PERSPECTIVE

The human lung: did evolution get it wrong?

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ABSTRACT: Some 300 million yrs ago, the ancestors of modern reptiles emerged from water and were committed to air breathing. They were exothermic and incapable of sustained levels of high physical activity. But from them evolved the two great classes of vertebrates with high levels of maximal oxygen consumption: the mammals and birds. A remarkable feature of these two divergent evolutionary lines is that, although the physiology of many organ systems shows many similarities, the lungs are radically different. A major difference is that the ventilation of the gas-exchanging tissue has a flow-through pattern in the bird but is reciprocating in the mammal. The result is that mammals have a reduced alveolar and arterial oxygen tension, a potential for uneven ventilation, and relatively large terminal air spaces. This in turn means that the pulmonary capillaries are poorly supported compared with the bird. The result is that the pulmonary capillaries in the bird have much thinner and more uniform walls, with more efficient gas exchange. Other advantages of the bird lung are that it utilises a more efficient cross-current pattern of gas-exchange, and the bird has separated the ventilatory and gas exchange functions. From a structure–function standpoint, the bird lung is superior.

TWO EVOLUTIONARY PATHS: MAMMALS AND BIRDS

Some 300 million yrs ago, the ancestors of modern reptiles finally emerged completely from water and made a commitment to air breathing. Like modern reptiles, they were exothermic and incapable of sustained levels of high physical activity. But from them developed the two great classes of vertebrates with high of maximal oxygen consumption: the mammals and birds. Specifically, the mammals are thought to have derived from a group of carnivorous reptiles, the cynodonts, while the birds descended from theropod dinosaurs [1]. A remarkable feature of these two groups is that although the physiology of the cardiovascular, renal, gastrointestinal, endocrine and nervous systems show many similarities, the lungs are radically different. The thesis of the present article is that the bird lung is superior to that of the mammal, and that evolution went along the wrong path for the latter.

FLOW-THROUGH *VERSUS* RECIPROCATING VENTILATION

The lung is a gas exchanger that is in many ways similar to a heat exchanger, for example the

radiator of a car. The radiator's function is to remove heat from the coolant fluid coming from the engine, just as the lung removes carbon dioxide from the blood coming from the tissues. At the same time, in the lungs, oxygen is taken up. Figure 1a shows the time-honoured design of a car radiator, where the coolant fluid is pumped through an array of small thin-walled tubes over which air is passed by a fan or the motion of the car. The gas-exchanging unit of the bird lung (the parabronchial tissue) is similar to this.

Figure 1b shows a variant where the gas or heat exchanger is placed in a bellows which is alternately inflated and deflated. This would work, although the fact that some air remains in the bellows at the end of deflation reduces its efficiency. Figure 1c shows another variant, where the small tubes through which the blood or coolant runs are alternately compressed and expanded by the bellows. An engineer might immediately object that this design is likely to be prone to problems, in part because the delicate tubes with their thin walls may be damaged by the repeated movement. However, amazingly, this is the arrangement that has evolved for the mammalian lung (fig. 2). This is even more surprising given that the more elegant and simple design of figure 1a evolved in the bird.
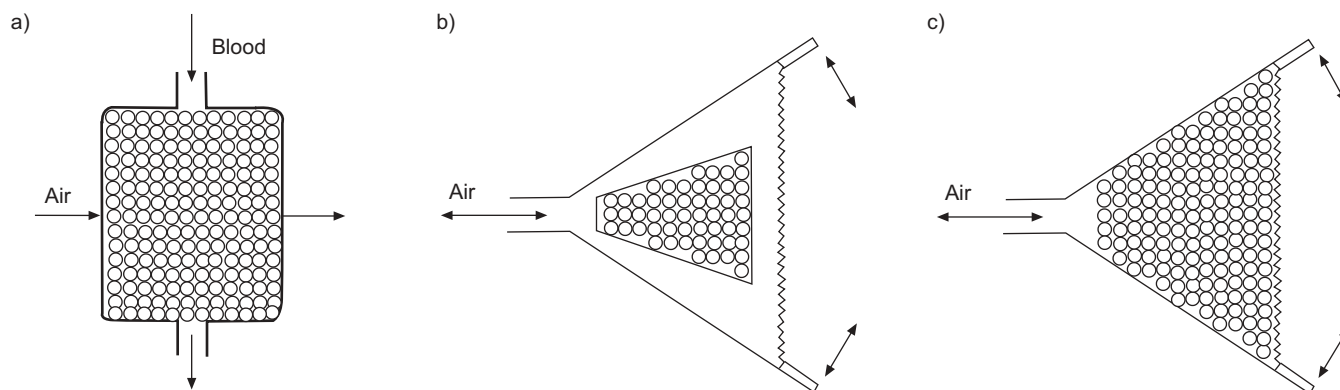
FIGURE 1. Possible configurations for a heat or gas exchanger. a) Coolant fluid or blood is passed through fine thin-walled tubes over which air is blown. This is the classical design of a car radiator and is similar in principle to that of a bird lung. b) Air is moved by a bellows. c) The gas-exchanging tissue is inflated and deflated as the bellows moves. This arrangement is similar in principle to that of the mammalian lung.

The pattern of reciprocating ventilation apparently developed as long as 200 million yrs ago in the nonavian theropod dinosaurs [2]. By contrast, flow in the avian lung is of the flow-through type. It is also unidirectional and continuous, although this is not obvious from figure 2. The reason is that aerodynamic valving results in the same direction of gas flow in the parabronchi during both inspiration and expiration, although the precise mechanism is still not completely understood [3, 4].

In fact, the reciprocating pattern of ventilation in the mammalian lung results in additional complications that are not apparent from figure 1c. The mammalian lung does not empty completely with each expiration, as could conceivably be the case with the arrangement depicted in figure 1c. The human lung, for example, maintains a resting gas volume of ~3 L, and during inspiration takes in ~0.5 L of air (fig. 3). The result is that convective flow alone cannot take the inspired gas to the periphery of the lung where some of the gas-exchanging
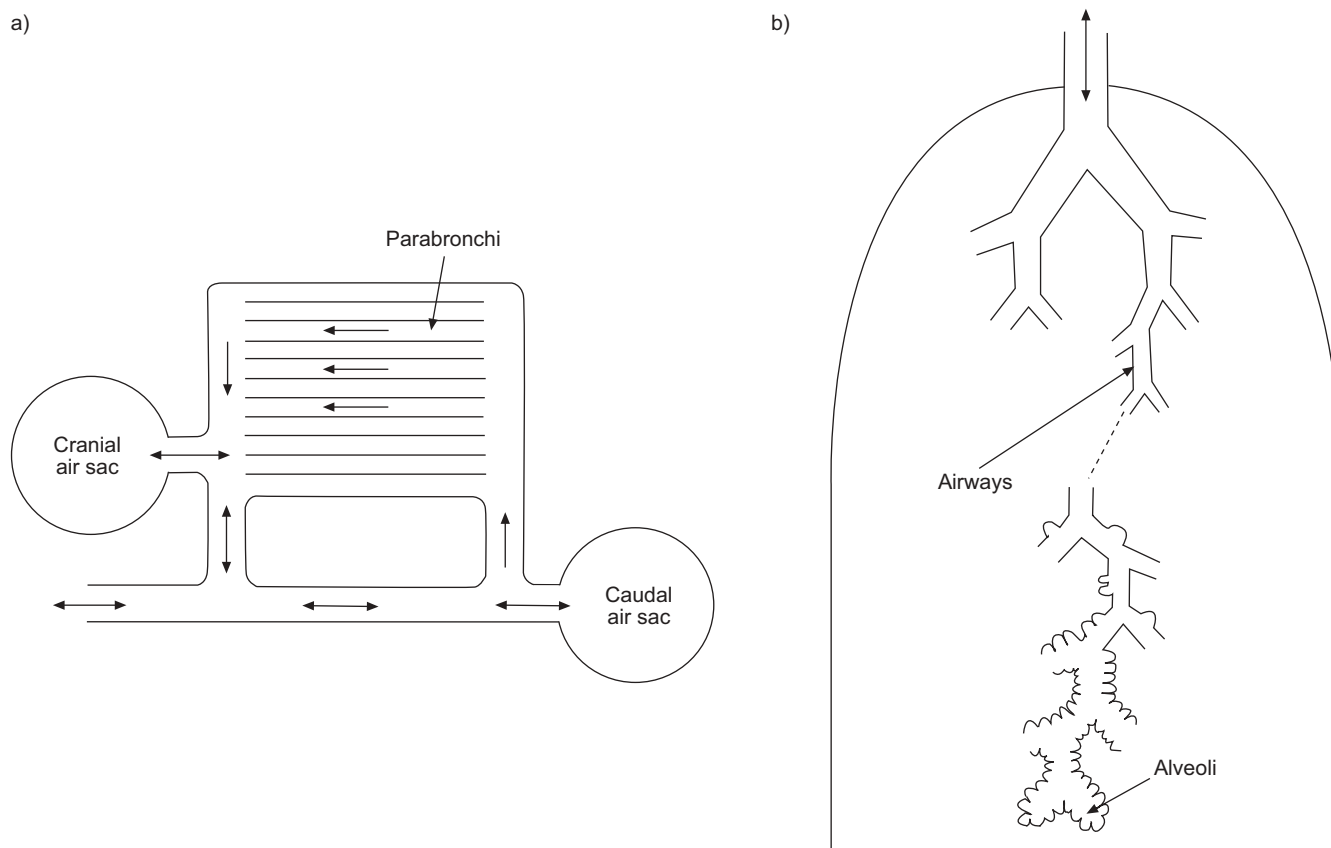

FIGURE 2. The a) bird and b) mammalian lungs, showing the flow-through arrangement for the gas-exchanging tissue in the bird, and the reciprocating pattern in mammals.
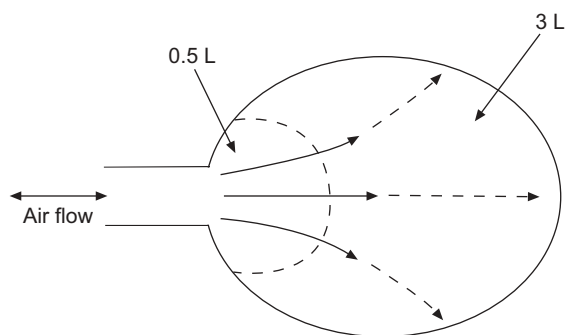
FIGURE 3. Diagram showing the typical reciprocating pattern of ventilation in the mammalian lung. In humans under resting conditions, the inspired volume of ~0.5 L is delivered in a volume of ~3 L and inspired gas can only reach the periphery of the lung by a combination of convection and diffusion.

alveoli are located. Instead the last part of the distance is accomplished by a combination of convection and diffusion within the airways. This necessitates relatively large peripheral airways to allow mixing of the inspired gas with that already in the lung, and the resulting large alveoli cause additional problems as discussed below. Table 1 lists some of the major differences between mammalian and avian lungs and their gas exchange.

The reciprocating pattern of ventilation in the mammalian lung results in three shortcomings compared with the bird lung.

Potential for uneven ventilation

An implication of figures 2 and 3 is that less inspired gas may reach the peripheral regions of the mammalian lung than the central portions. This type of uneven ventilation is known as stratified inhomogeneity. It is remarkable that the structure of the airways and alveoli is such that the degree of uneven ventilation as a result of this mechanism is small at rest in the human lung, but it probably increases during rapid breathing,

as in exercise, when less time is available for diffusion equilibration to occur. A related problem is that the most proximal alveoli in the acinus are preferentially provided with inspired oxygen, with the result that the more distal alveoli tend to receive less, a process known as screening [5]. The flow-through arrangement in the bird lung does not have these disadvantages, although it is true that some diffusion does take place in the small air capillaries that bud off the parabronchi or their extensions. However, the diffusion distance is small compared with that in the mammalian lung and is not believed to impose any limitation on gas exchange [6, 7].

The pool pattern of ventilation results in a low alveolar oxygen tension

As figure 3 emphasises, a relatively small volume of inspired gas is delivered into a large pool of gas already in the mammalian lung. The result is that the alveolar and therefore arterial oxygen pressure (P_{A,O_2} and P_{a,O_2}, respectively) are considerably lower than that of the inspired gas. For instance, in the human lung, P_{A,O_2} is typically ~13.3 kPa (100 mmHg) in contrast to the oxygen pressure of the inspired gas, which is ~20 kPa (150 mmHg). The flow-through system of the bird lung reduces this problem.

The reciprocating pattern necessitates large terminal air units

As figure 3 implies, inspired gas can only reach the peripheral regions of the mammalian lung by a combination of convection and diffusion, and this means the terminal air spaces must be relatively large to reduce the resistance within them. For example, in the human lung, the alveoli have a diameter of ~300 μm, whereas the air capillaries that surround the blood capillaries in the bird lung have a diameter ~5% of this (fig. 4), although this is variable depending on the species. As discussed below, this has important implications for the support of the pulmonary capillaries and the integrity of the extended alveolar walls.

| TABLE 1	Comparison of some features of mammalian and avian lungs and gas-exchange	
	Mammalian lung	**Avian lung**
Ventilation		
Gas flow	Reciprocating	Flow-through
Mode of gas flow	Convection and diffusion	Convection (almost entirely)
Stratification of inspired gas	Probable at times	None
Gas-exchanging tissue		
Parenchyma	Deformable	Rigid
Terminal air spaces	Large	Small
Support of blood capillaries	None at right angles to alveolar wall	Extensive from air capillaries
Mean thickness of the blood-gas barrier	Greater than in the bird	Minimal
Type I collagen cables in the parenchyma	Yes	No
Uniform thickness of blood–gas barrier	Yes	No
Gas exchange		
Highly efficient cross-current gas exchange	No	Yes
Vulnerability of parenchyma to aspiration	Large	Presumably small
Mass-specific maximal oxygen consumption	High	Higher
Aerobic scope	High	Higher
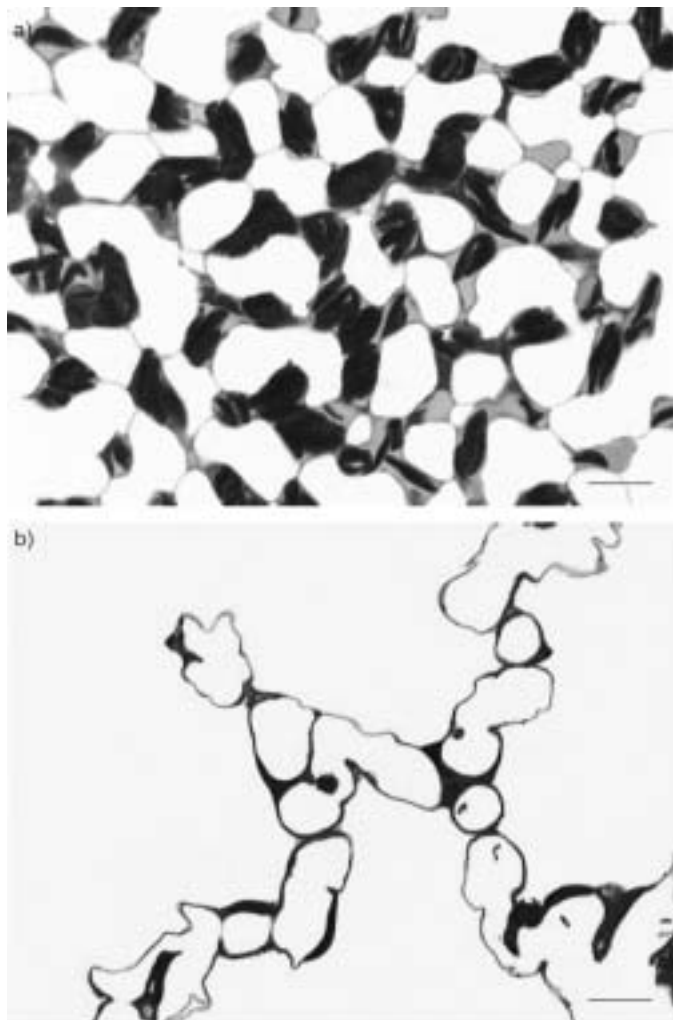
FIGURE 4. Typical microscopic sections of a) bird and b) mammalian lungs. In the bird, the pulmonary capillaries are supported by a dense honeycomb-like network of air capillaries. In the mammalian lung, the pulmonary capillaries are spread out along the free-floating alveolar wall. Scale bars=10 μm.

SEPARATION OF THE GAS-EXCHANGE AND VENTILATORY FUNCTIONS

One of the most fundamental differences between the structure of bird and mammalian lung is the separation of the gas-exchange function from the ventilatory function in the former. This is clear from figures 1 and 2. The bioengineering requirements of tissues for these two functions are so dissimilar that it is truly remarkable that the mammalian lung has combined the two functions. Gas-exchanging units require extremely thin walls because gas movement across them is by passive diffusion. In the human lung, for instance, approximately half of the blood–gas barrier has a thickness of 0.2–0.3 μm, and in the bird lung the barrier is typically even thinner (fig. 5). By contrast, ventilating structures need to be freely distortable so that they can increase their volume during inspiration. In the bird lung, this is done by nonvascular air sacs, which are robust, in contrast to the alveoli of the mammalian lung, which are necessarily delicate because of their extremely thin-walled capillaries.
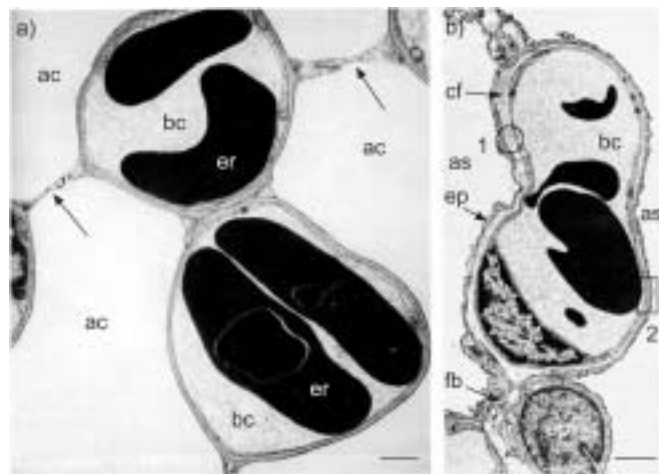

FIGURE 5. a) Electron micrograph of blood capillaries from a bird (chicken) lung. There is a very thin and uniform blood–gas barrier around the entire circumference. Arrows show the epithelial struts that support the blood capillaries. Reprinted with permission from [8]. b) Electron micrograph of a typical capillary in mammalian (dog) lung at the same magnification. The blood–gas barrier appears generally thicker, and the interstitium is particularly thick on one side (box 1) where it contains type 1 collagen fibres (cf). However, the thin side (box 2) is also thicker than in the bird. Reprinted with permission from [9]. ac: air capillary; bc: blood capillary; er: erythrocyte; as: alveolar space; ep: epithelium; fb: fibroblast.

In view of the different structural requirements for ventilation and gas exchange, it is remarkable that the mammalian lung does not encounter more frequent problems as a result of the combination of these two functions. However, potential problems arise in two settings.

Occlusion of airways by aspiration or secretions

A common serious problem in the post-operative setting is occlusion of an airway by aspiration or retained secretions. The result is that ventilation to many of the gas-exchanging units is abolished, with consequent hypoxaemia. Indeed, in some cases, the lung distal to the occlusion may become atelectatic. This is particularly likely to occur if the patient is inhaling an enriched oxygen mixture, because the alveolar gas is then more rapidly absorbed. Localised airway inclusion also commonly occurs in airway diseases such as chronic bronchitis and asthma. This scenario of substantial impairment of gas exchange following blockage of an airway is an inevitable result of combining gas exchange and ventilatory functions in the same lung parenchyma. Presumably the bird avoids these problems to a large extent, as inhaled material will end up in the nonvascular air sacs, with little resulting impairment of gas exchange.

Is repetitive distortion of alveolar tissue a factor in its destruction?

One of the commonest serious lung diseases in humans is emphysema, characterised by breakdown of the alveolar walls. Furthermore, the apparently normal ageing lung may also have some loss of alveolar walls. It is tempting to believe that the distortion that occurs in the delicate gas-exchanging parenchyma with every breath may be a factor in these conditions.

RIGID *VERSUS* DEFORMABLE GAS-EXCHANGING TISSUE

This is another major difference between the bird and mammalian lung, related to the separation of the gas-exchange and ventilatory functions discussed above. In the mammalian lung, the parenchyma is deformable, as of course it must be, because the lung changes its volume with inspiration and expiration. By contrast, there is good evidence that the parenchyma of the avian lung is extraordinary rigid. For instance, if the pressure around the parabronchi is increased during experiments on anaesthetised ducks, there is no collapse of the air capillaries as inferred from changes in the arterial blood gases [10]. This behaviour is completely different from that in the mammalian lung, where compression of the parenchyma causes cessation of ventilation, alveolar collapse and arterial hypoxaemia. Furthermore, there is evidence of rigid support of the pulmonary capillaries. In other experiments on anaesthetised ducks where the pulmonary artery to one lung is occluded, there is essentially no change in the pulmonary vascular resistance of the unoccluded lung [11]. Again, this a very different result from that in mammals, where the same intervention causes a dramatic fall in vascular resistance of the unoccluded lung as a result of distension and recruitment of capillaries. These demonstrations of the rigidity of both the air and blood capillaries in the bird emphasise the robustness of the gas-exchanging tissue in contrast to the delicate, vulnerable parenchyma of the mammalian lung.

SMALL *VERSUS* LARGE TERMINAL GAS UNITS AND SUPPORT OF THE PULMONARY CAPILLARIES

As indicated earlier, the combination of convection and diffusion necessary to transport gas to the periphery of the lung in the reciprocating mammalian pattern necessitates relatively large terminal airways. Typical histological sections are reproduced in figure 4. In a mammalian lung, the alveoli are relatively large and the pulmonary capillaries are strung out along the alveolar wall rather like a string of beads. Figure 4a shows the structure of the gas-exchanging tissue in a typical bird lung (chicken). The air capillaries, which constitute the terminal gas units, have a diameter of ~10–20 μm and form a honeycomb-like network around the pulmonary capillaries.

The present authors believe that this arrangement in the bird parabronchi has important implications for the mechanical support of the pulmonary capillaries. As figure 4b shows, the capillaries in the alveolar lung are only supported in one direction, that is along the alveolar wall, and they have no mechanical support at right angles to the wall. As a result, they are vulnerable to damage to their walls when the capillary transmural pressure rises to high levels, for instance during vigorous exercise. This damage, known as stress failure, occurs in many mammalian lungs under extreme physiological conditions, and also in many pathological conditions.

One of the best-known examples under physiological conditions is the exercise-induced pulmonary haemorrhage that occurs in essentially all thoroughbred racehorses in training [12, 13]. A less dramatic example is seen in elite human athletes exercising at maximal levels, where it has been shown that there are changes in the permeability of the blood–gas barrier. For example, bronchoalveolar lavage fluid removed after intense exercise shows increases in the concentration of red blood cells, total protein and the leukotriene B_4 [14]. Pathological conditions where stress failure of pulmonary capillaries occurs include high-altitude pulmonary oedema, neurogenic pulmonary oedema and overinflation of the lung caused by high positive end-expiratory pressure.

By contrast, the fact that the pulmonary capillaries in the bird are embedded in a honeycomb-like network of air capillaries means that they receive mechanical support from a number of directions. As can be seen from figures 4a and 5a, struts or bridges between adjacent air capillaries are attached to the pulmonary capillaries. These struts are composed of epithelial cell extensions without endothelial cells [15, 16]. They apparently explain the remarkable rigidity of the pulmonary capillaries referred to in the previous section, although in such small complex structures as shown in figures 4a and 5a, the distribution of stresses is not fully understood.

THE BLOOD–GAS BARRIER OF BIRDS IS MUCH THINNER AND MORE UNIFORM THAN IN MAMMALS

The present authors believe that the mechanical support provided to the pulmonary capillaries by the surrounding small air capillaries in the bird lung (figs 4a and 5a) means that the blood–gas barrier in the bird can be much thinner in the mammal with obvious advantages for gas exchange. Previous investigators have shown that the blood–gas barrier in the avian lung is typically thinner than in mammals [17] and that in fact some birds have thinner barriers than any mammals. Examples include the rock martin (*Hirundo fuligula*) and the violet-eared hummingbird (*Colibri caruscans*), where the harmonic mean thickness is <0.1 μm, compared with ~0.33 μm in the Eruscan shrew (*Suncus etruscus*), the mammal with the thinnest barrier [18].

Recent measurements in the present authors' laboratory have confirmed the very thin blood–gas barrier in the domestic chicken (*Gallus gallus*). In addition, the thickness of the three components of the blood–gas barrier (alveolar epithelium, capillary endothelium, and extracellular matrix (ECM) or interstitium between these two layers) has been measured, showing that the ECM in the chicken is extraordinarily thin [19]. This is a paradox because the ECM is believed to be responsible for the strength of the barrier [20], and birds are capable of extremely high maximal oxygen consumptions in relation to their body weight. Flying is a very energetic activity. Intense exercise raises the pulmonary vascular pressures, including the transmural pressure of the capillaries, and exposes the blood–gas barrier to large mechanical stresses. It is therefore paradoxical that the bird can have an extremely thin ECM in the blood–gas barrier and yet be capable of extreme physical activity. The present authors suggest that the solution to this paradox is that the support of the capillaries by the epithelial struts described above helps to maintain the integrity of the capillary walls [16]. An example of the very thin blood–gas barrier in the bird compared with the thicker barrier in a typical mammal is shown in figure 5.

Another important feature of the blood–gas barrier is apparent in figure 5. In figure 5b, the right-hand part of the blood–gas barrier is very thin, being composed only of the alveolar epithelium, capillary endothelium, and a thin layer of ECM (box 2). By contrast, the blood–gas barrier on the left-hand side
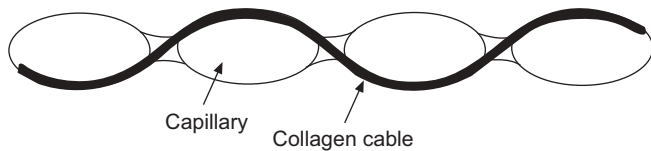
FIGURE 6. Type 1 collagen cables extend from one end of the alveolar wall to the other in mammalian lung. In doing so, they pass through one side or the other of the pulmonary capillaries.

of figure 5b (box 1) is much thicker, as the interstitium is expanded and includes type 1 collagen fibrils. These appearances are typical of mammalian pulmonary capillaries [9]. The collagen seen in box 1 is part of a type 1 collagen cable that runs from one end of the alveolar wall to the other, threading its way through one side or the other of the capillaries *en route* (fig. 6). The purpose of this collagen cable is to maintain the integrity of the long alveolar wall, which is generally poorly supported. The result is a ''polarised'' mammalian pulmonary capillary, whereby on one side the blood–gas barrier is extremely thin and well suited to gas exchange, while the other side is thicker because of the collagen cable.

Figure 5a shows that the structure of the blood–gas barrier in the bird is very different. First, the total thickness of the barrier is much less than in the mammalian pulmonary capillary. In addition, inspection of the blood–gas barrier in figure 5a shows that it is remarkably uniform and certainly does not show the polarisation characteristic of the barrier in figure 5b. The current authors believe that the explanation for this is that the pulmonary capillaries in the bird lung are embedded in a honeycomb-like structure of air capillaries, and there is no long alveolar wall, requiring a type 1 collagen cable for support.

Morphometric measurements confirm that typically about half of the blood–gas barrier of the mammalian lung has the characteristics of box 1 in figure 5b, whereas about half has the structure shown in box 2 [21]. The structure of the blood–gas barrier in the bird lung in figure 5a is clearly much more advantageous for gas exchange than the barrier of figure 5b. Not only is the barrier generally thinner, but it is also remarkably uniform. This appearance is contrasted with the generally thicker barrier in the mammalian lung and the fact that mammals apparently require a substantial type 1 collagen cable to maintain the integrity of the alveolar walls. In fact, the considerable thickness of the left-hand side of the capillary wall in figure 5b means that this region plays only a small part in diffusive gas exchange.

THE PATTERN OF CROSS-CURRENT GAS EXCHANGE IN THE BIRD LUNG IS VERY EFFICIENT

As described in connection with figure 3, the reciprocating pattern of ventilation in the mammal results in a pool system of gas exchange, which necessarily means that P_{A,O_2}, and therefore P_{a,O_2}, are substantially below the inspired values. The bird lung largely avoids this problem because of its flow-through pattern of ventilation. In addition, the avian lung has a remarkably efficient arrangement of air and blood capillaries for pulmonary gas exchange, which has been described extensively elsewhere [22] and will be summarised here. In the avian parabronchi, the blood capillaries run alongside the

air capillaries, which branch off the parabronchi or their extensions, and part of the effluent capillary blood is exposed to gas with an oxygen pressure close to the inspired value. The net result of this ''cross-current'' gas exchange, as it is called, is that it potentially allows the oxygen pressure of the blood leaving the lung to exceed that of the expired gas. This is impossible in the mammalian lung, where the best result that can be achieved is that the end-capillary blood reaches the oxygen tension of the alveolar gas which is subsequently exhaled. This special arrangement for gas exchange, which is unique to the avian lung, improves gas-exchange efficiency.

THE EVOLUTIONARY SUCCESS OF BIRDS: WHY DID MAMMALS TAKE A DIFFERENT ROUTE?

From our mammalian perspective, it might be thought that as a taxon, mammals have been more successful than birds. However, the opposite case can be made. For instance, some birds are superior to any mammals in their maximal oxygen consumption in relation to body weight [23], their aerobic scope [24], the number of extant species (9,000 in birds *versus* ~4,200 in mammals) and, arguably, their ecological diversity (the mountaineer struggling to reach the summit of Everest may see bar-headed geese flying far above).

So why did evolution take what appears to be such a flawed path in the mammal? The question is probably not a useful one. Evolution proceeds in an incremental way without a final goal. At various points along the line, there are changes in a few base pairs which confer an advantage or disadvantage for survival. But for those who work on the mammalian lung, it is fascinating that evolution found a better solution for the structure–function relationships of the lung in birds than in mammals.

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