Reviews

The Avian Respiratory System: A Unique Model for Studies of Respiratory Toxicosis and for Monitoring Air Quality

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There are many distinct differences (morphologic, physiologic, and mechanical) between the bird's lung–air-sac respiratory system and the mammalian bronchoalveolar lung. In this paper, we review the physiology of the avian respiratory system with attention to those mechanisms that may lead to significantly different results, relative to those in mammals, following exposure to toxic gases and airborne particulates. We suggest that these differences can be productively exploited to further our understanding of the basic mechanisms of inhalant toxicology (gases and particulates). The large mass-specific gas uptake by the avian respiratory system, at rest and especially during exercise, could be exploited as a sensitive monitor of air quality. Birds have much to offer in our understanding of respiratory toxicology, but that expectation can only be realized by investigating, in a wide variety of avian taxa, the pathophysiologic interactions of a broad range of inhaled toxicants on the bird's unique respiratory system. *Key words*: anatomy, birds, gas uptake, particle deposition, physiology, respiration, toxicology, ventilation. *Environ Health Perspect* 105:188–200 (1997)

To what extent do the pathophysiologic effects of inhaled substances, gaseous and particulate, depend on the particular structural and physiologic features of an animal's respiratory system? The anatomy, physiology, and mechanics of the avian respiratory system are distinctly different from that of mammals (*1*). We suggest that, due to their unique respiratory apparatus, birds may represent valuable experimental models in the study of respiratory toxicosis. Such comparative knowledge concerning the pathophysiology of inhaled substances may offer insights otherwise not available. Here we describe the structure, ventilation, and gas flow pattern of the bird's lung–air-sac system relative to the analogous features, if any, of the mammalian bronchoalveolar lung. We point out those anatomical and physiologic features of the bird's respiratory apparatus that may produce significantly different responses from the normal response to inhaled substances, gases, and particulates in mammals.

Concerns about the hazardous effects of gas and particle emissions from expanding industrial and agricultural (and natural) sources supporting a burgeoning population have led to considerable efforts toward understanding the effects of air quality on human health. Maintenance of natural diversity demands that we also understand the interactions between the bird's unique respiratory system, gas uptake, and the pathophysiologic effects of contaminating toxic gases and airborne particulates. Birds such as chickens and turkeys represent an important and expanding source of animal protein for human nutrition. The environment within modern poultry and egg production facilities, in which birds are densely housed, commonly exposes birds to high levels of aerosolized particulates and toxic gases such as ammonia and methane. Surprisingly, little research has been carried out in birds on gas uptake (other than O_2 and CO_2), particle deposition, and the toxicity and pathophysiology of inhaled substances.

Toxic gases and/or airborne particulates contaminate the environment and can have debilitating or destructive effects on birds (and other wildlife) via a variety of distribution modes (e.g., air or water) and biochemical mechanisms (*2–5*). Here we are concerned only with those gaseous and particulate contaminants that enter the bird via its respiratory tract, of which little is known or understood. If we understood the pathophysiology of inhaled environmental contaminants (gas and particulate) on birds (adult and embryonic), they could serve as sensitive, direct monitors of air quality. If the avian respiratory system is to add to our understanding of respiratory toxicosis, if we are to maintain the health of birds in agricultural and wild settings, and if birds are to become valuable monitors of air quality, then we must study the pathophysiology of a broad range of toxic gases and airborne particulates in a wide variety of species.

Functional Morphology of the Avian Respiratory System

Anatomy of the avian lung–air-sac system

Upper respiratory tract. The bird's respiratory tract cranial to the tracheal bifurcation is qualitatively similar to that of mammals; it has a nasal cavity with communicating sinuses, a larynx supported by cartilaginous plates, and a tracheal lumen supported by cartilaginous or ossified rings. However, the length of the bird's trachea is, on average, 2.7 times that of comparably sized mammals (*6*). A small increase in tracheal diameter (1.29 times that of comparably sized mammal) ameliorates any increases in resistance to flow expected from the considerably longer trachea. Although the bird's trachea is lined with a secretory (mucous), ciliated epithelium, there is no information about the performance of the mucociliary transport mechanism. Further, there are a few avian taxa (e.g., swans, cranes, birds of paradise) that have tracheal lengths up to four times that of comparably sized birds, the redundant coils of which are considered adaptations for phonation (*7*). Tracheal lengths 10 times that of comparably sized

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mammals suggest the need of possible novel mechanisms to assist in clearance.

In sharp contrast to the C-shaped cartilaginous rings supporting the tracheal lumen of mammals, the bird's tracheal rings are complete (i.e., O-shaped and commonly ossified). In the mammalian trachea, the collapsible membrane spanning the gap between the ends of the incomplete tracheal rings is considered an important feature of the clearance mechanism of the mammalian cough (*8*). Although birds do perform a coughlike action, we do not know if such behavior represents an effective mechanism for clearing debris from their longer tracheas. And if such a clearance mechanism exists, what are the mechanics involved? The avian vocal apparatus, the syrinx, is located at the point the main stem bronchi diverge from the caudal trachea (Fig. 1). At that site there are significant departures from the round geometry of the trachea and main stem bronchi which may influence particle deposition.

Bronchial system. Whereas the mammalian bronchial system ramifies (23 generations) like the roots of a tree throughout the pulmonary parenchyma (**Fig.** 2), the bird's primary bronchus extending from tracheal bifurcation to the ostium of the abdominal air sac has only two clusters of secondary bronchi (Fig. 1). From the cranial end of the bird's intrapulmonary primary bronchus arise 4 approximately equal-sized ventrobronchi, and from its caudal segment arise 7–14 variably sized dorsobronchi and a variable number (<6) of laterobronchi. The epithelium lining the primary bronchi and the initial segments of the secondary bronchi is similar to that seen in larger mammalian airways: pseudostratified ciliated epithelium with mucous-secreting goblet cells.

The mammalian bronchial system terminates in myriad (300 million in *Homo*) small, blind-end alveoli, which are the site of gas exchange and volume (tidal) expansion. In sharp contrast, birds have a nearly constant volume, flow-through lung in which the site of gas exchange is the parallel tertiary bronchi, i.e., parabronchi (few hundred to <2,000 depending on taxa), connected between the ventrobronchi and the dorsobronchi or laterobronchi (Figs. 1 and 3). The parabronchi complete an airway loop from the caudal primary bronchus to the cranial primary bronchus (via secondary bronchi), through which a unidirectional stream of fresh gas flows (Figs. 1 and 4). That is, birds have a flow-through lung (parabronchi) in contrast to the tidal ventilation that occurs in mammalian alveoli. The differences in ventilation of the pulmonary parenchyma between birds and mammals, resulting from their anatomical differences, have several important implications for gas-exchange physiology, toxic gas uptake, and particle deposition.

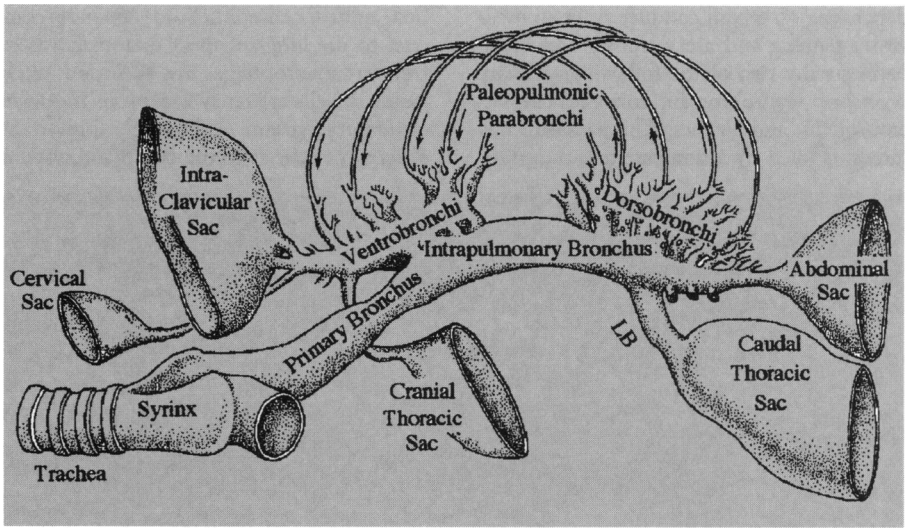

Figure 1. Diagram of the components of the avian lung–air-sac respiratory system. From the bird's intrapulmonary primary bronchus (Bronchus primarius, pars intrapulmonalis) arise two clusters of secondary bronchi: from its cranial end arise four ventrobronchi (Bronchi medioventrales), and, prior to its termination at the orifice of the abdominal air sac, arise the 8–14 dorsobronchi (Bronchi mediodorsales) and the laterobronchus (LB) (Bronchi lateroventrales), which connects the caudal thoracic air sac to the intrapulmonary bronchus. The constant-volume gas-exchange area of the avian lung–air-sac system, i.e., the parabronchi (for simplicity only a few are shown), is connected between dorsobronchi and ventrobronchi and is ventilated unidirectionally (arrows). The several air sacs are the sites of volume expansion and act as bellows to move gas through the bird's lung (parabronchi). [Modified from Wang et al., (*38*); reprinted with permission from John Wiley & Sons, Inc.]

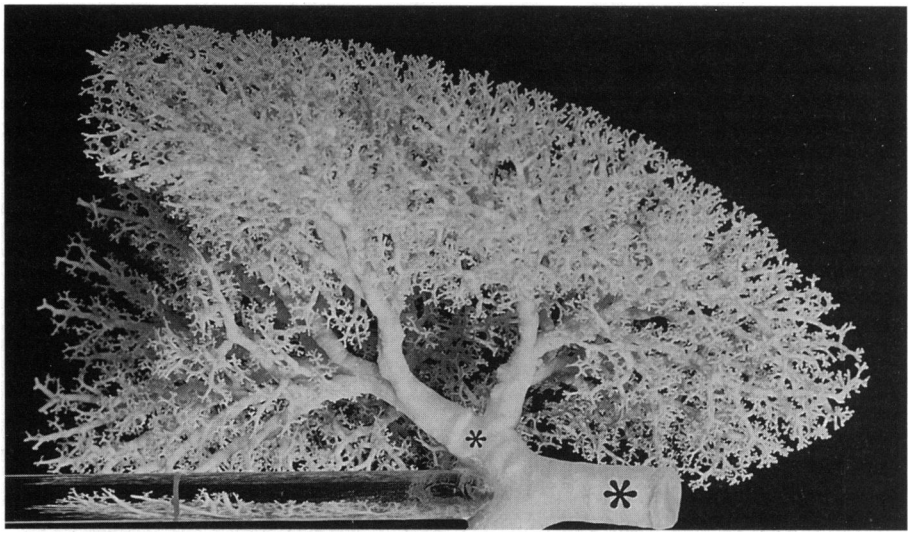

Figure 2. Bronchial tree of the human lung, latex cast, ventral view, left lung. The caudal trachea (large asterisk) gives rise to the primary bronchi (left main stem bronchi; small asterisk), from which the dichotomously branching (32 divisions) airway system leads to the blind-end alveolar ducts with their clustered alveoli (removed from this preparation), which are the site of both gas exchange and volume expansion in the mammalian lung. (Photo courtesy of W. Webes, Institute of Anatomy, University of Bern.)

Gas exchange tissues. The parabronchi are densely packed in a hexagonal array, similar to the wax-comb of honeybees (Fig. 3). Although there are no morphometric differences (*9,10*), parabronchi are separated into two categories based on their pattern of connections to secondary bronchi and flow regime. The majority of the parabronchial lung is composed of paleopulmonic parabronchi, connected between ventro- and dorsobronchi, through which gas flows unidirectionally (Fig. 1). A highly variable number of neopulmonic parabronchi [0 to <20% (usually <10%) of lung volume

depending on taxon] conduct air in an oscillatory pattern and are variously connected between any two of the following: primary bronchus, ventrobronchi, dorsobronchi, laterobronchi, and air sacs. The parabronchial lumen is lined by a nonsecretory, nonstratified, nonciliated epithelium. In sharp contrast to the lungs of most mammals where resident macrophages are common, such janitorial cells are rarely present in the avian respiratory system. Additionally, important differences exist as to the enzymatic systems present within the bird's lung tissue, which may lead to significantly different responses to inhaled toxicants (*11,12*).

Parabronchial dimensions are variable among avian taxa. The lumen (0.3–2.0 mm diameter) of each parabronchus (1–4 cm long) is surrounded by a mantle of gas-exchange tissue (0.2–0.5 mm thick) consisting of coextensive networks of narrow (3–10 µm diameter) air capillaries and blood capillaries (Figs. 3 and 5). The air capillaries communicate with the parabronchial lumen. The bird's gas-exchange barrier, formed by the air capillaries' squamous epithelium, the blood capillaries' endothelium, and the interposed basal lamina, is qualitatively similar to that of the mammalian alveolus and its pulmonary blood capillaries (*13*). Surfactant is

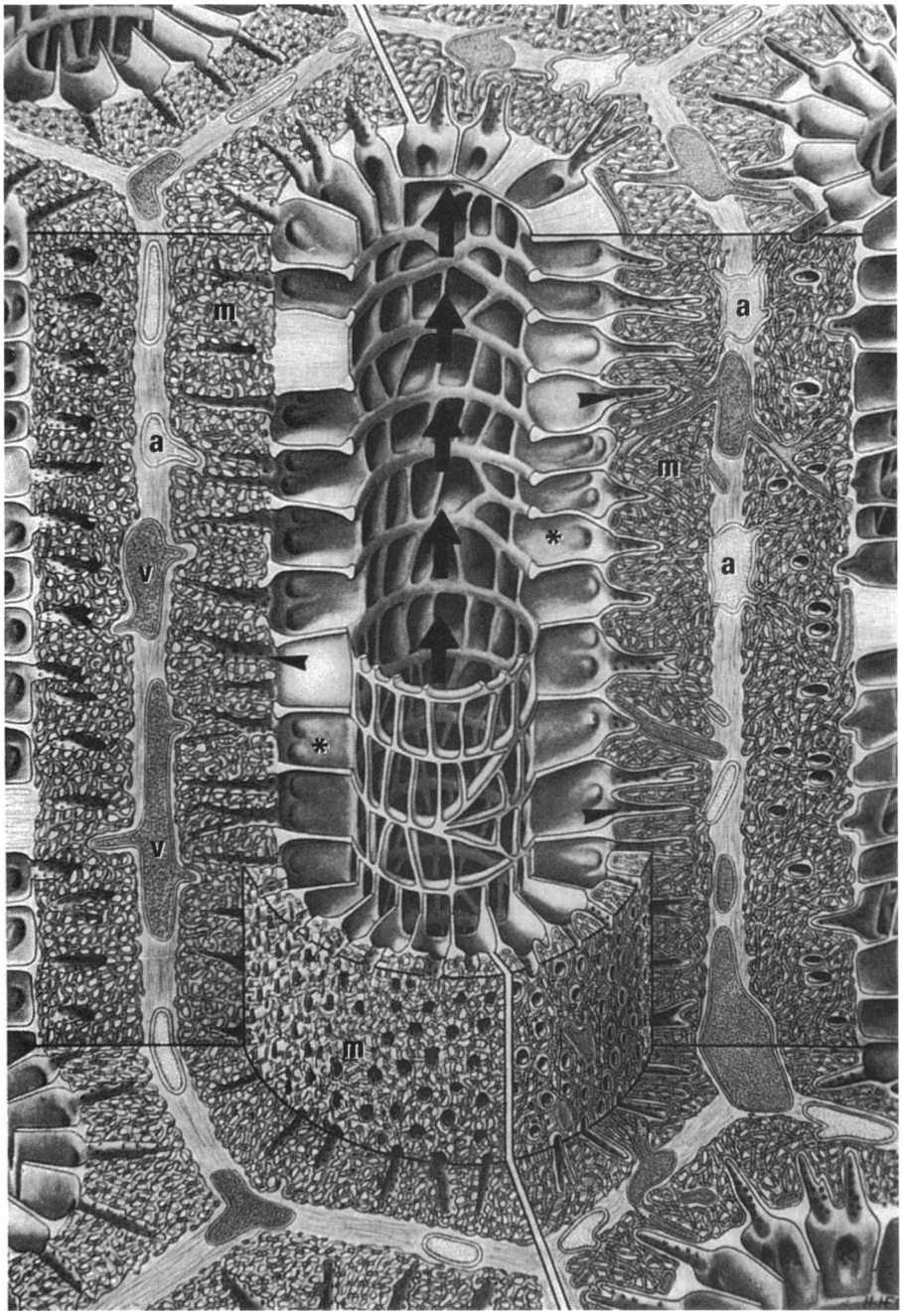

Figure 3. Diagram of parabronchial anatomy, gas-exchange region of the bird's lung–air-sac respiratory system. The few hundred to thousand parabronchi, one of which is fully shown here, are packed tightly into a hexagonal array. The central parabronchial lumen, through which gas flows unidirectionally during both inspiration and expiration (large arrows), is surrounded by a mantle (m) of gas-exchange tissue composed of an intertwined network of blood and air capillaries. Several air capillaries coalesce into a small manifold, i.e., the infundibulum (arrowheads), several of which in turn open into an atria (*) found along the parabronchial lumen. Air moves convectively through the parabronchial lumen, while O_2 diffuses radially (CO_2 diffuses centrally) into the air capillary network. Blood flows centrally from the pulmonary arteries (a) located along the periphery of the parabronchi to pulmonary veins located along the parabronchial lumen, which then are drained back to the peripheral veins (v). [Modified from Duncker (*107*); reprinted with permission from Springer-Verlag.]

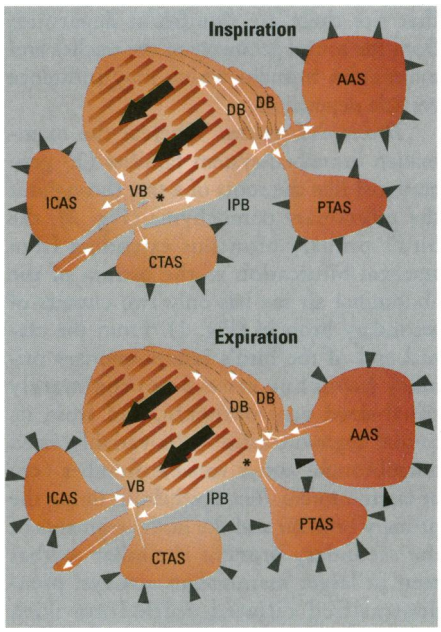

Figure 4. Air flow diagrams (arrows) of the avian respiratory system during inspiration and expiration. The air sacs act as bellows, contributing equally to the movement of gas through the bird's nearly constant-volume lung, filling simultaneously with inspiration and emptying simultaneously with expiration (arrowheads about air sacs). The unidirectional pattern of flow (large arrows) through the major exchange area of the bird's lung (paleopulmonic parabronchi) is maintained throughout inspiration and expiration. During inspiration there is no or little flow (*) in the ventrobronchi (VB) (i.e., inspiratory valving). Instead, nearly all the gas passes caudally through the intrapulmonary bronchus, half passing to the caudal air sacs and half entering the lung via the dorsobronchi (DB). During expiration there is little or no flow (*) in the intrapulmonary portion of the primary bronchus (IPB) (i.e., expiratory valving). Instead, nearly all the gas exiting the caudal thoracic (PTAS) and abdominal air sacs (AAS) passes through the parabronchi. ICAS, intraclavicular air sac; CTAS, cranial thoracic air sac. [Modified from Scheid (*108*); reprinted with permission from Springer-Verlag.]

present in the bird's nearly constant-volume lung (parabronchial lumen and air capillaries), although its functional significance is poorly understood. The mechanism that prevents collapse or flooding of the air capillaries secondary to the high surface tensions across the air-tissue interface of these structure's small radius (1–5 μm) of curvature is unknown. Arranged as a series of parallel units along the length of the parabronchi, the pulmonary blood flows radially into the mantle of exchange tissue from the arteries located along its periphery toward the parabronchial lumen, along which are located the pulmonary veins that drain the oxygenated blood back toward the periphery (Figs. 3 and 6) (*14*).

Significant differences between birds and mammals (excluding bats) exist in comparisons (body weight basis) of the surface density and the mean harmonic thickness of pulmonary gas-exchange tissues (*9,15*). Birds' lungs have about twice the surface density of gas-exchange tissue, resulting from the dense packing of their narrow air capillaries relative to the size (>300 μm diameter) of mammalian alveoli. The mean harmonic thickness of the bird's gas-exchange barrier is only about half that of the mammalian lung. However, other parameters of lung morphometry (body weight basis) are nearly identical between these two groups of homeotherms (*15*): lung volume, surface area of exchange tissue, surface area of exchange tissue per body weight, and pulmonary blood volume.

The thinness of birds' gas-exchange barrier has important implications for gas uptake. Uptake of a gas across the tissue barrier of the lung and into the blood ($\dot{M}_{g\text{-}b}$) is:

$$\dot{M}_{g\text{-}b} = D\left(\frac{A}{T_h}\right)\left(P_{AC} - P_{\bar{V}}\right) \quad (1)$$

where D is the diffusion constant of the gas, which depends on its solubility in blood (β_b) and molecular weight (MW), i.e., $D \propto \beta_b/MW^{-1/2}$; A is the surface area; T_h is the thickness of the tissue barrier across which the gas moves; P_{AC} is the partial pressure of the gas in the air capillary; and $P_{\bar{V}}$ is the partial pressure in mixed venous blood. Since the T_h of the bird's gas-exchange barrier is about half that of mammalian lung, given identical effective ventilation of gas-exchange tissues, a bird can take up approximately twice the amount of a gas from its ventilatory stream compared to a mammal. In addition, the unidirectional flow of fresh gas through the gas-exchange region of the bird's lung permits larger P_{AC}–$P_{\bar{V}}$ differences, in contrast to the situation in the mammalian lung where the gas-exchange region is filled with a functionally stagnant reservoir of gas, the P_{O_2} of which is governed by diffusive mechanisms. In following sections we describe several other morphologic and physiologic features of the bird's lung that enhance gas uptake.

Air sac system of birds. The avian bronchial system communicates with a system of air sacs filling >30% of the volume of the bird's thorax and abdomen (*16*) (Figs. 1 and 7). The air sacs are the sites of tidal volume expansion, functioning like bellows to move air through the avian lung–air-sac respiratory system. Changes in coelomic volume mediated by body-wall deformations are almost singularly reflected in volume changes within the several air sacs (Fig. 4). There is no analogous structure to the bird's air sacs in the mammalian respiratory system, in which the alveoli are both the site of gas exchange and volume expansion. The air sac walls are composed of a simple, nonstratified epithelium with a sparse distribution of small islands of ciliated cells and secretory cells supported by a diffuse connective tissue network composed primarily of elastin (*13*). In the absence of both a widespread mucociliary surface and airway macrophages, we do not know how air sac homeostasis is maintained. It is usually considered that little to no gas exchange occurs across the poorly vascularized walls of the air sacs; this is true for CO (*17,18*) yet there is toxicological evidence that highly soluble compounds such as SO_2 may indeed cross the air sac membrane (*19*).

The individual air sacs are anatomically (by site of connection to bronchial system) and functionally (see *Gas Flow Patterns*) divided into two main groups (Figs. 1, 4, 7): the cranial group, arising from the ventrobronchi, is composed of the paired cervical sacs, an unpaired intraclavicular sac, and paired cranial thoracic sacs; and the caudal group, arising from the caudal end of the intrapulmonary bronchus and connecting laterobronchus, is composed of the paired caudal thoracic sacs and paired abdominal sacs. The thin, highly elastic walls of these air sacs, in contact with adjacent sacs over a large percentage of their area (Fig. 7), are incapable of supporting pressure differences between

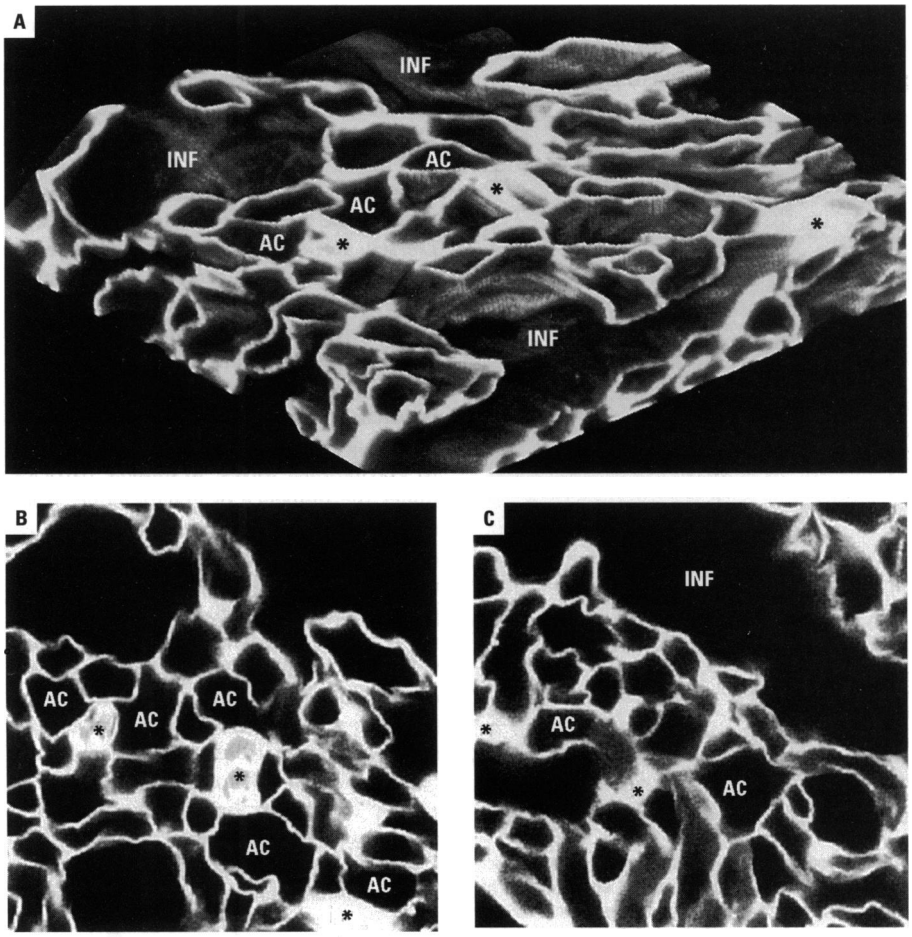

Figure 5. Confocal micrograph of gas-exchange region of parabronchus, goose. A) Three-dimensional reconstruction; (B) and (C) are two individual sections. Note the intimately intertwined network of blood capillaries, labeled with the presence of erythrocytes (*), and air capillaries (AC) that make up the parabronchi's mantle of gas-exchange tissue. Several air capillaries coalesce into an infundibulum (INF).

adjacent sacs. This fact is important in light of the inability of the air sacs to influence the unidirectional flow through the parabronchi (see *Gas Flow Patterns*). The several air sacs have communicating diverticula that invade most bones, nearly filling the medullary cavities of many, and extend between layers of soft tissues [e.g., between the layers of the large pectoral (flight) muscles]. These communicating diverticula and the small cervical air sacs lying along the neck are not considered to contribute to ventilation.

Avian airway geometry and particle deposition. Several physical mechanisms operate on inspired particles to increase the likelihood that a particle will contact (and deposit on) a respiratory surface, the most important being inertial forces, gravitational sedimentation, and Brownian diffusion. The extent to which each mechanism contributes to the deposition of a specific particle depends on that particle's physical characteristics (size, shape, density, ρ), airway geometry, flow pattern, and flow regime found within each component of the respiratory tract. Anesthetized chickens inhaling ^{125}I-labeled latex particles of a wide range of diameters (0.091, 0.176, 0.312, 1.1, 3.7, and 7 μm) showed regional deposition strongly linked to particle size (*20*). Convective transport of a particle throughout the respiratory system is mainly determined by that particle's density and size, specifically its aerodynamic equivalent diameter, D_{ae} ($D_{ae} \propto$ geometric diameter $\times \rho^{1/2}$). With larger D_{ae}, particle deposition is strongly influenced by inertial and sedimentation mechanisms. As D_{ae} becomes smaller, inertia and sedimentation play smaller roles in particle deposition, while Brownian diffusion becomes more important.

In a long, straight tube, the operative flow regime is mainly determined by the magnitude of the Reynolds number (Re), a dimensionless ratio of local inertial forces to viscous forces:

$$\frac{\rho u D}{\mu} \qquad (2)$$

where ρ is gas density; u is mean gas velocity; D is tube diameter; and μ is gas viscosity. When Re is <1, flow is primarily determined by viscous mechanisms, and inertial forces can be neglected. When Re is 10–2,000, both viscous forces and inertial forces are important, and at Re >2,000, inertial forces predominate. At Re <2,000 in a long, straight tube, the flow is usually laminar, which means there is little to no mixing of gas or particulates across streamlines. When Re is >2,000, flow becomes turbulent with extensive mixing. In the short, branched, curved tubes containing numerous choke points (site of sudden change in diameter or geometry) that make up the avian respiratory system, turbulent flow should be expected at flow regimes considerably less than Re = 2,000.

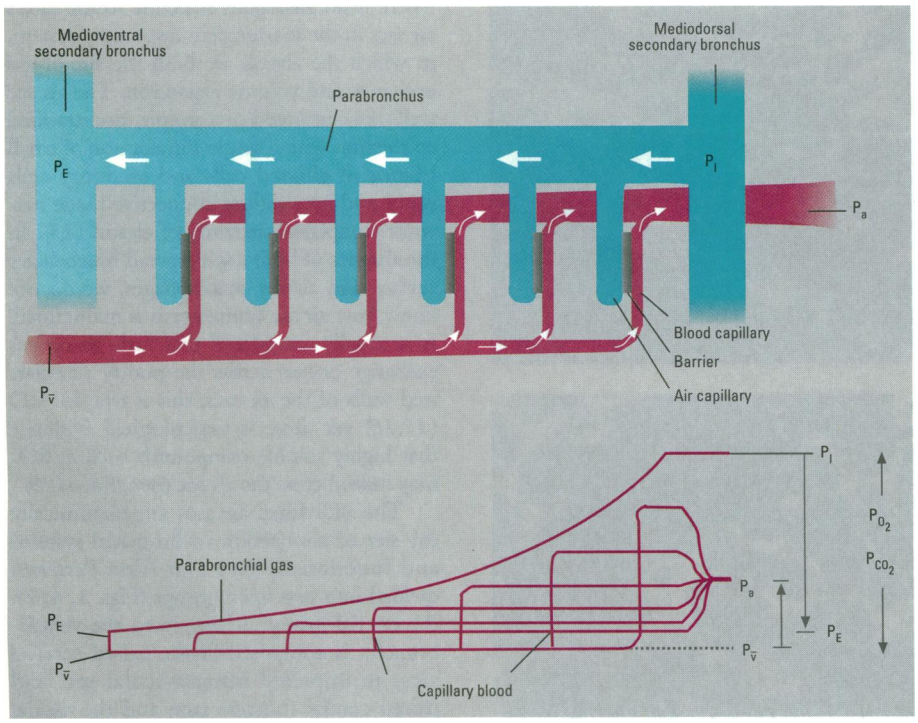

Figure 6. (Upper panel) Schematic of air flow (large arrows) and blood flow (small arrows) patterns constituting the cross-current gas-exchange mechanism operating in the avian lung. Note the serial arrangement of blood capillaries running from the periphery to the lumen of the parabronchus and the air capillaries radially departing from the parabronchial lumen. (Lower panel) Pressure profiles of O_2 and CO_2 from initial-parabronchial (P_I) to end-parabronchial values (P_E); and in blood capillaries from mixed venous ($P_{\bar{v}}$) to arterial blood (P_a). The P_{O_2} of arterial blood is derived from a mixture of all serial air-blood capillary units and exceeds that of P_E. In mammals, the Pa_{O_2} cannot exceed that of end-expiratory gas, (i.e., P_E). [From Scheid (*108*); with permission from Springer-Verlag.]

Inertial impaction. Inertia is the tendency of a moving particle to resist changes in direction and speed and is a function of the momentum (D_{ae}^2 and the local flow rate) of that particle. The highest linear flow velocities are found in the upper respiratory tract and central airways. At sites where there is an abrupt change in airflow direction (e.g., convoluted nasal passages or branching points of central airways), a particle, if it has sufficient momentum, will continue in its original direction crossing airflow streamlines and impacting on the airway wall instead of following the curvature of the airway with the airflow. In avian lungs, inertial impaction operates in central airways (bends in the trachea, syrinx, and branching points of secondary bronchi) and convoluted areas of extrathoracic (oropharynx, nasopharynx, and larynx). Associated flow regimes (for geese) found in those anatomical locations are the nose and bends in the trachea (u = 100 cm/sec, Re = 700); the narrowed syrinx and bends in the primary bronchi (u = 130 cm/sec, Re = 600); and the narrowed caudal end of the primary bronchus (u = 200 cm/sec, Re = 550). The expected sites of inertial impaction in the bird are similar to those in mammalian airways.

Gravitational sedimentation. Gravitational forces accelerate the fall of particles, and the terminal (constant) settling velocity is reached when viscous resistive forces of the air are equal and opposite in direction to gravitational forces. Respirable particles, under the influence of gravity alone, reach this terminal sedimentation velocity in less than 0.1 msec. The probability that a particle will deposit by gravitational settling is proportional to the product of its D_{ae}^2 and the residence time within airspaces in which velocities are low. In bird lungs, aerosol deposition by sedimentation would be important within the parabronchi and air sacs, where air flow velocities are low (parabronchi, u = 3 cm/sec, Re = 2) and residence times may be exceptionally long (e.g., possibly >1.0 min for complete change of air sac gas at rest). In the human lung, sedimentation is an important mechanism for particle deposition (D_{ae}>0.2 μm) within peripheral airways and alveoli (*21*).

Brownian diffusion. Brownian motion is a random process caused by collisions between particles and between particles and

gas molecules, and it may be a contributing factor in deposition of inhaled particulates. Diffusion is significant for particles with D_{ae}<1 μm. Unlike inertial or gravitational displacement, diffusion is independent of flow rate and particle density; however, it is affected by particle size and shape (*22*). The probability that a particle will be deposited by diffusion is a function of $(t/D_{te})^{1/2}$, where t is the residence time and D_{te} is the diameter of a sphere that has the same diffusional displacement as the particle. Diffusion, like sedimentation, is most important in the parabronchi and the air sacs where residence time is long.

Gas Flow Patterns in the Avian Lung–Air-Sac System

All the bird's air sacs, simultaneously filling with inspiration and emptying with expiration, contribute nearly equally to both inspiration and expiration (*23*) (Fig. 4). From flow probes inserted into the secondary bronchi, it has been established that gas flows unidirectionally (caudal to cranial) through the bird's paleopulmonic parabronchi during both inspiration and expiration (*24–28*). At the flows and breathing frequencies associated with exercise, the unidirectional flow through the dorsobronchi and parabronchi becomes continuous, although flows in the other parts of the bird's respiratory system are tidal.

Inspiration. During inspiration air flows caudally from the trachea through the intrapulmonary bronchus to the dorsobronchi, where the flow divides: approximately half goes to the parabronchi via the connecting dorsobronchi and half goes to the caudal group of air sacs (Fig. 4). Gas present in the lung from the previous expiration flows to the cranial group of air sacs via their ventrobronchial connections. As tidal volume is increased, gas flowing through the trachea traverses the entire length of the parabronchi via the dorsobronchi (as well as to the caudal air sacs) and enters the cranial sacs during a single inspiration.

Expiration. During expiration air flows from the caudal group of air sacs to the parabronchi via the dorsobronchi, and resident gas in the lung and cranial air sacs moves to the trachea via the ventrobronchi (Fig. 4). As tidal volume is increased, resident gas within the caudal air sacs from the previous inspiration flows completely through the parabronchi and out the trachea.

Valving in the avian lung. From Figure 1 it can be seen that 1) inspired gas has two possible pathways to follow when it reaches the junction between primary bronchus and ventrobronchi and 2) during expiration the gas exiting the caudal air sacs has two possible pathways when it reaches the junction of

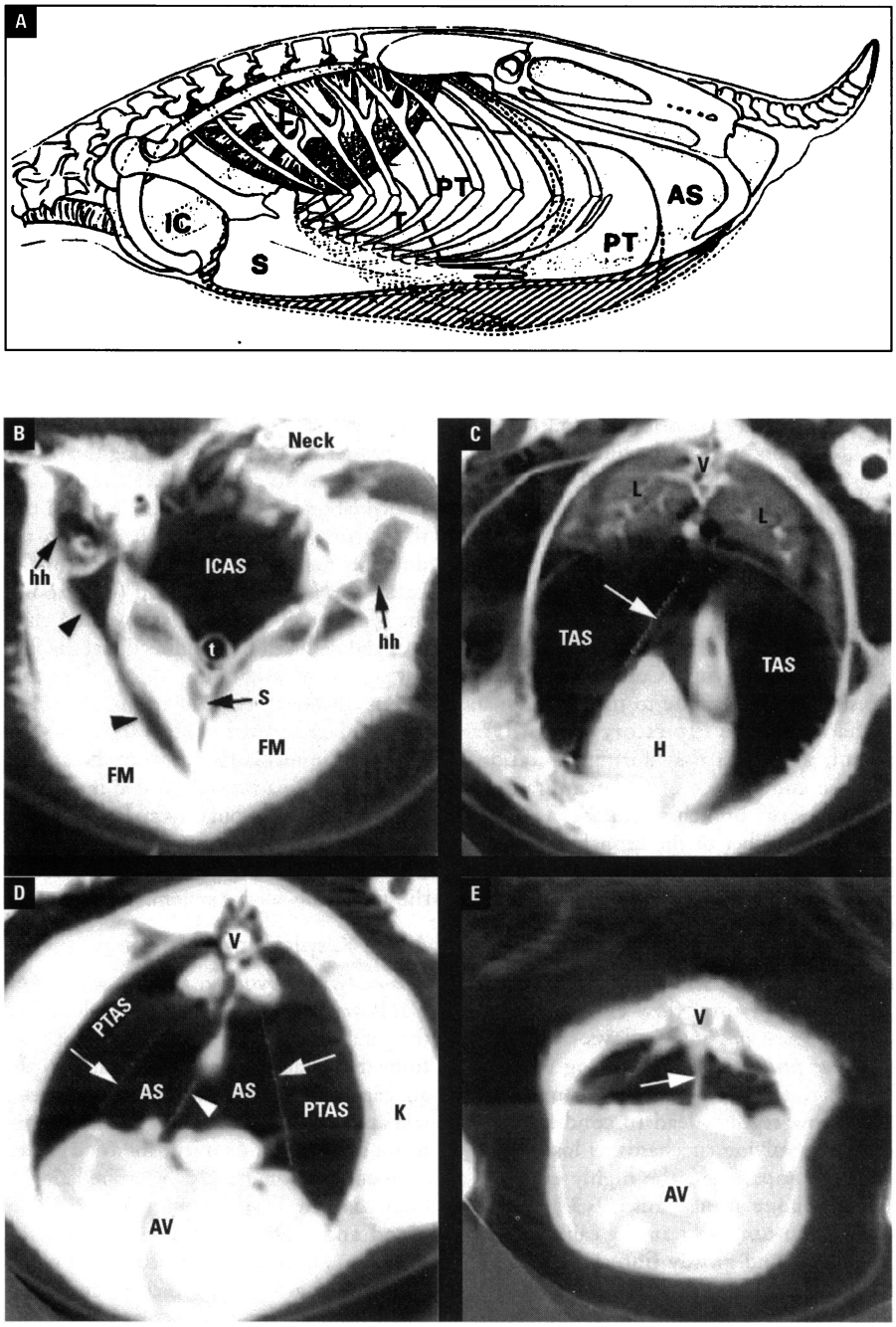

Figure 7. The avian air-sac system. (A) Diagrammatic *in situ* lateral view of avian air sacs. Note that from the body surface, the air sacs appear to nearly fill the bird's coelom, neck (left) to tail. The hatched area along the ventral body wall represents the change in coelomic volume with inspiration. IC, intraclavicular air sac; T, cranial thoracic air sac; PT, caudal thoracic air sac; AS, abdominal air sac; L, lung; S, sternum. (Reprinted from Duncker (*107*); with permission from Springer-Verlag.] (B–E) Computerized axial tomogram of an awake, spontaneously breathing goose; air is darkest. A large percentage of the bird's body is filled with the several air sacs. (B) At the level of the shoulder joints (hh, humeral head) is the intraclavicular air sac (ICAS), which extends from the heart cranially to the clavicles (i.e., furcula or wishbone). S, sternum; FM, large flight muscles with enclosed air sac diverticula, arrowheads; t, trachea. (C) At the level of the caudal heart (H) is the paired cranial thoracic air sacs (TAS). Arrowhead points to the medial wall of the air sac (contrast enhanced with aerosolized tantalum powder). The dorsal body cavity is filled with the lungs, which are tightly attached to the dorsal and lateral body wall. V, thoracic vertebrae. (D) At the level of the knees (K) is the paired caudal thoracic air sacs (PTAS) and paired abdominal air sacs, with the abdominal viscera (AV) filling the ventral body cavity. The membrane separating the abdominal air sacs from one another (arrowhead) and from the caudal thoracic air sacs (arrows) can be seen. (E) At the level of the caudal pelvis, the abdominal air sacs, which extend to the bird's tail, can be seen. Arrow, membrane separating abdominal air sacs.

dorsobronchi and caudal intrapulmonary bronchus. Yet we know from flow measurements that during inspiration there is little to no flow from the primary bronchus to ventrobronchi (i.e., inspiratory valving) and during expiration there is little to no flow craniad through the intrapulmonary bronchus between dorso- and ventrobronchi (i.e. expiratory valving) (Fig. 4). Originally, anatomic valves were postulated as the mechanism controlling flow in the bird's respiratory system (*29–31*), but the presence of such valves was never established (*16*).

Inspiratory valving. It is now known that an aerodynamic mechanism (i.e., convective inertia) is responsible for controlling the direction of flow in the bird's respiratory system during inspiration (*32*). The convective inertial momentum (ρu^2, where ρ = gas density and u = flow velocity) of the inspiratory gas stream flowing through the primary bronchus prevents the flow from turning the corner, so to speak, and entering the ventrobronchial orifices (*33,34*).

Expiratory valving. Convective inertial forces do not contribute to the operational mechanics of the expiratory valve (*35*). Instead, it appears that during expiration dynamic compliance of the membranous intrapulmonary bronchus results in a reduction of the caliber of the bronchus and an increase in resistance to craniad flow through the intrapulmonary bronchus. The increase in resistance is a direct function of the expiratory flow velocity and produces an expiratory valve with an efficacy (dorsobronchial flow:total flow exiting caudal sacs) of 95% at physiologic flows.

Valve failure. During panting in thermally stressed birds, the resulting nonsteady flow regimes lead to conditions in which the valving mechanisms lose effectiveness compared to the highly effective valving of nonpanting birds (*36,37*). As gas composition can affect airway caliber [e.g., CO_2 (*38*)], and airway fibrosis secondary to particle deposition (*39–43*) could affect airway caliber and compliance, the bird's respiratory valving mechanisms may be adversely affected by environmental contamination. Airway caliber strongly influences both the relative resistances to flow in the various parts of the bird's bronchial system and the velocity of the gas stream, which is a direct determinant of its convective inertia. Further, reduced airway compliance from tissue fibrosis secondary to particle deposition could greatly diminish or eliminate effective expiratory valving.

Particle deposition: homogeneous divisions of the avian system versus the heterogeneous mammalian system. In human lungs, below the level of the paired main stem bronchi, there is a highly heterogenous mixture of different aerodynamic environments (e.g., viscous flow in terminal bronchi and turbulent flow in larger airways). In sharp contrast, the various components within the bird's respiratory system, and their correspondingly different flow regimes, are found as discrete and isolated components. The unidirectional flow through the bird's primary and secondary bronchi and parabronchi allow the patterns of particle deposition to be examined without the confounding variable of bidirectional flow. These differences suggest that birds may represent a valuable tool in furthering our understanding of the deposition and clearance of inhaled particulates.

Dotterweich (*44*) was among the first to expose birds to soot particles under controlled laboratory conditions. He found that the particles deposited much more in the dorsobronchi than in the ventrobronchi. Later, Vos (*45*) and Hazelhoff (*46*) exposed the birds to air laden with powdered charcoal and deduced the unidirectional gas flow pattern in the avian lung. Adult, fully conscious chickens exposed to an aerosol of ^{99m}Tc-labeled particles (D_{ae} = 0.45 µm) and examined immediately thereafter had a predominance of particles deposited in the caudal areas of the respiratory system (*47*). All these investigations demonstrated the highly nonrandom pattern of particle deposition in the avian lung–air-sac system.

Avian Respiratory Physiology

Gas-exchange physiology in the parabronchi. Gas flows convectively through the lumen of the parabronchi, whereas movement of gases from the parabronchial lumen out into the air capillary network where gas exchange takes place is considered to be an entirely diffusive mechanism. As is true for avian as well as mammalian lungs, O_2 in inspired air diffuses passively into the pulmonary capillary blood and CO_2 diffuses in the opposite direction. However, the structure and physiology of the avian parabronchial lung is different from the bronchoalveolar mammalian lung and thus gas transport patterns are also different. These differences may have important implications in respiratory toxicology.

Cross-current gas exchange mechanism at the level of parabronchi. Uptake of O_2 and CO_2 loss via the bird's parabronchial lung is unaffected by direction of gas flow through the parabronchi, craniocaudal versus caudocranial (*48*). Such evidence demonstrates that at the level of the parabronchi, there is a cross-current gas exchange mechanism in the avian lung (Fig. 6), which is in strong contrast to the cocurrent gas exchanger operating in mammalian lungs. From air flowing convectively through the parabronchial lumen, O_2 diffuses radially into the air capillary network and then into pulmonary capillary blood across the thin blood–gas barrier, with CO_2 moving in the opposite direction (Figs. 3 and 6). Blood in the pulmonary capillaries flows opposite to that of the diffusive movement of O_2 in the air capillaries, i.e., radially and centrally from pulmonary arteries located at the parabronchial periphery (Fig. 8). The air–blood capillary units are arranged serially along the luminal axis of a parabronchus.

Because systemic arterial blood is a mixture of blood from all the serially arranged air–blood capillary units, arterial P_{O_2} can actually be greater than end-expired P_{O_2} (see Fig. 6); this cannot occur in the mammalian lung. While parabronchial P_{O_2} decreases with distance traveled through the lumen (and P_{CO_2} increases), the actual profiles of O_2 and CO_2 along the parabronchus are a function of ventilation; that is, with increases in ventilation, the end-parabronchial P_{O_2} can be increased with corresponding decreases in end-parabronchial C_{O_2}. Thus the diffusion gradients of the gases (parabronchial lumen to blood capillaries) can be increased along the distal portion of the parabronchi with increased ventilation.

Counter-current gas exchange mechanism at level of air capillary. Oxygen diffusing peripherally from the parabronchial lumen and pulmonary blood flowing centrally toward the parabronchial lumen along their common diffusion barrier produces a counter-current gas-exchange mechanism at the level of individual air capillaries (*48,49*) (Fig. 8). In such an arrangement, as blood travels centrally along the diffusion barrier separating it

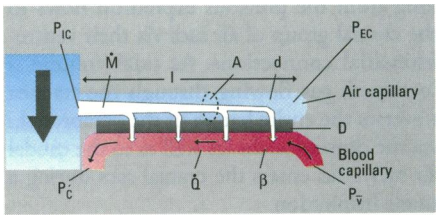

Figure 8. Schematic of the counter-current gas-exchange mechanism operating at the level of the air capillary. Air flows convectively through the parabronchial lumen (large arrow), from which O_2 diffuses radial from the opening of the air capillary (P_{IC}) to its end (P_{EC}). Blood flows opposite to the diffusion direction of O_2. P_{O_2} in the air capillary falls continuously from its opening to its end, while P_{O2} in pulmonary blood rises continuously from that of mixed venous blood ($P\bar{v}$) to a peak found in the blood capillary at its termination at the parabronchial lumen ($P_{\bar{c}}$); with P_{CO_2} following the opposite courses. This arrangement favors O_2 uptake (and CO_2 off-loading) by the blood as at all points along the air-blood capillary diffusion barrier (D): there is a higher P_{O_2} in the air capillary versus that in the blood capillary. [From Scheid (*108*); with permission from Springer-Verlag].

from the air capillary and takes up O_2, the concentration of O_2 in the blood is always less than the increasing concentration of O_2 in the air capillary as it nears its parabronchi's lumen (the opposite is true of the blood's P_{CO_2}). As such, the concentration gradients along the radial length of an air capillary continually favor more O_2 uptake and CO_2 release by the pulmonary capillary blood.

Ventilation. Tracheal volume in birds is about 4.5-fold that of comparably sized mammals due mainly to the considerably longer tracheal length of birds (*6*). In birds, tracheal volume approximates respiratory dead space (V_D) as all air passing the tracheal bifurcation also passes over the gas-exchange tissues of the parabronchial lung due to the effective valving of airflow in the bird's respiratory system and the maintenance of a unidirectional air flow through the lung per se (*50,51*):

$$\text{Avian tracheal volume (ml)} = V_D = 3.724(M_b^{1.09}), \quad (3)$$

where M_b = body mass in kilograms. Birds, at least partially, compensate for their larger tracheal dead space by increasing tidal volume and decreasing respiratory frequency relative to that of equally sized mammals (*52*). That behavioral adaptation reduces the percentage of the bird's tidal volume wasted in dead space ventilation with each breath so that minute tracheal ventilation in birds is only 1.5 to 1.9 times that of comparable mammals. In contrast to that of birds, respiratory dead space in mammals includes not only the volume of the trachea but also the volume of nearly all conducting airways above the level of the alveolar duct (*53*):

$$\text{Mammalian dead space (ml)} = V_D = 2.76(M_b^{0.96}) \quad (4)$$

For resting birds, the following mass-specific respiratory relationships (at BPTS) are found (*54,55*):

$$\text{Title volume (ml)} = V_T = 16.9(M_b^{1.05}) \quad (5)$$

$$\text{Frequency (per min)} = f = 17.2(M_b^{-0.31}) \quad (6)$$

$$\text{Ventilation (ml/min)} = \dot{V} = 291.0(M_b^{0.74}) \quad (7)$$

and for flying birds:

$$V_T = 27.8(M_b^{0.89}) \quad (8)$$

$$f = \text{independent of } M_b \quad (9)$$

$$\dot{V} = 5{,}000.0(M_b^{0.74}) \quad (10)$$

In contrast, mammals under resting conditions fit the following mass-specific relationships (*53*):

$$V_T = 7.69(M_b^{1.04}) \quad (11)$$

$$f = 53.5(M_b^{-0.26}) \quad (12)$$

$$\dot{V} = 379.0(M_b^{0.80}) \quad (13)$$

We can calculate effective ventilation (ml/min) of the gas-exchange regions of the lung ($\dot{V}_P$ = parabronchial ventilation in birds and $\dot{V}_A$ = alveolar ventilation in mammals), from minute ventilation ($\dot{V}$) and anatomic dead space ventilation ($\dot{V}_D = \dot{V}_D \times f$): for resting birds,

$$\dot{V}_P = \dot{V} - \dot{V}_D \quad (14)$$

$$\dot{V}_P = \left[291.0\left(M_b^{0.74}\right)\right] - \left[63.0\left(M_b^{0.78}\right)\right], \quad (15)$$

and for mammals,

$$\dot{V}_A = \dot{V} - \dot{V}_D \quad (16)$$

$$\dot{V}_A = \left[379.0\left(M_b^{0.8}\right)\right] - \left[146.0\left(M_b^{0.70}\right)\right]. \quad (17)$$

The above values and calculations for avian respiration are valid only in nonpasserine taxa. The order Passeriformes includes many of the common species such as song birds and sparrows, flycatchers, jays, and warblers. In passeriforms, under resting conditions, mass-specific oxygen consumption is approximately 65% higher, hence $\dot{V}$ and/or $\dot{V}_P$ are proportionally higher than those of nonpasserine taxa (*6,56,57*).

Comparisons of ventilation between birds and mammals. How then does ventilation in birds compare to that in mammals? Mass-specific ventilation, $\dot{V}$, in resting birds (nonpasserines) is 20–80% higher than mammalian values. Effective (parabronchial) ventilation, $\dot{V}_P$, in birds under resting conditions is 30–160% higher than the alveolar ventilation, $\dot{V}_A$, of comparably sized mammals. Those values are not surprising in light of mass-specific oxygen consumptions ($\dot{V}_{O_2}$), again under resting conditions, for birds that are 50% to >160% higher than that for mammals. Flight is the most metabolically expensive (O_2 ml/min/M_b) form of locomotion on a unit time basis (*58–60*). Mass-specific oxygen consumption in flying birds, which may or may not reach $\dot{V}_{O_2\,MAX}$, is 10–170+% higher than the maximum oxygen consumption in mammals. Peak O_2 consumption, measured in hovering hummingbirds that were limited not by aerobic capacity but by wing aerodynamics secondary to a low density atmosphere (80% He, 20% O_2), was approximately 70 ml/g/hr (*61*). Maximum oxygen consumption, $\dot{V}_{O_2\,MAX}$, is reached when $\dot{V}_{O_2}$ no longer increases with increasing exercise intensity, and anaerobic glycolysis must account for the additional energy consumed by the muscles.

Gas Uptake by the Avian Parabronchial Lung

The differences in respiratory anatomy and physiology in birds versus mammals results in several important differences in expected gas uptake, $\dot{M}$.

Gas phase. In the gas phase $\dot{M}_G$ depends on effective ventilation ($\dot{V}_P$ or $\dot{V}_A$), the solubility of the gas in question (β_G), and the difference between the partial pressures of that gas in the inspired (P_I) and expired (P_E) air in the following relationship:

$$\dot{M}_G = \dot{V}_P \beta_G \left(P_I - P_E\right). \quad (18)$$

The solubility of a gas depends only on temperature (T), that is $\beta_G = 1/(RT)$, where R is the ideal gas constant (*62*). There would, of course, be a slight (<1%) decrease in gas solubility due to the bird's higher body temperature (104–107°C) relative to that of mammals (99–102°C). However, from the above relationship, it can be seen that the higher (up to 160+% that of comparably sized mammals) effective ventilation in birds has important consequences in total gas uptake.

Gas to blood phase. As described earlier, the thinness of the bird's gas-exchange tissue, approximately half the thickness of mammals, has important implications for the uptake of gas into the blood from the surrounding air spaces. Given identical effective ventilation of exchange tissues, a bird will take up more (approximately twice as much) of a given gas (*63*). In addition, due to the cross-current arrangement of the air flow relative to blood flow through the avian lung, the partial pressure of a gas in arterial blood can exceed that of the end expiratory gas.

Blood phase. Finally, the transport of a gas in the blood, $\dot{M}_B$, depends on pulmonary blood flow ($\dot{Q}$), gas solubility (β_b), and the difference in partial pressures of the gas in arterial (P_A) and mixed venous ($P\bar{v}$) blood:

$$\dot{M}_B = \dot{Q}\beta_G\left(P_A - P\bar{v}\right) \quad (19)$$

Mass-specific pulmonary capillary blood volume, heart size, and heart rates are quite similar between birds and mam-

mals (*15*). Further, the binding properties of hemoglobin (e.g., to O_2, CO_2, and CO) are nearly identical between avian and mammalian blood.

Local concentration gradients in the avian parabronchi. Because of the cross-current gas-exchange mechanism in the avian lung, large concentration gradients can develop along the length of the parabronchi. That is, for a given $\dot{V}_P$ if the equilibration time constant [= 4 $V_C \times (T/(A \times D))$, where V_C = capillary blood volume] from gas phase to blood is much shorter than the gas transit time in the parabronchi, the local concentration at the dorsobronchial (inflow) end of the parabronchi will be significantly higher than that at the ventrobronchial (outflow) end. Thus, within the avian lung, local tissue exposures (doses) can be much higher than the average exposure; this is not the case in the mammalian lung, where all alveoli are exposed to nearly the same concentration of a gas.

Gas Uptake in Avian Embryos

During avian development there are three sequential stages of respiration (*64*): prenatal (embryonic), paranatal (hatching), and postnatal (posthatching). During the prenatal stage respiratory gas exchange occurs via diffusion between the external environment and the initial gas exchanger (i.e., the area vasculosa) in early embryonic life and later the vascular bed of the chorioallantois. The paranatal stage starts when the beak penetrates into the air pocket (air cell) between the inner and outer shell membranes (both internal to shell; i.e., internal pipping) this occurs during the last 2–3 days of incubation. During this stage, the lungs begin to replace the chorioallantois as the gas exchanger, yet diffusion remains the major mechanism moving gas across the shell per se. The postnatal stage begins when the beak penetrates the shell (i.e., external pipping). Here we are interested only in the prenatal stage (*65,66*).

The eggshell. The eggshell protects the embryo from variations in the environment, supplies necessary nutrients (most importantly calcium) and regulates gas exchange and water loss between egg contents and the environment external to the egg. The regulation of gas exchange and water loss (diffusion coefficient) is primarily a function of the density, diameter, and structure of the pores traversing the eggshell (*67,68*). Shell pore parameters vary between species and within a single species inhabiting different niches, e.g., humidity and altitudinal gradients (*67,68*). Further, shell thickness and pore architecture change during incubation (calcium reabsorbed for embryonic development), leading to changes in a gas's diffusion coefficient (*69*). Environmental factors affecting laying hens, such as nutritional stress, heat stress on laying hens, and environmental toxicants (e.g., organochlorine pesticides) can result in changes in eggshell thickness (*70,71*). The effects of eggshell thinning on gas-exchange physiology and the possible existence of concomitant changes in pore architecture with changes in shell thickness are not known.

Mechanisms of gas uptake by avian embryos. The flux of a gas transferred across the shell per unit time, $\dot{M}_S$, is (*64*):

$$\dot{M}_S = \left[A_P\left(\frac{D_S}{T_S}\right)\right]\beta_G(P_A - P_{CELL}), \quad (20)$$

where A_P = effective pore area of shell; D_S = diffusion coefficient of the gas across the shell; T_S = shell thickness; and the relative partial pressures of the gas in question between the air cell within the shell (P_{CELL}) and ambient (P_A). The flux of gas per unit time from the air cell within the shell to the embryo's blood, $\dot{M}_{AC,B}$, is:

$$\dot{M}_{CELL,B} = \left[A_{CELL}\left(\frac{D_{G,B}}{T}\right)\right]\beta_G(P_{CELL} - P_C), \quad (21)$$

where A_{CELL} = gas-exchange area between air cell and blood capillaries of extraembryonic membranes; $D_{G,B}$ = the diffusion coefficient from gas to blood; T = thickness of diffusion barrier from air cell to extraembryonic membranes; and P_C = partial pressures of the gas in the blood capillaries. In the blood phase, the controlling equation is the same as presented above for blood in adult animals, except in the case of the embryo, $\dot{Q}$ is the blood flow in the embryo's allantois. For a given egg at a given ambient gas concentration, the higher the diffusion coefficient and the higher the solubility of the gas in blood, the more the gas uptake into the eggshell or into the embryonic circulation. In addition, a lipid-soluble gas will deposit primarily in the yolk due to its high fat content.

Avian Respiratory Toxicology

Inhaled Particulates

Birds living in environments contaminated with aerosolized particulates show significant pathology after only a short duration of exposure, for example, Kiwis foraging within loose dust and sand (*43*), birds living in or near desertlike conditions (*44*), or birds exposed to volcanic ash (*72*). Modern, population-intensive confinement methods of poultry production often expose birds continuously to extremely high levels of aerosolized particulates, which commonly results in significantly decreased performance (production) and observable pathologic changes (*45–47,73,74*). Such conditions also represent significant threats to the health of the humans (*45*). What are the mechanisms responsible for the clearance of particulates from the bird's respiratory system following high and prolonged dust exposures?

We are unaware of any studies examining the pathophysiology of such particle exposures. Airway macrophages, responsible for much of the particulate clearance from the lower airways of mammals, are rarely found in the bird's respiratory tract. Do such phagocytic cells appear only when needed? Under experimental conditions (e.g., stimulation with Freund's adjuvant or Sephadex instilled into air spaces) phagocytic cells physiologically similar to mammalian alveolar macrophages can be induced to enter the bird's pulmonary spaces (*75,76*). Birds, like mammals, have bronchus-associated lymphoid tissue within the epithelium lining their lungs and bronchi, which contributes to clearance (dissolution and antibody labeling) of paticulates from the respiratory tract of mammals (*77*).

In chickens, after exposure to aerosols of relatively small respirable particles, no particles were found in the vascular system, kidneys, ovaries, or the heart, indicating that the particles were not absorbed across the epithelial membranes of the respiratory tract (*26*). Of the initial lung deposition, 54% remained 1 hr after exposure and 35% remained 36 hr after exposure, suggesting an early fast phase of lung clearance followed by a slower phase as found in mammals. The fast component of clearance is assumed to result from particles cleared from the respiratory tract via mucociliary transport and then eliminated via the gastrointestinal tract. What are the mechanisms involved in the slow phase of particle clearance? Inspired particles (nontoxic iron oxide) within the lung have been found trapped in the trilaminar substance (assumed to be a surfactantlike material), in the respiratory epithelial cells, and in adjacent interstitial macrophages (*43,78*). It is possible that the particles were phagocytosed by the epithelial cells at the air side and exocytosed into the interstitium and then phagocytosed by interstitial macrophages.

Toxic Gases

Observation of caged canaries served as the standard for mine safety during the nineteenth and early twentieth centuries in regard to the highly toxic gases carbon monoxide and methane (*79*). Despite the early recognition of the substantial differences in metabolic rate, toxic gas uptake, and pathophysiology between birds and mammals, little additional investigation has followed.

Sulfur dioxide. Sulfur dioxide (SO_2) is well known to be capable of producing pathologic changes in animals, including birds, as well as causing generalized degradation to the environment (e.g., acid rain). However, there are only a few high-dose laboratory studies of the effects of SO_2 on sedentary, domesticated geese and chickens (*19,80–83*).

Carbon monoxide. The pathophysiologic effects of carbon monoxide on a range of animal taxa have been well documented and indicate the following relative sensitivities (*84–89*): canaries (most sensitive), sparrows, pigeons, chickens, mice, guinea pigs, rabbits, and dogs (least sensitive). In the beginning of this century, Burrell et al. (*84*) cited Haldane as stating that "a mouse weighing one-half an ounce consumes about 15 times as much oxygen as one-half ounce of the human body would consume in the same time" and strongly recommended the use of small animals such as mice and canaries for the purpose of detecting CO in the aftermath of explosions and fires in mines. Yet, despite all the studies of the toxicity of CO in a variety of animals, we do not know the physiologic basis for the different sensitivities among the different kinds of animals. A list of physiologic possibilities would include ventilatory demands, gas-exchange physiology, the design of the respiratory system, and specific biochemical sensitivity.

Ammonia. Exposure of chickens to the levels of ammonia occurring in confinement poultry houses (about 20 ppm) produced gross and microscopic damage to the respiratory tract (e.g., loss of cilia) and made the birds more susceptible to infection (*73,90*). Other investigators showed acute physiologic changes on initial exposure (5–10 sec) to ammonia at low doses (1–100 ppm) (*80,82*), similar to the effects of ammonia on the mammalian respiratory tract.

Hydrogen sulfide. Hydrogen sulfide (H_2S) is a toxic gas that inhibits enzyme systems in animals (*91*), and a single inhalation of 1,800 ppm can produce death in mammals (dog and humans) (*92*). Inhaling 500–1,500 ppm for long periods can lead to respiratory failure and death (*93–95*). Chickens inhaling 500 ppm H_2S for 30 min did not exhibit changes in ventilation; inhaling 2,000–3,000 ppm H_2S for 30 min resulted in irregular and variable tidal volume and respiratory frequency; inhaling 4,000 ppm H_2S for 15 min caused death (*96*). It is not clear why chickens are more resistant to H_2S toxicity than humans or dogs.

Ozone. Newly hatched chicks are especially susceptible to the toxic effects of ozone and died after 5 days of continuous exposure to 1–4 ppm ozone (*97*). Exposure of young chicks to 0.3–0.7 ppm ozone results in pulmonary hemorrhage within the bronchi and air capillaries (*98*).

Carbon dioxide. The effects of CO_2 on avian respiration and acid–base balance are not reviewed here because CO_2 is viewed as nontoxic, although this gas has been shown to have pathophysiologic effects. Additionally, CO_2 may have important effects on avian airway geometry (*35,38*).

Polytetrafluroethylene. Teflon and Silverstone (EI Du Pont de Nemours and Co., Inc., Wilmington, Delaware) are common nonstick coatings on cooking utensils and appliances. When heated to temperatures above 260°C, this otherwise stable material emits several fluorinated pyrolysis products (e.g., carbonyl fluoride, hydrogen fluoride, and perfluoroisobutylene) that are known to be rapidly lethal to birds (*99–101*). Severe necrotizing and hemorrhagic respiratory pathology is found after exposure, but the pathologic mechanism underlying this condition is not understood, as there are several breakdown products, gases and particulates, emitted. Would caged birds be a valuable adjunct to kitchen safety in regard to the presence of toxic gases?

Discussion

The morphology and physiology of the avian lung–air-sac respiratory system is strikingly different from that of the bronchoalveolar lung of mammals. We suggest that the bird's unique respiratory apparatus can be productively exploited from two different viewpoints as a valuable resource in our understanding of respiratory (inhalant) toxicosis. First, the comparative study of animals with significant differences in their respiratory anatomy and physiology (e.g., birds versus mammals) may produce insights otherwise unobtainable (*102*). Second, the ubiquitous distribution of birds makes these animals potentially valuable in the study and monitoring of environmental contamination (*4,5*). If birds are to be utilized to fulfill those broad scientific goals, we need to systematically study, on a wide variety of avian taxa (adult and embryonic), the short- and long-term pathophysiologic effects of the inhaled toxic gases and particulates that are present or released in the environment.

Comparative Respiratory Physiology and Toxic Gases

Observation of caged canaries, with experimental validation (*79,84*), served as the standard for mine safety during the nineteenth and early twentieth centuries. The popular press continues to occasionally report situations in which caged birds are used to detect the presence of toxic gases. What are the unique features of the bird's respiratory physiology and/or physiology in general (e.g., metabolic rate, exercise patterns, enzymatic makeup) that lead to intoxification by at least some inhaled substances sooner than other animals and prior to the development of potentially lethal pathology in those other animals?

Reviewing the dose-related pathophysiology of a spectrum of orally administered toxicants to a range of domestic animals suggests that, in general, birds (most research has been completed using domestic fowl) are not automatically and predictably more sensitive to orally administered toxicants than comparably sized mammals (*103*). That is, birds may have a higher or lower, depending on the specific intoxicant, sensitivity to an orally administered toxicant or environmental contaminant relative to comparably sized mammals. Not only is the direction (higher or lower) often not predictable *a priori* as to differences in sensitivity between mammals and birds in regard to a specific toxicant, but there are differences among related (below ordinal level) avian taxa (*104,105*). In comparative investigations of susceptibilities to toxicants, it appears that often no attempt was made to examine the effect of differences in metabolic rate (*104,105*). In regard to inhaled toxicants (gas and particulate), there is insufficient information to make any predictions concerning relative sensitivities.

Some gases (e.g., CO) have a toxicity that appears to be a direct function of metabolic rate and its associated ventilatory demands, such as carbon monoxide (*85*). But the available information regarding the pathophysiology of toxic gases in birds cannot be explained simply as a result of their higher metabolic demands. Although some gases have been shown to have an increased toxicity in birds [e.g., breakdown products of Teflon, polytetrafluroethylene (*99,100*)], others have been found to be less toxic in birds [e.g., hydrogen sulfide (*92,96*)] and still other gases show about the same toxicity in mammals and birds [e.g., ammonia (*74,80*)]. These limited results suggest that there is a complex relationship between a species' respiratory physiology, its pathophysiologic response to a potentially toxic gas, and other physiologic factors.

The respiratory apparatus of birds has evolved from the primitive, saclike, falveolar lungs of reptiles in response to the large metabolic demands of flight. That evolutionary process has produced a respiratory system with substantial physiological differences relative to the comparable features of other vertebrates. Among the most important of these respiratory differences are that

birds have higher mass-specific minute ventilation, $\dot{V}$; higher mass specific effective ventilation of gas-exchange tissues, $\dot{V}_P$; cross-current (parabronchi) and countercurrent (air capillaries) gas-exchange mechanisms; and a gas diffusion barrier half the thickness of that of mammals. We suggest that such differences can be usefully exploited in our understanding of the uptake and pathophysiology of toxic gases, but only if we study the interactions of respiratory system structure and function and the species-specific pathophysiologic responses to inhaled gases and particulates in a broad range of avian taxa.

Comparative Respiratory Physiology and Aerosolized Particulates

Birds often live in environments, especially those found in population dense, poultry production buildings, in which they are exposed to high levels of aerosolized particulates. Although it is well established that birds suffer pathological consequences to the deposition of inhaled particles, we are unaware of any investigation into the mechanisms responsible for such damage in birds. Further, we have little knowledge concerning the clearance mechanisms of the bird's lung–air-sac system. Comparative respiratory physiology, in regard to the response to inhaled particulates, has much to teach us from two dichotomous standpoints. First, we may find broad physiological generalizations in the manner by which animals respond to certain environmental stresses that increases our understanding of basic physiological mechanisms. Second, we may find animal-specific physiological processes for maintenance of the homeostasis of the respiratory system when contaminated with aerosolized particles, which will provide insights into alternative responses to such insults.

Are there modifications in the bird's mucociliary transport or cough mechanisms that are indispensable for the clearance of particulates along their longer tracheas? Surprisingly, much of the birds' respiratory system appears to lack any of the clearance mechanisms attributed with maintaining respiratory homeostasis and health in mammals. The bird's air sacs appear to be perfectly adapted for the unhindered development of respiratory infections. That is, the air sacs have a flow regime (large residence times) that assists in particle deposition, no available macrophages to remove foreign debris, and an epithelial surface nearly devoid of a mucocillary transport mechanism. What are we to make of the bird's apparent absence of airway (alveolar) macrophages when such scavenger cells are primarily responsible for particle clearance from the lower airways in mammals? Oddly, it appears that in birds the phagocytic function of the mammalian airway macrophage has been taken over by epithelial cells lining parts of the birds respiratory tract. Much more work needs to be done using different avian species on the fate and distribution of inhaled particles, collection efficiency, avian responses (pathophysiology), and comparison with mammals of similar body mass under similar experimental conditions.

Early observations of the highly nonrandom distribution of particle deposition in the avian respiratory tract provided the initial clues as to the strikingly unusual unidirectional pattern of gas flow through the bird's lung (*23–25*). We suggest that the contrasting flow patterns found in the various components of the bird's lung–air-sac system can be advantageously exploited in our understanding of the deposition and clearance of inhaled particulates, e.g., unidirectional flow in several well-defined areas; discrete regions of the bird's respiratory tract with distinct flow patterns and flow regimes versus the heterogeneous mammalian lung; and comparatively stagnant flow in the air sacs and their diverticulae.

Birds as Monitors of Air Quality

Birds are ubiquitously distributed in essentially all of the environments inhabited by humans; thus, if we understood the effects of a broad range of inhaled environmental contaminants (gas and particulate) on a wide variety of avian species, they could serve as highly effective and sensitive monitors of air quality (*2–5*). Several common avian species such as House sparrows (*Passer domesticus*, and closely related allies) and starlings (*Sternus vulgarus*) have colonized almost every environmental niche (urban, suburban, and rural) across a wide expanse of the regions inhabited, utilized, and contaminated by *Homo sapiens*. Such commonly encountered species, available in large numbers, means that a uniform biological monitor, meeting the relevant–reliable–repeatable criteria of Calow (*106*), is in place and currently sampling the environment. Several avian taxa inhabit environments not readily accessible to humans (e.g., pelagic sea birds) and would potentially be excellent monitors of air quality when examined upon their return to land from such inaccessible areas.

Adult birds moving about their environment, taking up the large mass-specific amounts of oxygen required for flight, along with any other gases or particulates present, could be used as sensitive monitors of environmental contamination by gases or airborne particulates at low concentrations. If we understood the pathophysiology of an inhaled toxicant on a species, would it not then be possible to detect environmental contamination prior to the appearance of clinical signs (e.g., analysis of expired gas, body fluids such as blood or examination of tissues)? Embryonic birds, once the egg is laid in the nest, experience a much more local exposure to gases (particulates not considered here) than their foraging parents who may cover large distances in search of food. Examination of the embryo (and other egg constituents) within the immobile egg could be utilized as a monitor of local air quality. That is, with the dilution of a contaminant with increasing distance from its source, eggs at different distances from the source would be expected to take up (embryonic respiration) different quantities of the gaseous contaminant. The differential uptake of a contaminant by eggs found in different locations might provide information as to the dispersion pattern or point to the source of a contaminant.

If we are to prevent loss of the natural diversity, then it is essential that we understand, on a broad range of taxa, the pathophysiologic effects of the substances that are released into the environment. The survival of birds depends on the condition of the environment that humans intimately share with these flying dinosaurs. Yet whether we are interested in birds as monitors of air quality or as tools to understand the pathophysiology of inhaled gases and particulates from a comparative viewpoint, we need to study the relationships between the physiology of the bird's unique lung–air-sac respiratory system and the pathophysiology of inhaled substances, gases, and particulates (including those not now considered toxic to *Homo sapiens*) on a wide variety of avian taxa.

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