesiologists consider it the functional unit. The word "alveolus" is used very loosely to describe a mystical
structure usually drawn as a ball on the end of a tube (the airway) (fig. 1). Let us be more precise in our choice of words. The term alveolus possesses a very specific anatomical meaning and should be used only when describing "... the ultimate respiratory chamber, the finest subdivision of the alveolar sac." 30

THE STRUCTURAL UNIT OF THE LUNG

Miller 25 considered the primary lobule to be the unit of structure. To him this meant the alveolar duct and all its distal ramifications arising from a third order respiratory bronchiolus (table 1). Hayek 43 used the continuity of alveolar epithelium as the criteria for measuring the extent of the lung unit. This leads to a larger unit than Miller's composed of a second order respiratory bronchiolus and all its associated alveolar ducts and alveoli. Macklin 39 chose a still larger quantity of lung tissue as "the single anatomical unit," namely a first order respiratory bronchiolus and its subdivisions. Thus, there has been a range of choice for the anatomical unit but never anything less than an alveolar duct system.

THE FUNCTIONAL UNIT OF THE LUNG

If the structural unit of the lung is the alveolar duct system or some multiple of it why do physiologists persist in using the alveolus as the functional unit? Hayek 43 and Weibel and Gomez 118 have estimated that there are about 300 million alveoli in human lung and 14-15 million alveolar ducts.† Thus each duct is encompassed by 20 alveoli. The primary units of structure described would include many of these alveolar ducts. For example, Hayek estimates his unit contains 2,000 alveoli (100 ducts). Figure 2-5 and figure 4-8 may help in visualizing the physical extent of these units. Figure 2-5 shows a thin fixed section along an alveolar duct system in a guinea pig lung. The alveoli completely surround the duct lumen. Figure 4-8 is a view of a section of frozen unfixed guinea pig lung showing several multi-duct units. One unit is outlined. To achieve a full three dimensional effect one must imagine that the unit rotates around the axis of its main bronchiolus. Hayek has shown that these “trees” are nearly spherical and there is almost no interdigitation between adjacent units. He has estimated there are 150,000 structural units of his type in the human lung. At a functional residual capacity (FRC) of 3,000 ml the gas volume of the average unit would be 0.02 ml. A sphere of the same volume would be about 0.35 cm. in diameter. At a total lung capacity (TLC) of 6,000 ml the average unit volume would be double but its diameter would increase only to 0.45 cm. These dimensions become significant when compared to the diffusion rates of the respiratory gas molecules, O₂ and CO₂. Their permeability coefficients (diffusion coefficient × solubility) in air are large (approximately 0.22 cm.²/sec × atmospheres for O₂ and approximately 0.18 cm.²/sec × atmospheres for CO₂ at 37°C.). Altschuler, Palmes, Yarmus and Nelson 2 give 0.6 cm./sec as the root-mean-square displacement of O₂ in air. These numbers mean that O₂ and CO₂ molecules can diffuse back and forth easily and rapidly in a unit of the size we have computed. The permeability coefficients of O₂ and CO₂ in water are, respectively, 0.07 × 10⁻⁵ and 1.4 × 10⁻⁵ cm.²/sec × atmospheres at 37°C., that is, some 300,000 and 13,000 times less than in air. The respiratory gases can diffuse as quickly through 0.45 cm. (4,500 microns) of air at a partial pressure difference of 1 mm. of mercury as they can through 2 microns 51 of alveolar capillary membrane at a partial pressure gradient of 130 mm. of mercury for O₂ and 6 mm. of mercury for CO₂.

From these calculations we can define the normal functional unit which is homologous to the structural unit. The ventilation unit of the lung is an assemblage of alveolar ducts and alveoli whose total extent may reach the dimensions of Hayek's structural unit. Krogh 52 mentioned a functional unit with a diameter of 0.2 cm. (which is similar to the one we are considering) and he equated it with a possible unit of structure. Respiratory transients, respiratory quotient, rate of breathing and the pattern of fresh air distribution within the unit will have important

† The term alveolar duct includes the alveolar sacs which, for convenience, may be regarded as short ducts. See table 1.
TABLE 2. Explanation of Symbols Used in Text

- $V$: Gas volume in general.
- $\dot{V}$: Gas volume per unit time (flow rate or ventilation).
- $Q$: Vascular volume in general.
- $\dot{Q}$: Blood volume per unit time (flow rate or perfusion).
- $V_e$: Pulmonary capillary blood volume. Should be $Q_e$ according to above definitions. Unfortunately the term $V_e$ is deeply ingrained in the literature.
- $\dot{V} \cdot \dot{Q}$: Ventilation-Perfusion ratio.
- $D_{lX}$: Diffusing capacity of the lung for gas X in terms of the quantity taken up per unit time per unit pressure gradient.
- $D_{l,max}$: The theoretical maximal possible diffusing capacity of the lung.
- $D_m$: Diffusing capacity of the alveolar-capillary membrane and plasma portion of the total diffusion path in the alveolar septae.
- $D_t$: Diffusing capacity of all the red cells in the pulmonary capillaries.

* Except for $V_e$ the symbols conform to those recommended for respiratory physiology. (Fed. Proc. 9:602-605, 1950.)

modifying effects and will have to be considered carefully in detailed computations.

VENTILATION OF THE TERMINAL AIR UNITS

The term “alveolar ventilation” is widely used in discussing lung function. It is just as much a misnomer as the “alveolus” is for the functional unit. If the unit of ventilation includes alveolar ducts and respiratory bronchioles then alveolar ventilation must also belong in part to these structures. Weibel and Gomez have calculated that 35–40 per cent of the alveolar air volume is in the ducts. Figure 2–(5 and 6) are compatible with their value.

Macklin believed that during normal breathing none of the alveolar ventilation goes to the alveoli but remains in the alveolar ducts and diffuses into the alveoli. He described the alveolar ducts as the bellows portion of the lung and believed that the alveoli change shape but not volume during breathing. Recently, we reinvestigated the location of the volume changes during breathing and found in cats, at two levels of lung volume, that alveoli as well as ducts changed volume. Under the conditions of our experiment, both structures changed volume by the same fraction of original volume, that is, their specific compliances were the same. The alveolar duct and its alveoli seemed to be ventilated as a unit. We interpreted these results as indicating that a ventilation unit is considerably larger than the alveolus.

This raises another problem involved in the term ventilation: The actual volume change in the lungs must be equal to the whole tidal volume and not just the alveolar ventilation. The difference, of course, is due to the reinpiration of the dead space gas. Altshuler and his associates studied the problem of where the fresh air goes in the terminal unit by using particles that are huge compared to the ordinary respiratory gas molecules and therefore diffuse very short distances in the gas phase in the time available for one breath. Their data suggest that the fresh air component of respiratory unit ventilation is distributed to a very small portion of the total gas phase. They interpreted this to mean that intrapulmonary mixing of fresh air is principally by molecular diffusion.

We would like to know in which portion of the ventilation unit the fresh air goes. The most likely distribution as suggested by Macklin is in the alveolar ducts since they are part of the conducting airway as well as of the alveolar volume. It is noteworthy that even if the ducts are the sites, the fresh air mixing volume computed by Altshuler’s group (10–20 per cent of alveolar volume) is considerably less than the fraction occupied by the ducts. Two models of what may happen during inspiration are shown in figure 5. The
walls at this level are determined in large part by the gas tensions in the air spaces.\(^{42, 101, 3}\)

**Control of Unit Ventilation and Perfusion**

It should be possible to regulate locally the ventilation and perfusion of the functional unit. The anatomical arrangement of one airway and a closely related inflow artery suggest that this is possible (fig. 2–3 and 4; fig. 4–8). Certainly regulation would be a simpler matter at the entrance to the unit than elsewhere. It remains, however, to demonstrate the control mechanisms. Unfortunately, we are only at the beginning of unit analysis in the lung. The smallest readily available part is the lobe, which contains thousands of units. However, even at the level of unilateral lung analysis some evidence consistent with the hypothesis of local intrapulmonary control can be cited.

Swenson, Finley and Guzman\(^{199}\) and Severinghaus, Swenson, Finley, Lategola and Williams\(^{199}\) have shown that unilateral pulmonary artery occlusion leads to decreased ventilation in the affected lung in both man and dog mainly by airway constriction caused by the low airway P\(_{\text{alveolus}}\). Thus we have a possible mechanism whereby a decrease in unit blood flow would lead to decreased P\(_{\text{alveolus}}\) in the gas and tissues of the unit and would induce constriction of the bronchiole to the affected unit.

Most investigators accept a direct constrictor action of low oxygen on the pulmonary vascular bed.\(^{100}\) In recent work using unilateral hypoxia in cats we have obtained direct anatomical evidence that the vasoconstriction is in the pulmonary arterioles at the level of the terminal bronchiole, respiratory bronchiole and alveolar duct; that is, in the arterioles leading into the terminal ventilation unit exactly where it would be expected if local control of perfusion to ventilation existed.\(^{106, 35}\)

These evidences are crude and admittedly large changes in gas tensions are needed to produce measurable responses. In spite of these objections, I think the probability is high that local mechanisms controlling a unit are important in the moment to moment regulation of ventilation to perfusion within the lung. Of course, they are not the only mech-

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**Fig. 5.** Model of ventilation unit designed only to show how fresh air may be distributed during tidal inspiration. (A) Fresh air distributed widely along core of ducts. No sudden changes in alveolar gas composition. (B) Fresh air confined to respiratory bronchioles and first order ducts. No sudden changes in alveolar gas composition.
anisms nor are they necessarily completely adequate, but in the light of a known structural and probably functional unit, it is likely that some degree of autonomous control has developed. Further analysis of smaller lung segments using both physiologic and morphologic comparisons will eventually settle the issue.

**Forces Acting at the Alveolar Level.**

The discovery by von Neergard of the importance of the gas-fluid interface in the alveoli and the recent broad development of the subject of surface forces cannot be treated extensively here. Mead's review provides an excellent discussion. However, one or two points concerning the geometry involved are pertinent (see previous section also).

In the normal lung inflated at physiologic pressures, the alveoli are not hemispherical (fig. 2–5 and 6; fig. 4–9, 14 and 16). The respiratory tissue density is too low to permit such wasteful shapes. Histologists have maintained that alveoli are irregular polygons. In lung fixed lungs, Boren found the usual alveolus to be a 10-sided geometrical figure, one side opening onto the alveolar duct. He stated that there was no appreciable curvature of the walls. These findings are compatible with the form of bubbles in foams and with close packing theory. The argument has been given, however, that histologic preparation shrinks and distorts the lung so that any tendency toward spherical alveolar shapes is lost. The rapid freezing technique that we use does not lead to more than 1–2 per cent linear dimensional shrinkage during the actual freezing. Since the lungs can be examined while still frozen and without further processing, the alveolar shapes ought to be the same as in life. Figure 4–9 shows an example from a dog lung. The alveoli are polygonal. The septae are mostly flat. Some appear curved, but the curvature is nearly always in the same direction on both sides. Sharp curvatures are present in the corners (fig. 4–14). Figure 4–16b is especially significant because at low lung volume with more or less constant alveolar tissue volume one would expect to see spherical alveoli if they exist normally. Instead, the picture shows folding of alveolar walls with little change in the septal junctions.

The fact that alveoli are not normally hemispherical should not be taken to mean that calculation of the work of lung inflation based on such models is incorrect. The problem of increasing alveolar surface is nearly the same regardless of shape. But theories evolved from spherical models to explain surface force effects on various blood vessels in the respiratory unit need to be carefully examined. We have already mentioned that the intralobular blood vessels (other than capillaries) are generally located at the junctions of alveolar septae. If one contends that surface forces help to hold these corner vessels open (see previous section), then we must face the problem of possible edema fluid accumulation because the same forces act to draw water out of the tissue and vessels. Because the corner curvature is so pronounced, the inward force even at modest surface tensions is large. On the other hand, if alveolar surface tension is very low then no fluid would be sucked out of the vessels into the alveoli, but neither would the surface forces be of much value to vessel expansion. Unfortunately, there is no present method for directly determining the surface tension in a given alveolus.

The manner of change in the shape of alveoli with changing lung volume deserves one further comment. The phrases "alveolar closure" and "alveolar collapse" are in common use to explain certain mechanical aspects of lung ventilation. Assuming that the physiologist means the proper anatomical alveolus we may ask the question, "What does a closed or collapsed alveolus resemble?" Figure 2–7e shows true alveolar closure due to alveolar duct constriction which draws the alveoli passively into long narrow pockets. It is difficult to imagine alveolar closure by any other mechanism. We have not seen this phenomenon in any normal animal lungs. It is possible that physiologic closure involves the entire functional unit and is a manifestation of changes in unit resistance and compliance rather than an actual physical shutting off such as may occur pathologically.

Collapse of individual alveoli (atelectasis) is not seen normally after the early postnatal
period. Atelectasis of entire ventilation units occurs in airway obstruction with resorption of the gas phase or by external compression. Individual alveoli can fill up with fluid in pulmonary edema (Nagano, Pearce, Sagawa, Nakamura and Staub, unpublished data), or with exudate as in pneumonia, but they should not be described as collapsed or atelectatic.

When the lung is deflated to low volumes a point is reached at which the alveolar tissues are no longer stretched. This is defined as their rest length. Beyond that point the alveolar walls gradually fold up (fig. 4-16b). Collapse of the intralobular airways would also occur at these low volumes because the traction force holding them open is gone (see previous section).

**Alveolar-Capillary Gas Exchange**

The key processes in normal lung function is the exchange of $O_2$ and $CO_2$ between the blood flowing in the alveolar capillaries and the surrounding gas. As far as we know the exchanges occur passively by diffusion.

The evolutionary solution to the problem of efficient gas exchange is the increased partitioning of the lung through which the internal surface available for diffusion has been enormously extended (fig. 2-5 and 6). There is no mechanical device that can approach the lungs in terms of blood-gas exchange efficiency. As the discussion of the ventilation unit implied, the high degree of partitioning seen in the mammalian lung has little to do with diffusion in the gas phase. It is almost entirely related to the blood phase and the need to distribute a great quantity of blood into a very thin film in such a manner that even under stressful circumstances (1) the capillary transit time during which gas exchange occurs is long enough to permit near equilibration; (2) the tissue phase of gas diffusion is minimized; (3) the resistance to flow in the pulmonary vascular bed is kept very low. In accord with this concept the comparative studies of Tenney and Remmers reveal a good correlation between alveolar surface area and resting oxygen consumption (cardiac output) among 23 mammalian species.

**The Physiologic Diffusion Process**

The diffusion process in the lungs of man or animals is measured by various tests of the diffusing capacity, $D_{L}$. An exhaustive analysis of the subject has been given by Forster. In essence, any gas can be used to measure $D_{L}$ if it is much more soluble in blood than in tissue (water) and is therefore limited in its uptake by the permeability of the alveolar-capillary membrane. There is very little implied in the description of the diffusion measurement about the structural basis for the process. The lungs may be (and all too often are) regarded as a black box. Such a viewpoint is not very helpful when one is trying to interpret diffusion data.

Of the gases that are more soluble in blood than water only oxygen and carbon monoxide (in low concentrations) have been used to measure diffusing capacity. The increased solubility of these gases in blood depends upon their chemical combination with hemoglobin in the red cells in the alveolar septal capillaries. The chemical reactions are not infinitely fast and therefore offer resistance to the process of gas exchange. Boughton and Forster used this property of gas exchange to separate the total diffusion process into the diffusion component of the alveolar-capillary membrane and plasma, $D_{M}$ and the simultaneous diffusion and chemical reaction component in the red blood cells, $D_{H}$. Of great theoretical and practical clinical interest is the fact that the equation for $D_{L}$ includes a term for the instantaneous effective pulmonary capillary blood volume, $V_{e}$.

**The Anatomical Basis for Diffusion**

Figure 4-10 through 16 show some of the morphological features at the alveolar septal level in man and experimental animals. These features have been thoroughly described and partially quantitated.

The septae are covered on both sides by a thin, continuous epithelium which has been proven to exist beyond doubt by electron microscopic studies. The actual air-fluid boundary, however, appears to be an attenuated non-cellular layer containing lipoprotein which is outside the epithelial layer. Between the epithelium and the capillaries
there is a connective tissue layer. It is also very thin but not essentially different from interstitial connective tissue elsewhere. The capillaries have a continuous endothelium without pores or other openings.

In the inflated human lung, the septae are 5-10 microns thick near full lung volume (fig. 4-14). According to Meesein the average path that an oxygen molecule would take from the septal-air interface to the erythrocytes in the capillaries is only 1.6 microns of which half (0.8 micron) is comprised of various layers of alveolar-capillary membrane and the remainder plasma within the capillary. While the preparative methods used for electron microscopy may be criticized for producing shrinkage, nevertheless the numbers given cannot be far wrong. In figure 4-14, by examining the alveolar septal profile which was prepared from rapidly frozen material, one can readily see that the tissue diffusion pathway to the red cell surface is very short. At most, it is no more than half the thickness of the total alveolar wall (2.5-5 microns).

In analyzing the frozen lungs of anesthetized animals at low ventilation pressures and with pulmonary blood flow intact, one notes that the alveolar septae are fairly smooth and flat except at the corners where the septae join and where as stated in the first section the majority of small conducting vessels lie (fig. 2-5 and 6; fig. 4-14). Some previous observers believed that the capillaries bulged into the alveolar lumen. These findings are not confirmed in our studies even in the congested lung (fig. 4-15) where the pulmonary vascular pressure was high and the transpulmonary inflating pressure was low. There is good evidence that capillaries normally behave as nondistensible tubes so that increased intravascular pressure would not be expected to cause normal pulmonary capillaries to expand into the air spaces. The old findings can be explained by the high intravascular fixation pressures used in dead lungs and by differential shrinkage of the intercapillary tissue during fixation.

All workers agree that the normal alveolar septal area when viewed full face as in figure 4-(10, 11 and 13) is mostly occupied by the capillary network (75 per cent in man). In embryological development the septal capillary network develops by the fusion of separate nets, each lying adjacent to a future alveolar surface. As the interstitial tissue decreases near term, the two nets fuse. As a consequence capillary beds in areas where there is only one side to a septum (pleural surface alveoli and those adjacent to airways and vessels) have only half the usual density of the remainder of the capillary bed.

We would like to know the size of the total anatomical capillary bed in the lungs of man. Weibel has calculated capillary volume from measured samples of alveolar septae in three adult human lungs fixed in the inflated state. He obtained an average value of 170 ml.

We can make an estimate based upon values for pulmonary tissue volume obtained by the acetylene extrapolation method and from data on the extravascular water space of the lung. The acetylene method may measure more than just the volume of the alveolar walls (airway surface and small vessels) but it will provide an upper limit. Cander and Forster report an average tissue volume of 627 ml at total lung capacity in 5 healthy men. The extravascular water space in normal humans averages 3 ml/kg. body weight. Since lung tissue is normally 79 per cent water the extravascular tissue volume is about 270 ml in a 70-kg. man. By subtraction the maximal capillary volume is about 350 ml. Until more refined data are available, let us take the value of 350 ml as the upper limit and 170 ml as the lower limit for maximal capillary volume. Chinard, Evans and Nolan have also made estimates of maximal Vc. They state the volume is 3 or 4 times that computed by Roughton and Forster which would come to some 300 ml.

Finally, before passing on to the correlation of structure and function we should note that modern studies of alveolar septae by electron microscopy do not show any nerve fibers. The filaments and nerve nets reported in the literature using light microscopy may have been reticulum which is abundant in the alveolar wall.
DIFFUSION PROBLEMS IN THE LIGHT OF STRUCTURE-FUNCTION RELATIONS

The physiologic $V_c$ near full lung volume in man at rest measured by the Broughton and Forster method generally gives values between 50 and 100 ml. This is considerably less than the maximal computed volume range and implies a large functional reserve for diffusion surface since meaningful gas exchange occurs only in capillaries perfused by red cells.

Anatomical studies of alveolar walls frozen in living animal lungs during blood flow show that normally the alveolar capillaries are not maximally filled with blood (fig. 4–11) and there may be uneven distribution of red cell content among capillaries in adjacent alveolar walls. Taken together the anatomic and physiologic data agree that only part of the total capillary bed is being used at any instant at rest.

It deserves to be pointed out that the $V_c$ measurement by the diffusing capacity method really determines the instantaneous total capillary hemoglobin. The assumption of some hematocrit value ($\bar{O}_2$ capacity) is necessary to obtain volume. Broughton and Forster assumed that pulmonary capillary hematocrit equals large vessel hematocrit. They realized that this assumption is incorrect, but since every $V_c$ is (or should be) corrected to a constant $\bar{O}_2$ capacity they are readily comparable. In recent studies we determined the pulmonary small vessel hematocrit using radioisotope tracers for red cells and plasma in rapidly frozen cat lungs. The average hematocrit in pulmonary vessels less than about 500 microns in diameter was 15% per cent less than the aortic blood hematocrit. The capillary hematocrit may be even lower. This means that the $V_c$ measured by the diffusion method actually occupies a larger volume of capillaries, e.g., a $V_c$ of 60 ml. fills 70 ml. or more of capillaries.

Using rapid frozen lung techniques we are now in a position to determine the alveolar capillary hematocrit directly (at least in some individual septae). Figure 4–13 shows two preparations in which the capillary walls (basement membrane) are stained so that we can measure the surface projection of the capillaries. If we had profile sections as in figure 4–14, stained to show capillary walls, we could determine an average cross sectional area and together with the surface projection compute the luminal volume. By counting the red cells in the capillaries and using average values for red cell volume we could calculate the hematocrit. From a more pragmatic view, it may be just as useful and far easier to compute an index of capillary hemocoit from the ratio of the number of red cells per alveolar septum to septal area. By this approach we can readily see that the hematocrit of the septae in figure 4–13 is greater than in figure 4–11 but less than in figure 4–10.

During exercise values up to 200 ml. are obtained for $V_c$. These values equal or exceed those reported by Weibel suggesting that he has underestimated maximal $V_c$. On the other hand, even the highest physiologic values reported are less than the upper limit of our estimate. However, one cannot use this as an argument that we have overestimated maximal $V_c$ until it is established that the physiologic $V_c$ has reached a limit. As yet, neither $D_{l_{\bar{O}_2}}$ nor $V_c$ shows any sign of plateauing at a maximum. But the failure to find a maximal $D_{l_{\bar{O}_2}}$ does not mean that one does not exist. Due to the finite size of the lung capillary bed, it must! I have estimated the maximal diffusing capacity for carbon monoxide by extrapolating to $V_c$ the equal to 170 and 350 ml. $V_c$ and $D_M$ data of Johnson, Spicer, Bishop and Forster. The $D_{l_{\bar{O}_2}}$ ranges between 65 and 110 ml./minute $\times$ mm. of mercury, respectively.

Newman, Smalley and Thomson have measured single breath $D_{l_{\bar{O}_2}}$ in exercising athletes and in two subjects found $D_{l_{\bar{O}_2}}$ of 75 and 82 ml. minute $\times$ mm. of mercury at $V_{\bar{O}_2}$ of 4 liters minute. Their $V_c$’s should be about 250 ml. which is still less than our upper limit. Since $D_{l_{\bar{O}_2}}$ probably equals or exceeds $D_{l_{\bar{O}_2}}$ in heavy exercise it would appear that $D_{l_{\bar{O}_2}}$ may be well over 100 ml. minute $\times$ mm. of mercury, indicating that diffusion would not normally be a limiting factor in exercise.

There are no anatomic data on the alveolar capillaries in exercise. If, however, the increase in $V_c$ is related to pulmonary vascular pressures then pulmonary congestion...
produced by elevation of pulmonary venous pressure (fig. 4-15) should provide a clue to the distensibility of the capillary bed.

As already stated, areas of alveolar septae that are not being perfused by red cells are not available for gas exchange. Therefore, there ought to be a good correlation between $D_m$ (which includes the diffusion area) and $V_c$. In normals $D_m$ and $V_c$ do tend to change correspondingly but the correlation is not very good and the data are variable among investigators. Part of the problem may be the difficulty of calculating $D_m$ which is very sensitive to the accuracy of the absolute values of $D_i$, but I do not believe that is the whole explanation. We need a much better understanding of the nature of the blood flow in the alveolar capillaries before a satisfactory explanation of the experimental results is reached. Observations of blood flow on the lung surface have not been very useful in this regard because of the great difficulty in quantitating what can be seen even if one is willing to assume that the surface vessels are truly representative of those within the lung. Theoretical discussions have failed to clarify the picture. Model experiments have given contradictory results.

Are increases in $V_c$ accomplished by perfusing more of the total capillary net or by stuffing more erythrocytes through capillaries already being perfused? The latter can occur despite our earlier statement that the capillaries are not distensible normally. Figure 4-13 shows clearly that the alveolar capillaries are larger than individual red cells and examination of the red cell clusters in figure 4-(10 and 11) will show many instances where more than one red cell occupies the same capillary cross section.

Prothero and Burton in their experiments on models assumed that pulmonary capillary flow was like that in skeletal muscle capillaries where the red cells may be slightly larger than the capillary lumen and therefore flow by being squeezed through as plugs. In linear cylindrical model systems the trapped plasma between cells is rapidly stirred and the authors conclude that the stirring aids significantly in gas diffusion into the blood. Unfortunately, the pulmonary capillaries do not fit this model very well which points up the risk of extrapolating data obtained from studying other organs. In their experiments, Moll and Pauschinger assumed that the capillaries were slightly larger than the red cells. In linear cylindrical models they found no effective plasma stirring. However, it should be noted that neither model system took into account the tremendous branching of the bed, possibly oval as opposed to circular cross section, the extreme plasticity of the red cells and the pulsatility of flow (see below). Until simultaneous diffusion and anatomical data are obtained, the explanation of the relation of $D_m$ to $V_c$ will remain unsettled.

Another problem in diffusion physiology concerns the possible uneven distribution of $D_i$ in different parts of the lung. We have already discussed the physiological ventilation perfusion unit (previous section). Such a unit would also be a diffusion unit and have a single $D_i$. There are many possible ways of describing the distribution of $D_i$ based on various ratios such as $D_i/V, D_i/V$ and $D_i/Q$. The last mentioned is of some anatomical interest because of the relation of pulmonary capillary flow to $V_c$. We might expect to see a close relation between flow and volume so that capillary transit times in the lung would show only a narrow distribution of unevenness. One problem is that when we look at the alveolar capillary bed as shown in figure 4-(11, 12 and 13) we cannot be certain that the red cells seen are taking part in flow, that is, there may be stagnant capillaries containing red cells. There is little evidence on this point. In systemic vessels closure of the precapillary sphincter generally leads to washout of any cells in the capillary due to influx of tissue fluid as filtration pressure falls below colloid osmotic pressure, but in the lungs where the hydrostatic pressure is already low such a mechanism is unlikely. In fact, when the pulmonary vascular bed is completely obstructed by intravenous injection of kerosene in cats so that pulmonary blood flow drops rapidly to zero, the lungs (studied after rapid freezing) appear normal as far as the filling of the capillary bed goes (Staub, unpublished data). This could be a serious problem because the $V_c$ measured by carbon monoxide diffusion would not distinguish be-
between flowing and stagnant blood. Thus the $V_e$ for oxygen uptake may be less than the carbon monoxide $V_e$. As of the moment, we assume the same $V_e$ for CO and O$_2$. Recently Ramos, Tuller, Lehr, and Fishman and Kral have offered evidence that could be used in support of the stagnant $V_e$ hypothesis. These investigators showed that injection of dye into the right ventricle of anesthetized animals did not diffuse the lung evenly; in fact, some areas as large as second ary lobules were completely free of dye. We have observed a similar phenomenon in rapidly frozen lungs of a cat following dye injection into the right ventricle. But in order to establish the importance of stagnation normally, much more work will have to be done.

Another form of regional variation of $D_l$ could be due to hydrostatic gradients between apex and base of the lung (approximately 30 cm, in man) and to pulsatile flow with each heart beat. From an anatomical point of view there may be local pulsation in a given alveolar septum or regional hydrostatic pulsations. Probably both occur and lead to regular variations in $V_e$. Since the measurement of $V_e$ is not instantaneous the reported values must be an average over time. Fluctuation of $V_e$ is pertinent to clinical syndromes in which pulsatile flow may appear to permit some portion of each stroke volume to flow through the capillary bed too rapidly to obtain gas exchange equilibrium.

Finally, what controls the perfusion and capillary volume in a single alveolar septum? Factors that alter total lung blood flow and $V_e$ must do so by changing individual alveolar values. Since the pulmonary micro-circulation has no known sphincters and no innervation as judged by electron microscopy I see no other choice than to conclude that the perfusion pattern within the $VQ$ unit is entirely random subject to minor factors such as microemboli, leukocytic plugs, random orientation of cells and the angle of capillaries with respect to the supply vessels.

The relation of alveolar pressure to capillary pressure is relevant to this problem because as stated before the capillaries are easily compressed by external forces. There is evidence that blood can successfully perfuse the lung even when capillary pressure is a few centimeters of water less than alveolar pressure. To explain this phenomenon it has been suggested that alveolar surface tension forces counteract some of the apparent pressure on the capillaries. Unfortunately, the anatomical evidence that the alveolar walls in inflated lungs are generally flat except at the corners (fig. 2–5 and 6; fig. 4–9) does not support this theory very well, especially in man where the alveoli are large (fig. 2–6). However, we must keep an open mind toward this and other possible explanations of these phenomena until simultaneous anatomical evidence is presented that the flow patterns are the same as in normal lungs.

**Things to Come**

I have indicated throughout this review that the solution to many vexing problems of clinical pulmonary physiology and pathology belongs to those investigators who appreciate and make use of the strong interdependence between function and structure. Physiologists who reason only with simple models will be superseded by those who visualize the total lung and its dynamic structure. Pathologists who examine only bits of collapsed formalin-fixed tissue will be superseded by those who perform post-mortem function tests and who study thick and thin sections of lungs fixed in the inflated state. This does not mean that simplified models and routine pathological sections will have no place; rather their limitations will be clearly recognized and the final authority will be whether concepts are compatible with known lung structure.

Many associates and research fellows contributed to the ideas and work that form the basis of this review. The project would have been impossible without the excellent histologic sections prepared by Mrs. Elizabeth Probert. Special acknowledgment is given to Dr. J. H. Comroc Jr. who offered helpful advice and criticism in the preparation of the manuscript.

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