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What makes a good lung?

The morphometric basis of lung function

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Summary

The functional capacity of the human lung as gas exchanger is to a large extent determined by structural design. Quantitative structure-function correlations can be established by morphometry. A very large surface of air-blood contact, together with a very thin tissue barrier, are required to permit adequate oxygen uptake under work conditions. However, these design features also pose problems, such as how to ventilate and perfuse this large surface evenly and efficiently, or how to ensure mechanical stability against surface forces with a minimum of supporting tissue. The discussion focuses on the extent to which novel design principles are used to overcome such problems by designing the airways as a fractal tree and the fibre support system as a tensegrity structure.

Key words: pulmonary diffusion capacity; bronchial tree; pulmonary acinus; gas exchange; lung mechanics; morphometry; fractal geometry; tensegrity

Introduction: a personal history

The design of the human lung is impressive. The largest organ in our body is built with only about half a litre of tissue that separates roughly the same amount of blood from a large but varying air volume of several litres. And this tissue supports a very large gas exchange surface between air and blood – nearly the size of a tennis court – that must be ventilated and perfused with blood. This suggests that lung design is the result of bioengineering optimisation, making it a "good lung" serving its function, gas exchange, well and efficiently.

But is this design really essential in all its aspects? Do we need such a large surface, for example? We know of course that a loss of gas exchange tissue, as occurs in pulmonary emphysema, leads to severe impairment of the gas exchange function. Indeed, the functional impairment is often much more severe than one would expect from the mere loss of alveoli and capillaries, because the distortion of peripheral airways causes maldistribution of air and blood supply to the gas exchange units. Similarly, the structural changes in fibrosis result in impaired gas exchange due to thickening of the barrier, but equally by deformation of the airway system and the blood vessels. It thus appears that any alteration to the delicate and well-organised structure of the pulmonary gas exchanger and its supporting structures leads to a loss of gas exchange function. The question is whether, and on what basis, we can understand and estimate the pathophysiological importance of such structural alterations.

I was confronted with this type of question in February 1959 by two eminent cardiopulmonary scientists, André F. Cournand and Dickinson W. Richards, at Bellevue Hospital in New York after giving a seminar on the structural basis of collateral circulation to the lung, a study done in Zurich [1]. Cournand and Richards had been awarded the Nobel Prize in Physiology or Medicine in 1956 for their seminal work on the pulmonary circulation which had been rendered possible after their introduction of cardiac catheterisation [2]. By this approach they were able, among other things, to measure mixed venous oxygen tension. Together with estimates of arterial and inspired P_{O2} and of O_2 uptake, they now had measurements of the four most important functional input parameters for the pulmonary gas exchanger, but otherwise the lung was a black box: what happened inside the lung could at best be imagined and modelled. But, to accomplish this, essential data on the organisation and performance of the gas exchanger were lacking [3, 4]. In particular, it was apparent that structure should have a definable effect on function, as evidenced from the disturbances of gas exchange in certain disease states, but little was known of this subject. After my seminar, therefore, Cournand invited me to join his Cardio-Pulmonary Laboratory and offered me a job. When I asked him what he ex-

No conflict of interest to declare.

pected of me he bluntly said: "Do anything on the structure of the lung that is of interest to physiology." For a young Swiss morphologist that was a challenge, and I accepted.

But: what is "of interest to physiology"? What can a morphologist contribute to the understanding of the functional processes that occur deep in the lung, inaccessible to direct observation? The answer to these questions came soon after my arrival at Bellevue Hospital from Domingo M. Gomez, a Cuban cardiologist and biomathematician [5] who had fled Fidel Castro's revolution and been given refuge by André Cournand. With his sharp mind for theoretical consideration of physiological principles, and motivated by Cournand's questions about what is happening in the black box, he had been engaged in developing models of pulmonary function and in particular gas exchange. So he asked me questions such as "how many alveoli are there in the human lung?" As there was no information to be found on this we developed a method for counting "particles" and arrived at an estimate of about 300 million alveoli in an adult human lung [6]; using a more appropriate method this number was recently corrected to 480 million [7].

But that was not what Gomez really wanted to know. He wanted to use this number to calculate parameters such as the alveolar surface area by means of simple geometric models in order to estimate the role of the internal lung surface in delivering oxygen to the capillary blood. What he wished to arrive at was a theoretical value of the conductance of the lung for diffusive gas exchange, equivalent to the pulmonary diffusing capacity DL_{O2}. This functionally most important parameter had been analysed just two years before by Roughton and Forster [8], who proposed a model for DL_{O2} with two sequential steps: the barrier's diffusion conductance and the blood's conductance and O_2 binding properties. This model suggested that structural parameters should be important determinants of pulmonary gas exchange capacity. It thus was clear that what really interested physiologists were accurate quantitative data on lung structure that could be used in formulating models of lung function.

The programme I had to engage in was what we would later call "morphometry of the human lung", a really vast and also challenging programme because the methods of obtaining such information were not readily available at the time. The problem was that, to study alveoli and capillaries, or the tissue barrier and its cells, thin sections and the microscope had to be used. This introduced two serious problems: (1) what one is looking at in the microscope is a minuscule fraction of a very large organ, and so we have a sampling problem; (2) perhaps more seriously, the three-dimensional alveolar surface appears on the section as a linear trace, and thus the problem was how to estimate the 3D surface area from 2D measurements on sections. This was again a sampling problem, but one related to the geometric probability of hitting a surface with a section plane as a geometric probe [9]. Sound solutions to such problems depended primarily on collaboration with mathematicians [10–12] and this led to the development of a powerful set of measuring methods called stereology [13–17]. Stereology is still the state-of-the-art methodology to obtain efficiently accurate quantitative information on cell, tissue and organ structure [18, 19]. And in 1960 it provided me with the tools to undertake the study of lung structure in a way that "was of interest to physiology" [20].

The morphometric basis of pulmonary gas exchange

The model that Domingo Gomez wanted to formulate was based on the equation introduced in 1909 by Christian Bohr [21] describing the O_2 uptake $\dot{V}_{O2}$ as the product of the O_2 partial pressure difference between alveolar air and capillary blood as driving force, and the conductance of the system called the pulmonary diffusing capacity DL_{O2}:

$$\dot{V}_{O2} = (PA_{O2} - Pb_{O2}) \cdot DL_{O2}.$$

As suggested above, DL_{O2} is largely determined by morphometric parameters of the alveolar-capillary complex. Figs. 1–4 show that the capillaries form a very dense network in the alveolar septa; the capillaries are about the size of an erythrocyte and they are exposed to alveolar air on both sides. We also note that the barrier separating the erythrocytes from the air is composed of a tissue membrane – made of thin lamellae of epithelial and endothelial cells joined by a very thin interstitial space or simply a basement membrane (fig. 4) – and a layer of blood plasma; these are the layers that must be traversed by diffusion driven by the O_2 partial pressure difference between air and blood. The oxygen molecules then enter the erythrocyte to be eventually bound to haemoglobin, a process determined by the combination of diffusion and chemical reaction between oxygen and haemoglobin. Roughton and Forster [8] proposed a model for DL_{O2} that divides the total conductance into two serially arranged partial conductances, one for the membrane, DM_{O2}, and one for the erythrocytes, De_{O2}. The conductance DL_{O2} is obtained by adding the two partial resistances, i.e. the reciprocals of the conductances:

$$DL_{O2}^{-1} = DM_{O2}^{-1} + De_{O2}^{-1}.$$

The two partial conductances can be formulated as a function of the determinant morphometric parameters, together with appropriate physi-

Figure 1

Scanning electron micrograph of human lung parenchyma. Alveolar duct is surrounded by alveoli, which are separated by thin septa.

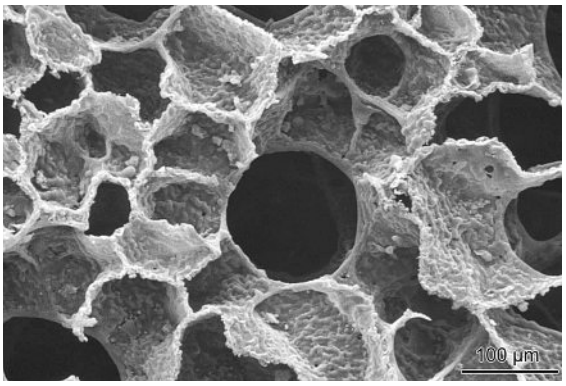


Figure 2

In the alveolar wall, shown in a scanning electron micrograph from a human lung, the capillary blood with its erythrocytes is separated from the air by a very thin tissue barrier.

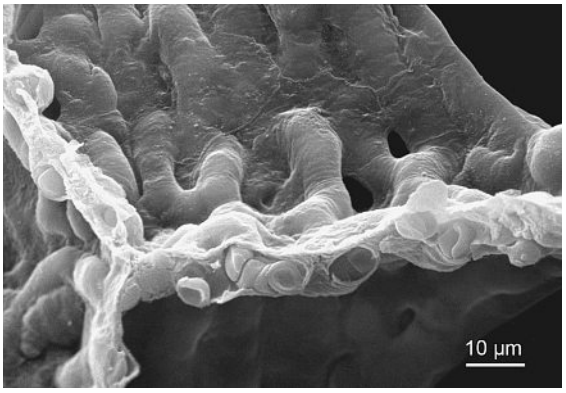


Figure 3

Unit of capillary network in alveolar wall connected to terminal branches of pulmonary artery and vein; blood plasma labeled with colloidal gold.

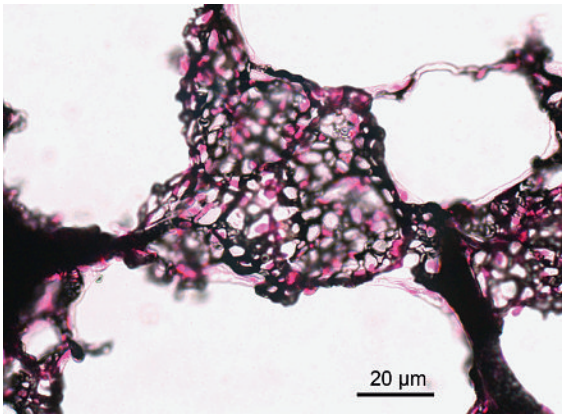


Figure 4

Alveolar capillary bounded by endothelial cell sits in alveolar septum lined by type 1 epithelial cells on both sides. Note thin tissue barrier on top and slightly thicker barrier with some connective tissue fibres and fibroblasts at bottom.

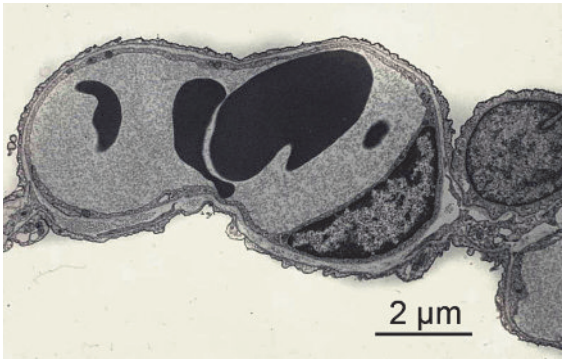


Table 1

Morphometric estimate of DL_{O2} for young, healthy adult humans of 70 kg body weight, measuring 175 cm in height[a].

Morphometric data (mean ± 1 SE)			
Total lung volume (60% TLC)	4340	±285	ml
Alveolar surface area	130	±12	m^2
Capillary surface area	115	±12	m^2
Capillary volume	194	±30	ml
Tissue barrier harmonic mean thickness	0.62	±0.04	µm
Total barrier harmonic mean thickness	1.11	± 0.1	µm
Diffusing capacity DL_{O2}	158		ml/min/mm Hg

[a] Data from Gehr et al. [29] and Weibel et al. [24].

cal coefficients [22, 23]. Thus the membrane conductance is

$$DM_{O2} = K_{O2}\cdot[S(a) + S(c)]/2\cdot\tau_{hb}$$

where K_{O2} is the diffusion coefficient for oxygen in the tissue, S(a) and S(c) are the alveolar and capillary surface area respectively, which are averaged to define the gas exchange surface; τ_{hb} is the harmonic mean thickness of the barrier measured as the distance between the alveolar surface and the erythrocyte membrane, i.e. tissue and plasma layers combined into one layer [24]. The diffusion conductance of the erythrocytes is a more complex phenomenon because oxygen molecules that diffuse into the haemoglobin mass also enter a binding reaction with haemoglobin; as there is no easy solution for this complex process, Roughton and Forster [8] proposed a simple relationship:

$$De_{O2} = \theta_{O2}\cdot V(c)$$

where V(c) is the volume of capillary blood, and the factor θ_{O2} is the reaction rate of oxygen with whole blood as measured *in vitro*, a factor difficult to estimate experimentally [25, 26].

It is evident that this model of the pulmonary diffusing capacity DL_{O2} formulates the quantitative effect of lung structure on gas exchange function on the basis of morphometric data: surface areas, volumes and barrier thickness. Such data were not available in 1959, and there was no obvious way of obtaining them; hence the task we were facing was (1) to develop the necessary morphometric methods, (2) to prepare reasonably fixed lungs from normal humans, and (3) to perform the measurements that yielded a set of data usable in the model calculations. But this turned out to be a lengthy and difficult process. Because gas exchange occurs in structures at the sub-micrometer scale, electron microscopy is required to achieve adequate resolution; the human lung specimens available at the outset of the programme were adequate for light microscopy [6, 27], but fixation for electron microscopy was achievable only for small animal lungs [28]. Also, efficient stereological methods had to be developed that would allow accurate estimates of microstructural parameters in very large specimens. All these methods were gradually developed over the ensuing years until, in 1978, Peter Gehr and Marianne Bachofen had obtained all the necessary estimates on a set of normal human lungs and could calculate DL_{O2} for the first time [29]; these data, in part revised on the basis of later studies [24] are reported in table 1.

The first remarkable finding is that the area of the alveolar gas exchange surface is on the order of 130 m^2, an area equivalent to about ¾ of a singles tennis court, and that the capillary surface area is similar. The capillary blood volume amounts to about 200 ml; spread out over this large surface this represents an extremely thin layer of blood, just about half as thick as an erythrocyte, because the capillary is contained in the walls between two alveoli and is thus exposed to air on both sides of the septum (figs. 2 and 4). As

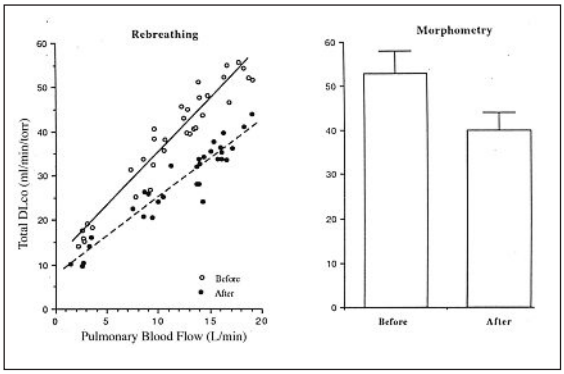


Figure 5

Effect of left pneumonectomy in dogs on pulmonary diffusing capacity for CO, estimated physiologically by rebreathing technique at increasing exercise intensities measured by blood flow (left), and morphometrically (right) before and after pneumonectomy. Adapted from [32, 65].

we note from fig. 4, the tissue barrier between air and blood varies greatly in thickness, from the thicker parts where epithelial or endothelial cells as well as fibre strands are contained, to the much vaster thin parts where the barrier corresponds merely to two very thin cytoplasmic lamellae of the endothelial and type 1 epithelial cells separated by a single basement membrane; the average thickness of this tissue barrier amounts to about 1.6 µm. This estimates tissue mass but is not relevant for the estimation of diffusion conductance: because O_2 flow across the barrier is inversely proportional to local thickness, it is greatly favoured by the thin parts. The relevant thickness estimate is therefore the harmonic mean, i.e. the mean of the reciprocal thicknesses, and this is estimated at 0.6 µm (table 1). On the other hand, the model for calculating DM_{O2} is formulated to require an estimate of the harmonic mean *total* barrier thickness, tissue and plasma taken together [24]; the justification for this choice is that diffusion across these layers is much faster than blood flow, and thus the plasma layer is quasi-static; total barrier thickness in the human lung is estimated at a little over 1 µm, and thus nearly twice the tissue barrier (table 1).

With all these estimates at hand we can now calculate a theoretical value for the pulmonary diffusing capacity DL_{O2}. This yields a value of about 150 mLO_2 per min for a P_{O2} difference of 1 mm Hg, and we find that the two serial resistances of membrane and erythrocytes contribute about equally to the overall resistance. This theoretical value means that an O_2 uptake of 400 mL/min, what a normal human would need under resting conditions, can be achieved with a P_{O2} difference of only 3 mm Hg. This seems very low, and we know that physiological estimates of DL_{O2} in the clinical laboratory are commonly found to be about 30 $mL \cdot min^{-1} \cdot mm\ Hg^1$, thus ⅕ of the theoretical value. Does the theoretical value of 150 make any sense? Probably yes, because an O_2 uptake rate of 400 and a DL_{O2} of 30 correspond to a person completely at rest, but the lung can hardly be designed to satisfy merely this condition. As soon as we engage in any kind of activity O_2 needs increase rapidly and in heavy exercise easily reach an O_2 uptake rate of 4 L/min, hence 10-fold the resting value, and the lung must be fit to allow this high flow rate as well. Physiological estimates of DL_{O2} in heavy exercise yield values of the order of 100 $ml \cdot min^{-1} \cdot mm\ Hg^{-1}$ [30], which is closer to the theoretical value but still somewhat lower.

The first question is whether we can trust the theoretical value of DL_{O2} calculated from accurate morphometric data and using the best available physical coefficients. This cannot easily be determined on the human lung, and hence we must have recourse to experimental studies where physiological and morphometric measurements can be done on the same lungs and under exercise conditions. One such set of studies is the assessment of the functional loss of gas exchange capacity following reduction of the gas exchange structure by partial pneumonectomy in dogs [31, 32]. In these studies the pulmonary diffusing capacity was estimated using CO as a tracer gas that binds avidly to haemoglobin, and the theoretical value of DL_{CO} was calculated with the same morphometric approach as described above, except that physical coefficients for CO rather than O_2 were used. These studies have shown that the functional estimate of DL_{CO} under heavy exercise conditions agrees with the morphometric estimate: two years after left pneumonectomy, where 40% of the gas exchange tissue is lost, the physiological as well as the morphometric DL_{CO} were reduced to 70% of controls (fig. 5); this is higher than expected for the 60% residual lung, because the capillary network becomes enlarged since now the entire blood flow must pass through the reduced vascular system, but there is no tissue growth [32]. This general finding was confirmed in further studies [33], and thus we can apparently accept the theoretical estimate of DL_{O2} in general and for the human lung in particular.

We must therefore conclude that, in contrast to dogs, the human lung has an excess gas exchange capacity by a factor of about 1.5. It is interesting that this has a corollary in earlier findings comparing goats to dogs and cows to horses, i.e. "normal" sedentary animals to notoriously athletic species [34, 35]: whereas the dogs and horses fully exploited their pulmonary diffusing capacity in heavy exercise, both the goat and the cow did not: they had an excess DL_{O2} of about 30%, which is thus similar to what we found in "normal" humans. It is now interesting to note that well-trained human athletes, such as marathon runners, achieve a maximal O_2 consumption rate that is about 1.5 times higher than the untrained "normal" human of the same size [36]. It may now be speculated that the athletes fully use the diffusing capacity of their lungs, thus exploiting the reserve to supply O_2 to their muscle at the higher rate. And we may further speculate that in athletes the lung can become a limiting factor for endurance performance. A number of arguments could be advanced in support of such a hypothesis: the first is that apparently, in the adult, the lung is unable to increase its gas exchange structures to accommodate the higher O_2 flux rate required by exercise training, whereas we

know that muscles increase their mitochondria and capillaries under such conditions [37]. This failure to adjust lung structures to need is also shown in the pneumonectomy studies on dogs, where true compensatory growth of lung structures, capillaries and alveolar walls, occurred only if the pneumonectomy was performed in puppies but not in adults [38].

This then leads to the conclusion that a "good lung" is made of a gas exchanger designed to offer a large surface and a thin barrier, to ensure the O_2 supply required when we work at a high rate. That DL_{O2} is designed with a certain excess capacity appears to serve as a safety factor to ensure oxygenation of the blood even when working under unfavourable conditions, and it may enable athletes to train their muscles and the supplying vasculature up to the limit set by the capacity of the pulmonary gas exchanger.

Problems of servicing a very large surface and stabilising it with little tissue

The two key design features of a "good lung" are hence a very large surface area and a very thin tissue barrier, features that are precarious and raise two questions of physiological significance: (1) how is it possible to accommodate this surface within the limited space of the chest cavity and still allow for efficient ventilation and perfusion; and (2) how is it possible to support, maintain, and stabilise a surface area of the size of a tennis court with so little tissue?

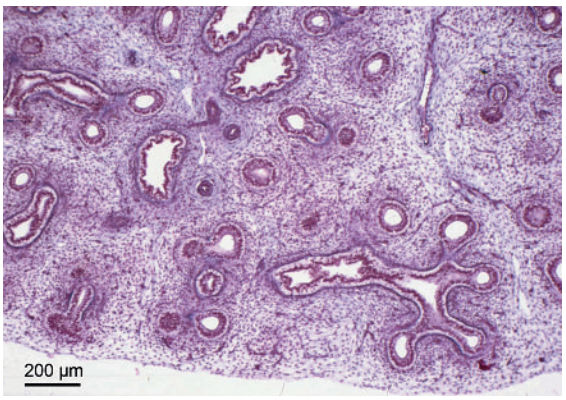


Figure 6

Section of foetal human lung showing the branching of epithelial airway tubes by dichotomy within the mesenchyme containing branches of the pulmonary artery (close to airways) and veins (in septa).

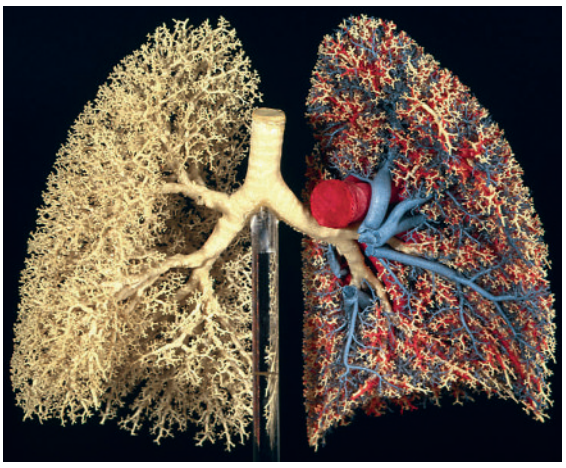


Figure 7

A resin cast of the human airway tree shows the dichotomous branching of the bronchi from the trachea and the systematic reduction of airway diameter and length with progressive branching. In the left lung the pulmonary arteries (*red*) and veins (*blue*) are also shown.

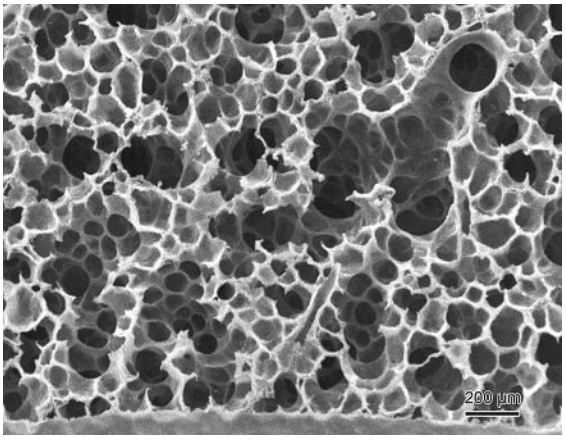


Figure 8

Scanning electron micrograph of alveolar ducts and sacs in a perfusion fixed rabbit lung.

With respect to the first question the bioengineering problems to be solved by design are (a) how to build a sprinkler system to supply a few hundred million gas exchange units with O_2-rich air and with blood, and (b) how to fold up a sheet of 130 m^2 to fit into a space of 5 liters – equivalent to packing a letter into a thimble – while ensuring precise connections of the sprinkler system to the surface units. The solution found is to develop both these features together during morphogenesis of lung structure, and the result shows that principles of fractal geometry [39–41] come into play both in designing airways and blood vessels and in the process of folding up the surface: airways form a space-filling tree on whose terminal generations the gas exchange surface is formed.

Lung morphogenesis starts with an anlage in the form of an epithelial tube derived from the foregut, which branches sideways forming the two lung buds. These grow and branch by dichotomy into the mesenchyme of the visceral pleura (fig. 6), by a fractal pattern of growth and division to form a space-filling structure until eventually a tree of 23 generations is formed. Blood vessels form in the mesenchyme as a vascular network around the tips of the airways, connected to branches of the pulmonary arteries that lie close to the developing airway tubes, whereas the pulmonary veins lie in the septa (fig. 6). The result of this is a system of three closely related trees (fig. 7): the pulmonary arteries branch in parallel with the airways whose course they closely follow, whereas the pulmonary veins take an intermediate position between broncho-arterial units, using interlobular or intersegmental septa as guiding structures.

The gas exchange surface forms on the wall of the most peripheral generations of the airway tree tubes by a complex process: while the mesenchyme is reduced to thin sheets, a capillary network forms in close association with the epithelial

airway lining. The capillaries thus become intercalated between two air saccules to be exposed to air on both sides; secondarily, alveoli are formed by pulling in septa with a network of strong connective tissue fibres which will constitute the walls of the alveolar ducts [42]. The packing of the large surface into a limited space is thus achieved by sequential subdivision of an originally simple "bubble" into a foam-like structure (fig. 8), a process that follows principles of fractal geometry [39, 40] as the surface increases by systematic "internal crumpling" without increasing the containing volume.

Designing the airway tree for efficient ventilation

If we first consider the airway tree more closely we note that, in spite of some irregularity, its branching pattern is basically the same at all levels, from the large airways to the small peripheral bronchioles (fig. 7): as the airway divides into two branches the length and diameter of the daughter branches are reduced by a constant factor, at least from the trachea out to the terminal bronchioles; this feature is called self-similar branching and is one of the hallmarks of fractal trees [39, 40], as represented by the model tree of Mandelbrot (fig. 9), which in fact represents the basic features of the bronchial tree quite well. This has fundamental consequences for the functional design of the airway tree: such a structure is naturally space-filling, i.e. its tips are rather homogeneously distributed in the lung space, with the functional consequence that the distance along the airways from the trachea to the terminal (gas exchange) units is approximately the same for all units whether they are located near the pleura or near the central airways, a design property that favours homogeneous ventilation of all units. This is, of course, a gross simplification as there is considerable irregularity resulting from the fact that the two daughter branches may have different diameters and lengths to accommodate to the local space conditions, so that there is some degree of variation in the path length to the terminal units [27]. But the main point here is to find the basic construction principle by which all points in a defined space, here the chest cavity, can be reached in the most efficient manner; reality, of course, is not as perfect as the models predict and this may contribute to uneven ventilation, for example.

When, in 1962, Domingo Gomez and I analysed the cast of a human bronchial tree similar to the one shown in fig. 7 we found, by searching for a basic construction principle, that the diameter of the airways was reduced with each generation by an approximately constant factor (fig. 10) that, on average, was equal to the cube root of ½ or 0.79 [6]. It turns out that this factor corresponds to an optimised hydrodynamic condition of air flow in a branched tube system as formulated in the Hess-Murray law [43, 44], which tends to minimise (a) work to overcome flow resistance as well as (b) dead space volume. It thus appears that the airway tree is designed according to optimality principles with respect to hydrodynamics. However, a recent re-analysis of these data by Mauroy and Sapoval [45] revealed that the reduction factor is about 0.85, and thus a little larger than the ideal factor of 0.79. What this means is that flow resistance falls gradually towards the smaller airways [46]. This has been interpreted as a safety factor preventing the ill-effects of increased flow resistance in bronchioles when narrowed by the action of their smooth muscle sleeve or by interstitial oedema such as occurs in asthma. This safety factor is paid off by a slightly larger dead-space volume, but this fact is of lesser consequence: we should remember that the volume of the airway tube increases with the square of the diameter, whereas, according to the law of Poiseuille, resistance is affected in proportion to the 4th power of the diameter.

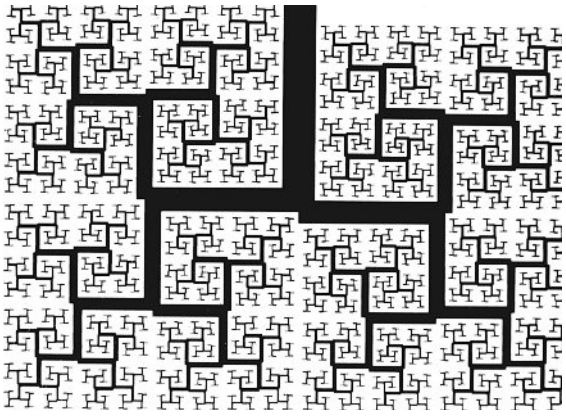


Figure 9

Fractal tree of Mandelbrot. From [39] by permission.

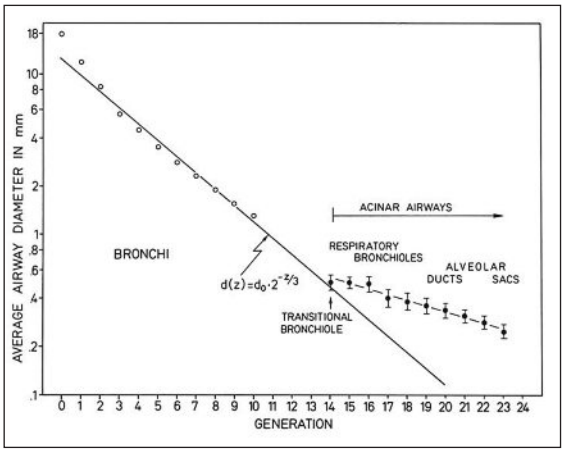


Figure 10

Average diameter of airways in human lung decreases with generations of airway branching.

Architecture of the gas exchanger and its functional consequences

If we now consider the way in which the airway system leads into the gas exchanger, we note that, for a human airway tree with an average of 23 generations of dichotomous branching, generations 0–14 are conducting airways (fig. 11) lined by a bronchial epithelium and with the branching properties described above. In generation 15, on average, alveoli with gas exchange surface begin to be incorporated in the airway wall and the first order respiratory (or transitional) bronchiole is formed. After about three generations the airway wall is completely decorated with alveoli; alveolar ducts thus formed (fig. 12) continue to branch until, in the last generation, the alveolar sac is blind-ending (figs. 8 and 11). Accordingly, generations 15–23 form what is called a pulmonary acinus, the unit of the gas exchanger that is ventilated by one transitional bronchiole: on inspiration fresh air flows along the conducting airways into the acinus, and all of the approx. 10 000 alveoli of an acinus receive O_2-rich air from the same supply source, and this may have functional implications.

This architecture is therefore very different from the classical models of the gas exchanger as it appears in most textbooks, where a bubble-like alveolus, associated with a capillary, is attached to the end of the last airway branch (fig. 13a). As a result of the combined development of the airway tree and the gas exchange surface, as described above, the gas exchange units, basically represented by alveoli, are arranged on the surface of the alveolar ducts, forming the approx. 8 terminal generations of the airway tree (fig. 11 and 13b). Thus, when O_2-rich air reaches into these acinar airways during inspiration, the sequentially arranged alveoli are ventilated in series (fig. 13b): the most central alveoli see fresh air whereas the air reaching more peripheral alveoli has already lost some O_2 on its passage through some gas exchange units. This is functionally significant because the arrangement of the blood vessels is different: capillary network units, which are about the size of an alveolus, are supplied by a terminal branch of the pulmonary artery and drained by a similar venous branch (fig. 2), so that all capillary units receive mixed venous blood of the same O_2 content. As a result, we can say that the alveolar-capillary gas exchange units are perfused in parallel whereas they are ventilated in series (fig. 13b). Since gas exchange occurs wherever mixed venous blood is exposed to O_2-rich alveolar air, we may suspect that central alveoli are favoured, the driving force for diffusive O_2 uptake being high,

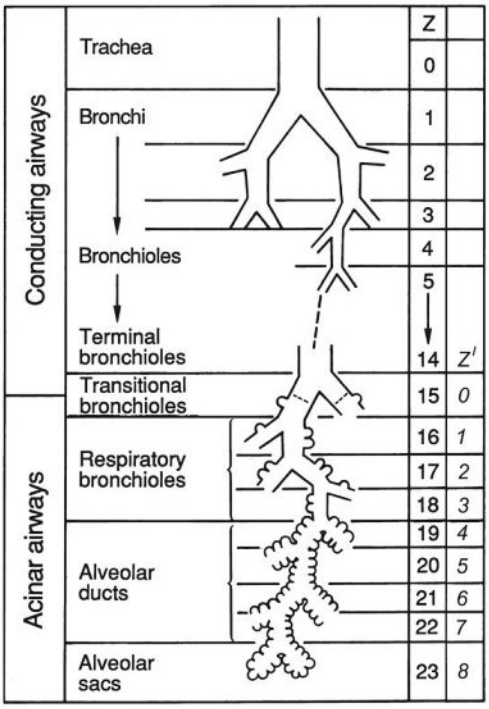


Figure 11

Model of airway branching in human lung by regularised dichotomy from trachea (generation z = 0) to alveolar ducts and sacs (generations 20 to 23). The first 14 generations are purely conducting; transitional airways (generation 15) lead into the acinar airways with alveoli branching over eight generations (z'). *Modified after [27].*

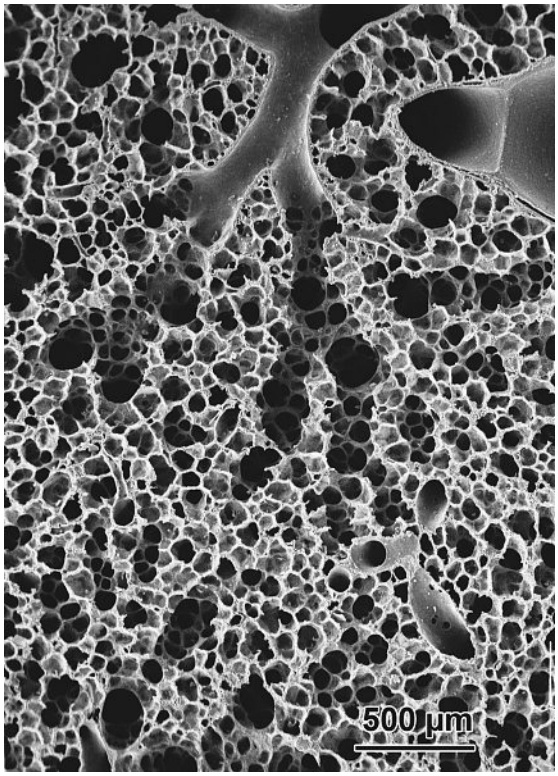
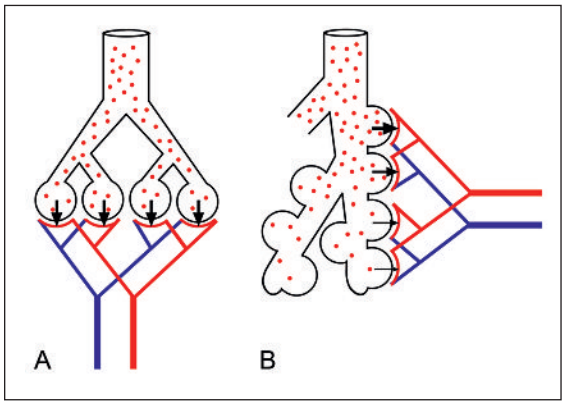


Figure 12

Terminal conducting airways branch by dichotomy and lead into the alveolar ducts that constitute the pulmonary acinus.

Figure 13

Models of ventilation-perfusion relationship in the mammalian pulmonary gas exchanger. *A.* Parallel ventilation/parallel perfusion. *B.* Serial ventilation/parallel perfusion. [*From 47*]



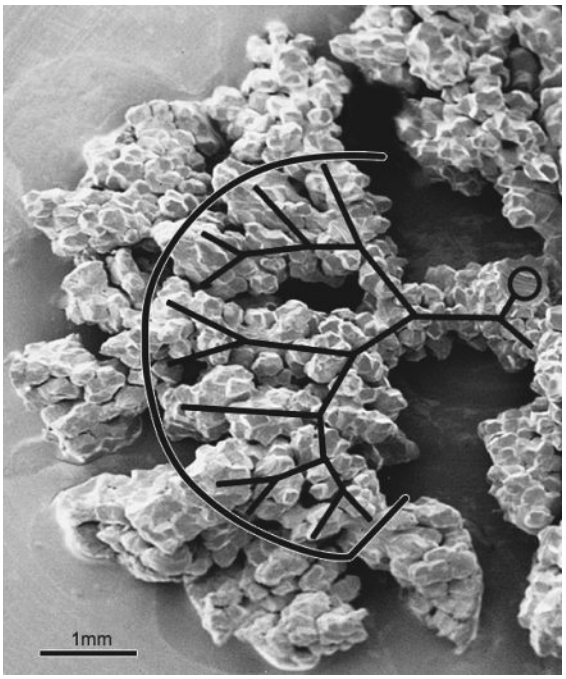


Figure 14

Alveolar ducts in acinus of human lung shown in silicon rubber cast spread out to show the course of the subsequent branchings. The curved line marks the approximate boundary to the last generation, to show that this generation of alveolar sacs comprises over half the gas exchange area of the acinus.

corresponding to the difference between inspired and mixed venous P_{O2}. This extracts some O_2 from the air in the alveolar ducts so that a P_{O2} gradient forms along the acinar airways (fig. 13b), a process called "screening" which may cause the O_2 concentration in the air space to become very low towards the periphery [47]. This may well introduce a functional problem, namely the danger that the last alveoli do not receive enough O_2 to oxygenate the blood, which would cause venous shunts to occur. This could be of great functional significance because, as a result of sequential branching, the last generation of acinar airways contains at least half the entire gas exchange surface (fig. 14) and thus must receive an adequate O_2 supply.

In order to estimate the importance of screening we must note that, upon inspiration, fresh air flows into the first orders of acinar airways – deeper in exercise than in resting ventilation – but beyond this the air flow velocity becomes so slow that O_2 proceeds to the more peripheral generations by diffusion in the air phase [47]. Hence gas exchange is dependent on two diffusion steps: O_2 diffusion through the air phase to the gas exchange surface, and O_2 diffusion across the barrier into the blood. Screening is determined by the relationship between the conductance to *reach* the gas exchange surface and the conductance to *cross* the barrier into the blood. Each of these conductances is determined by a physical factor and a morphometric parameter: the physical factors are D_{O2}, the O_2 diffusion coefficient in air, and W_{O2}, the O_2 permeability of the barrier; the morphometric parameters are S(A), the gas exchange surface that determines the conductance to cross the barrier, and L(ac), the size of the acinus that determines the conductance to reach the surface. The physical analysis of this process predicts that screening becomes a problem if the ratio of the physical factors D_{O2}/W_{O2} is larger than the ratio of morphometric parameters S(A)/L(ac) [47]. Optimal conditions are ensured if these two ratios are about equal: the physical factors being given quantities, the morphometric parameters must be adjusted to match them during morphogenesis. A detailed analysis of this situation has shown that the morphometric properties of the mammalian acinus, including the human, are indeed well matched to the physical conditions, so as to avoid screening [47, 48]. Problems may, however, occur in some disease states, for example in emphysema where the size of the acinus is enlarged and the surface area reduced, causing the morphometric ratio S(A)/L(ac) to be much smaller than the physical ratio D_{O2}/ W_{O2}; this results in severe screening, is one of the important contributing factors to impaired gas exchange, and may explain why gas exchange disturbance can be much greater than the mere loss of alveolar surface area would predict.

What is then the virtue of this architecture where the gas exchange surface is distributed along the last generations of branching airways? The first point is that packing of the alveolar surface into a very limited space is maximised, thus optimising the conditions for "ventilation of the surface by diffusion". By limiting the size of the acinus the conditions for "ventilation by air flow" can be optimised by (a) designing a well proportioned branched bronchial tube system (see above) with (b) a smooth surface, that, above all, can also be provided with a "catchy" surface lining designed to capture the load of nanoparticles etc. which should be prevented from reaching the alveoli, thus serving as a cleansing device for inspired air [49]; by enwrapping the particles in a film of surfactant they are made hydrophilic and can thus be displaced into the hypophase [50, 51], where they may be removed, e.g. by macrophages, or penetrate through the tissue into the capillaries [52]. Mammalian lungs are apparently designed in a highly favourable way, considering all these boundary conditions. With respect to the architecture of the gas exchanger in the acinus, the rule is that "smaller is better – but not too small" [47].

The problem of maintaining stability of the airspace complexity

Perhaps one of the most remarkable features of lung structure is that a rather extensive and complex architecture is established with so little tissue for support: the very large gas exchange surface is supported by a tissue sheet less than 1 µm thick, which is exposed to blood pressure on the

Figure 15

Fiber continuum of human lung with axial fibres deriving from the airways (red), peripheral fibres connected to the pleura (black) and septal fibres in alveolar walls (green).

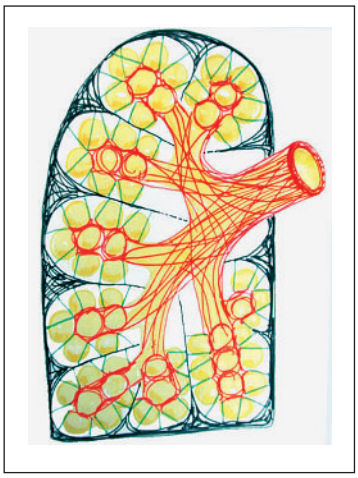


Figure 16

The relation between axial, septal and peripheral fibers in an alveolar duct and their relation to the surface forces acting on the alveolar complex, marked by arrows; these tend to shrink alveoli and to push on the free edge of the alveolar septa at the alveolar duct, which is supported by a strong fibre bundle of the axial network (see fig. 17B).

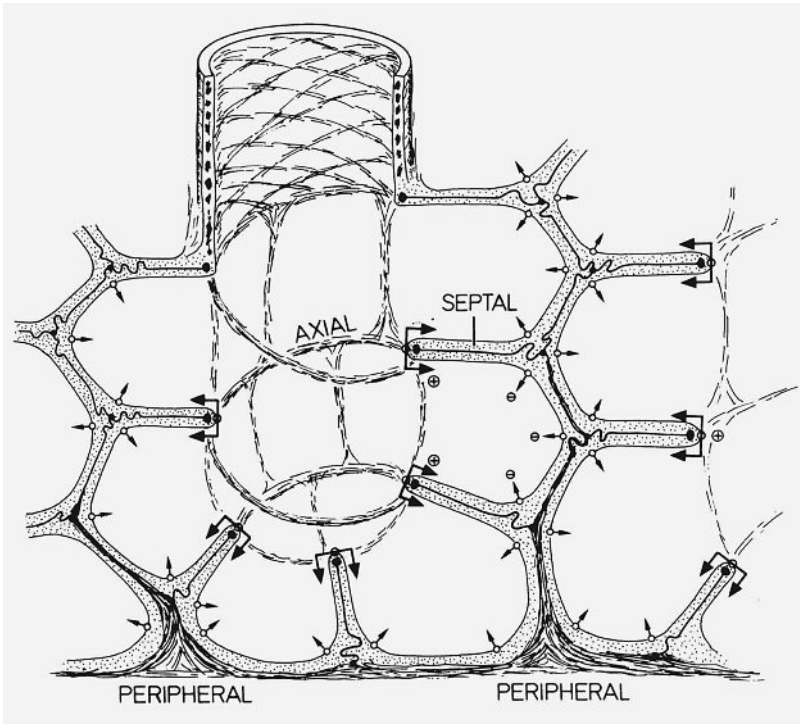
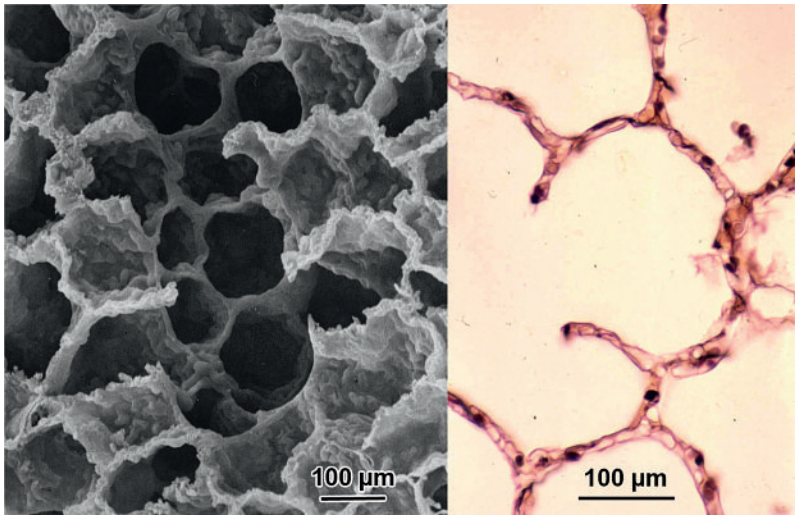


Figure 17

Alveolar duct shown (A) in scanning electron micrograph to illustrate the relation of alveoli, septa and ducts with the network of alveolar entrance rings forming the wall of the duct, and (B) in light micrograph where the elastic fibres are stained black to demonstrate the strong fiber support of the free edge of the alveolar septa.



side of the capillaries and to surface forces on the air side. Such a structure can only be maintained stable by adequate design of the supporting structures.

The first design feature of importance is the establishment of a fibre continuum which pervades the entire lung tissue system from the pleura to the major airways. This fibre system can be divided into three parts (fig. 15):

– the *axial fibre system*, anchored in the hilum, forms the wall of airways all the way out to the alveolar ducts and sacs in the acinus, and thus establishes a branched axial scaffold of lung parenchyma (fig. 16);
– the *peripheral fibre system* originates in the connective tissue bag of the visceral pleura and extends into lung parenchyma as a hierarchical system of interlobular septa, and is thus located at the periphery of the acini;
– the *septal fibre system* forms within the alveolar walls in close association with the capillary network and is anchored in both the axial and the peripheral fibre systems, thus establishing a fibre continuum that spans across the acinus as a 3D maze (figs. 16 and 17).

Examining the architecture of the alveolar septum in more detail, we note first that its very delicate network of elastic and collagen fibers is interwoven with the capillary network (fig. 18), the fibre strands thus appearing alternately on one side or the other of the capillary; this measure is designed to efficiently reduce the thickness and the diffusion resistance of the air-blood barrier, leaving half the capillary surface with a minimal barrier composed only of the endothelial and epithelial leaflets with a fused basement membrane (fig. 4). This arrangement also allows the capillary network to be supported in a simple fashion with a minimum of fibres spanning between the peripheral fibres of interlobular septa to the strong axial fibre tracts forming the wall of the alveolar duct (fig. 16). There are no loose ends in this fibre system (fig. 17).

This fibre system is now under constant tension through the outward pull of the visceral pleura which is transmitted to the septal fibres and the axial fibre system. The lung thus becomes a tensegrity structure [53, 54] whose form is maintained by the tension on the fibre continuum; if one fibre of this continuum is cut the structure will collapse, at least in the part of the alveolar complex that "hangs together" in the acinus; this results in deformation of the peripheral airways in emphysema, particularly in its centrilobular form where parts of the axial fibre system are snapped, causing collapse of the peripheral airways.

But is this fibre continuum enough to stabilise the complex inner architecture of lung parenchyma? The answer is no, the problem being surface tension in the small bubbles that would tend to collapse the alveolar complex, especially since alveoli are all open to the airway sys-

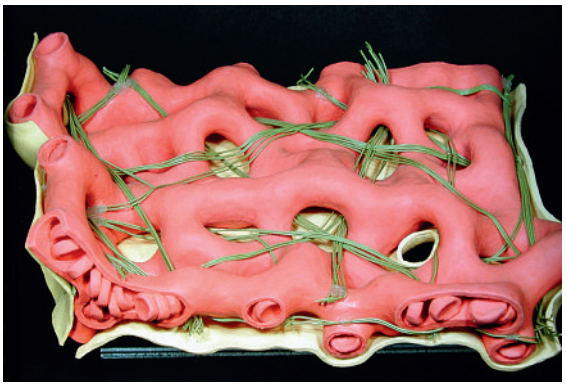


Figure 18

Model of capillary network in alveolar septum (compare with fig. 2) interwoven with the meshwork of connective tissue fibres (green) with strong fibre bundle in free edge of septum at right.

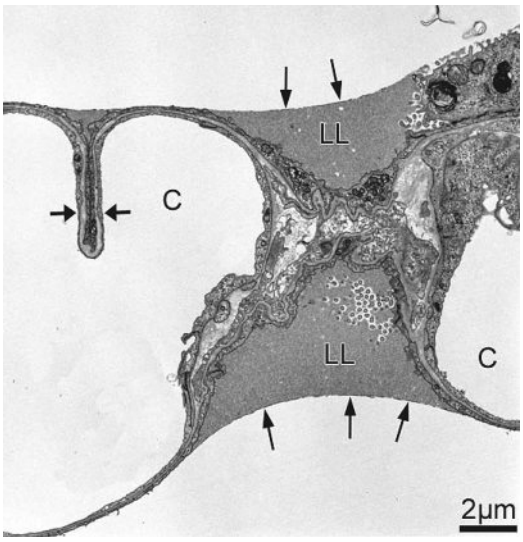


Figure 19

Alveolar septum of human lung fixed by perfusion through blood vessels shows alveolar lining layer in crevices between capillaries (C) topped by surfactant film that appears as a fine black line. Note the type II cell with lamellar bodies and the fold in thin tissue barrier.

tem. The fibre system cannot support the tensions that form, for example, on the free edge of the alveolar entrance rings (fig. 17 and 18a). To prevent collapse the alveolar surface is provided with a duplex lining layer (fig. 19), with a watery hypophase that smoothes surface irregularities, topped by a film of surfactant at the air-liquid interface [55, 56], secreted by the type 2 alveolar epithelial cells (fig. 20) [57, 58]. This film has dynamic properties that enable the lung to cope with the problems associated with ventilation dynamics [59, 60]: on expiration alveoli become smaller, and this would cause the surface force to increase, with the danger of alveolar collapse. But due to its biophysical properties [61] the phospholipid surfactant film reduces its surface tension to nearly zero as it is compressed when the alveoli shrink, with the result that the collapsing surface forces vanish; upon inspiration the alveoli can then re-expand easily. In this dynamic process the fibre continuum plays a central role as it distributes the forces generated by the respiratory muscles in the chest and diaphragm to the alveolar septa throughout the lung, thus ensuring that the gas exchange surface remains unfolded to allow diffusion of O_2 from the air into capillary blood.

How to build and maintain a thin air-blood barrier

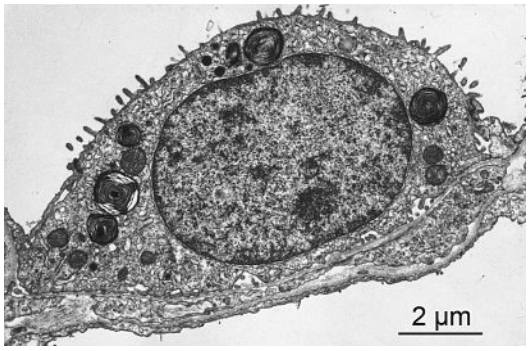


Figure 20

Type 2 alveolar epithelial cell as secretory cell for surfactant stored in lamellar bodies (black).

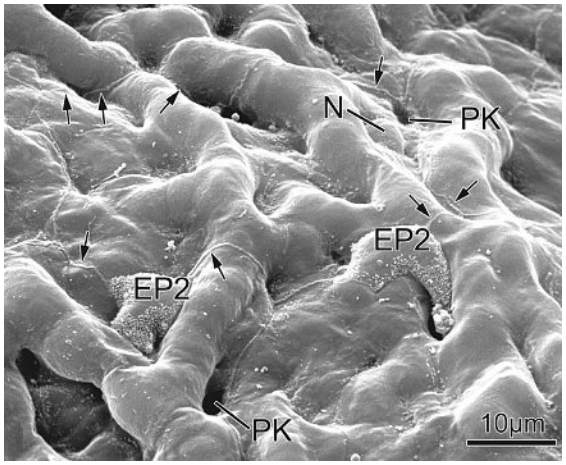


Figure 21

Surface of the alveolar wall in the human lung seen by scanning electron microscopy reveals a mosaic of alveolar epithelium made of type I and type II (EP2) cells. Arrows indicate boundary of the cytoplasmic leaflet of the type I cell which extends over many capillaries (C). Note the two interalveolar pores of Kohn (PK). N = nucleus of type I cell.

As shown in fig. 4, the tissue barrier separating air and blood consists of two cell layers, each with a basement membrane, and a very slim interstitial space in between that is even reduced to the fused basement membranes in the thinnest parts. The capillary endothelium is of a uniform squamous cell type with the thin cytoplasmic leaflets consisting of two plasma membranes with a small amount of cytoplasmic matrix and some vesicles. The alveolar epithelium, in contrast, is a mosaic of two cell types (fig. 21): the type I cell has some similarity with endothelial cells, in that it also forms thin cytoplasmic leaflets (fig. 4); the type II cell is inserted in the epithelial lining as a cuboidal cell (figs. 20 and 21). While type I cells cover 97% of the alveolar surface they constitute only ⅓ of the epithelial cells in number, and even though they appear as "small cells" they are in fact twice as voluminous as the type II cells [62].

The rich cytoplasm of type II cell with endoplasmic reticulum, Golgi complex, granules and lamellar bodies (fig. 20) serves its function as secretory cell for the different constituents of the surfactant complex, phospholipid film as well as the surfactant-associated proteins [57, 58]. The type I cell, on the other hand, is a very special cell type in that its form is complex: it is not a simple

squamous cell like that of the endothelium. Rather, it forms multiple branches that penetrate across the alveolar septum where they form patches of the lining on the opposite side; these patches were long recognised as a peculiarity of the alveolar epithelium and were called "kernlose Platten" as they appear devoid of a nucleus [63]. This cell architecture has two important consequences: (1) the cells are vulnerable because of the vast extension of the very thin cytoplasmic leaflets – 5000 μm² for each nucleus –, and (2) they are unable to divide by mitosis. As a result, any defect in the epithelial lining must be repaired by type II cells that also serve as precursor cells for the entire epithelial cell population. To maintain a tissue sheet as thin as the air-blood barrier depends crucially on the integrity and vitality of the two bounding cell layers that also must be tight enough to prevent any leakage of fluid into the likewise slim interstitial space [64].

What then makes a good lung?

We have seen that the functional capacity of the lung as gas exchanger requires a very large surface of contact between air and blood to be maintained with an exceedingly small amount of tissue for support. This in turn demands an ingenious architectural design by observing rules of fractal geometry in the packing of the large surface into the limited space of the chest cavity, as well as in designing a system of airways and blood vessels which reach all points on the gas exchange surface evenly and efficiently. The resulting hierarchical design with small acini attached to a branched bronchial tree then allows economical use of fibres and cells to provide mechanical support for the very delicate structure whereby stability of the air-exposed surface is achieved by the dynamic properties of alveolar surfactant. This taken together makes a good lung, fit to provide our organs with the oxygen they need at rest and in work [65].

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