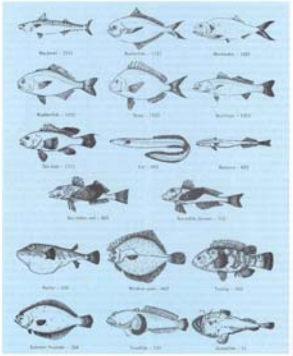
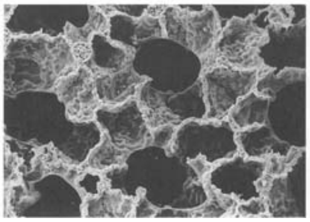
Lecture 21
05 March 2008

Vertebrate Physiology
ECOL 437 (MCB/VetSci 437)
Univ. of Arizona, spring 2008

Kevin Bonine & Kevin Oh



1. Respiration (Ch 20-21)



MAMMALIAN LUNG Scanning electron micrograph of the lung structure of a wildebeest (*Connochaetes taurinus*). The capillaries, filled with red blood cells, are visible as a bulging network in the alveolar walls. The distance across the photograph corresponds to about 0.5 mm in the lung. [Courtesy of Ewald Weibel, University of Berne, Switzerland]

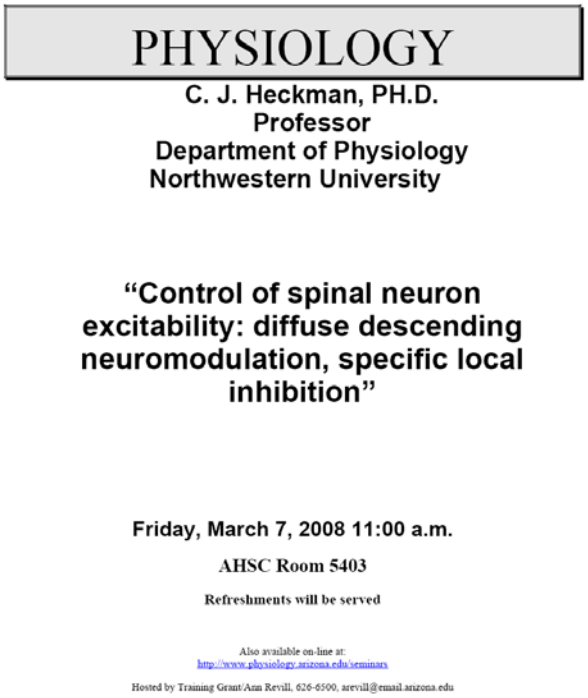
http://eebweb.arizona.edu/eeb_course_websites.htm

Housekeeping, 05 March 2008

Upcoming Readings
Wed 05 Mar: Ch20, 21 (respiration)
LAB Wed 05 Mar: Dickinson reading on website
Fri 07 Mar: Ch 21
Mon 10 Mar: Ch 21, 22
Wed 12 Mar: Ch 23 (circulation)
LAB Wed 12 Mar: no reading
Fri 14 Mar: EXAM TWO (through respiration)
SPRING BREAK

Lab discussion leaders: 05 March
1pm – Julia, Matt C.
3pm – Dalziel, Nick

Lab discussion leaders: 26 Mar
1pm – Vangie & Christina
3pm – Prasun & Ajay



PHYSIOLOGY

C. J. Heckman, PH.D.
Professor
Department of Physiology
Northwestern University

"Control of spinal neuron excitability: diffuse descending neuromodulation, specific local inhibition"

Friday, March 7, 2008 11:00 a.m.

AHSC Room 5403

Refreshments will be served

Also available on-line at:
http://www.physiology.arizona.edu/seminars

Hosted by Training Grant/Ann Revill, 626-6500, arevill@email.arizona.edu

---

The Edges of Life Lecture Series

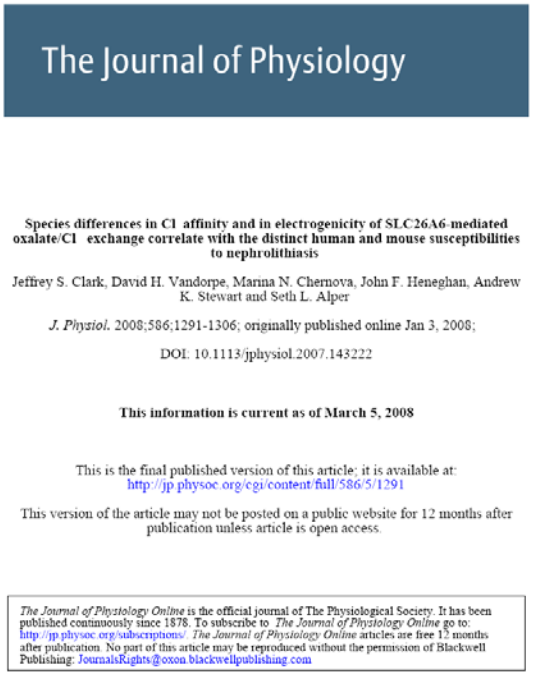
The Edges of Life – 7pm at Centennial Hall

Wednesday, March 5
Life's Technological Edge: The Singularity is Near: When Humans Transcend Biology
Ray Kurzweil, *via Teleportec Teleporter*
Founder, Chairman and Chief Executive Officer, Kurzweil Technologies

Humanity is on the edge of a vast transformation, when what it means to be human will be both enriched and challenged. Inventor and futurist Ray Kurzweil will introduce this radically optimistic singularity, an era when we break our genetic shackles to create a nonbiological intelligence trillions of times more powerful than today. In this new world, humans will transcend biological limitations to achieve entirely new levels of progress and longevity.

This lecture co-sponsored by: UA College of Engineering and UA College of Science

These do not count as physiology lectures.



The Journal of Physiology

Species differences in Cl affinity and in electrogenicity of SLC26A6-mediated oxalate/Cl exchange correlate with the distinct human and mouse susceptibilities to nephrolithiasis

Jeffrey S. Clark, David H. Vandorpe, Marina N. Chernova, John F. Heneghan, Andrew K. Stewart and Seth L. Alper

J. Physiol. 2008;586;1291-1306; originally published online Jan 3, 2008;

DOI: 10.1113/jphysiol.2007.143222

5

J Physiol 586.5 (2008) pp 1291–1306

Species differences in Cl$^-$ affinity and in electrogenicity of SLC26A6-mediated oxalate/Cl$^-$ exchange correlate with the distinct human and mouse susceptibilities to nephrolithiasis

Jeffrey S. Clark, David H. Vandorpe, Marina N. Chernova, John F. Heneghan, Andrew K. Stewart and Seth L. Alper

Molecular and Vascular Medicine Unit and Renal Division, Beth Israel Deaconess Medical Center and Department of Medicine, Harvard Medical School, Boston, MA 02215, USA

The mouse is refractory to lithogenic agents active in rats and humans, and so has been traditionally considered a poor experimental model for nephrolithiasis. However, recent studies have identified *slc26a6* as an oxalate nephrolithiasis gene in the mouse. Here we extend our earlier demonstration of different anion selectivities of the orthologous mouse and human SLC26A6 polypeptides to investigate the correlation between species-specific differences in SLC26A6 oxalate/anion exchange properties as expressed in *Xenopus* oocytes and in reported nephrolithiasis susceptibility. We find that human SLC26A6 mediates minimal rates of Cl$^-$ exchange for Cl$^-$, sulphate or formate, but rates of oxalate/Cl$^-$ exchange roughly equivalent to those of mouse slc2a6. Both transporters exhibit highly cooperative dependence of oxalate efflux rate on extracellular [Cl$^-$], but whereas the $K_{1/2}$ for extracellular [Cl$^-$] is only 8 mM for mouse slc26a6, that for human SLC26A6 is 62 mM. This latter value approximates the reported mean luminal [Cl$^-$] of postprandial human jejunal chyme, and reflects contributions from both transmembrane and C-terminal cytoplasmic domains of human SLC26A6. Human SLC26A6 variant V185M exhibits altered [Cl$^-$] dependence and reduced rates of oxalate/Cl$^-$ exchange. Whereas mouse slc26a6 mediates bidirectional electrogenic oxalate/Cl$^-$ exchange, human SLC26A6-mediated oxalate transport appears to be electroneutral. We hypothesize that the low extracellular Cl$^-$ affinity and apparent electroneutrality of oxalate efflux characterizing human SLC26A6 may partially explain the high human susceptibility to nephrolithiasis relative to that of mouse. SLC26A6 sequence variant(s) are candidate risk modifiers for nephrolithiasis.

(Received 15 August 2007; accepted after revision 19 December 2007; first published online 3 January 2008)

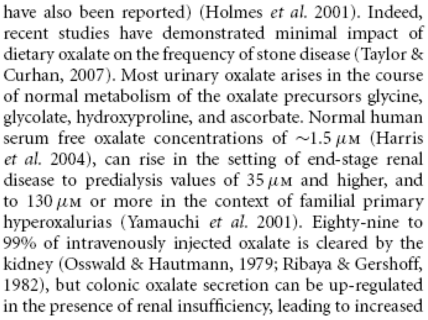
Corresponding author S. L. Alper: Molecular and Vascular Medicine Unit, Beth Israel Deaconess Medical Center E/RW763, 330 Brookline Avenue, Boston, MA 02215, USA. Email: salper@bidmc.harvard.edu

5% of females and 10–20% of males in the US population will experience at least one kidney stone over the course of a lifetime. 80% of these kidney stones contain calcium, and most are predominantly calcium oxalate (Coe *et al.* 2005; Taylor & Curhan, 2007). Elevation of urinary oxalate excretion is a major risk factor for nephrolithiasis. As urinary oxalate represents the sum of dietary intake and endogenous production, control of dietary oxalate intake has been recommended as part of standard treatment. However, absorbed dietary oxalate has been estimated as the source of only 5–20% of excreted urinary oxalate (although values of up to 42% have also been reported) (Holmes *et al.* 2001). Indeed, recent studies have demonstrated minimal impact of dietary oxalate on the frequency of stone disease (Taylor & Curhan, 2007). Most urinary oxalate arises in the course of normal metabolism of the oxalate precursors glycine, glycolate, hydroxyproline, and ascorbate. Normal human serum free oxalate concentrations of ~1.5 μM (Harris *et al.* 2004), can rise in the setting of end-stage renal disease to predialysis values of 35 μM and higher, and to 130 μM or more in the context of familial primary hyperoxalurias (Yamauchi *et al.* 2001). Eighty-nine to 99% of intravenously injected oxalate is cleared by the kidney (Osswald & Hautmann, 1979; Ribaya & Gershoff, 1982), but colonic oxalate secretion can be up-regulated in the presence of renal insufficiency, leading to increased

---

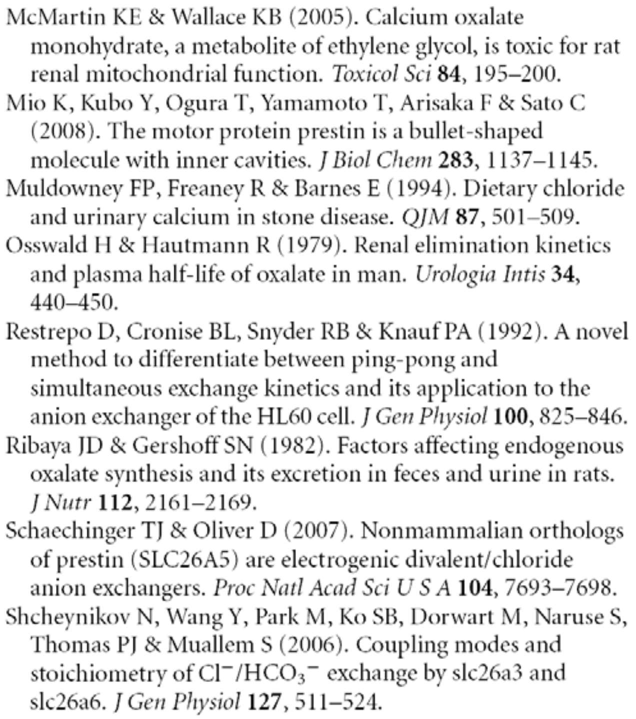
This paper has online supplemental material.

DOI: 10.1113/jphysiol.2007.143222



have also been reported) (Holmes *et al.* 2001). Indeed, recent studies have demonstrated minimal impact of dietary oxalate on the frequency of stone disease (Taylor & Curhan, 2007). Most urinary oxalate arises in the course of normal metabolism of the oxalate precursors glycine, glycolate, hydroxyproline, and ascorbate. Normal human serum free oxalate concentrations of ~1.5 μM (Harris *et al.* 2004), can rise in the setting of end-stage renal disease to predialysis values of 35 μM and higher, and to 130 μM or more in the context of familial primary hyperoxalurias (Yamauchi *et al.* 2001). Eighty-nine to 99% of intravenously injected oxalate is cleared by the kidney (Osswald & Hautmann, 1979; Ribaya & Gershoff, 1982), but colonic oxalate secretion can be up-regulated in the presence of renal insufficiency, leading to increased

6



McMartin KE & Wallace KB (2005). Calcium oxalate monohydrate, a metabolite of ethylene glycol, is toxic for rat renal mitochondrial function. *Toxicol Sci* **84**, 195–200.

Mio K, Kubo Y, Ogura T, Yamamoto T, Arisaka F & Sato C (2008). The motor protein prestin is a bullet-shaped molecule with inner cavities. *J Biol Chem* **283**, 1137–1145.

Muldowney FP, Freaney R & Barnes E (1994). Dietary chloride and urinary calcium in stone disease. *QJM* **87**, 501–509.

Osswald H & Hautmann R (1979). Renal elimination kinetics and plasma half-life of oxalate in man. *Urologia Intis* **34**, 440–450.

Restrepo D, Cronise BL, Snyder RB & Knauf PA (1992). A novel method to differentiate between ping-pong and simultaneous exchange kinetics and its application to the anion exchanger of the HL60 cell. *J Gen Physiol* **100**, 825–846.

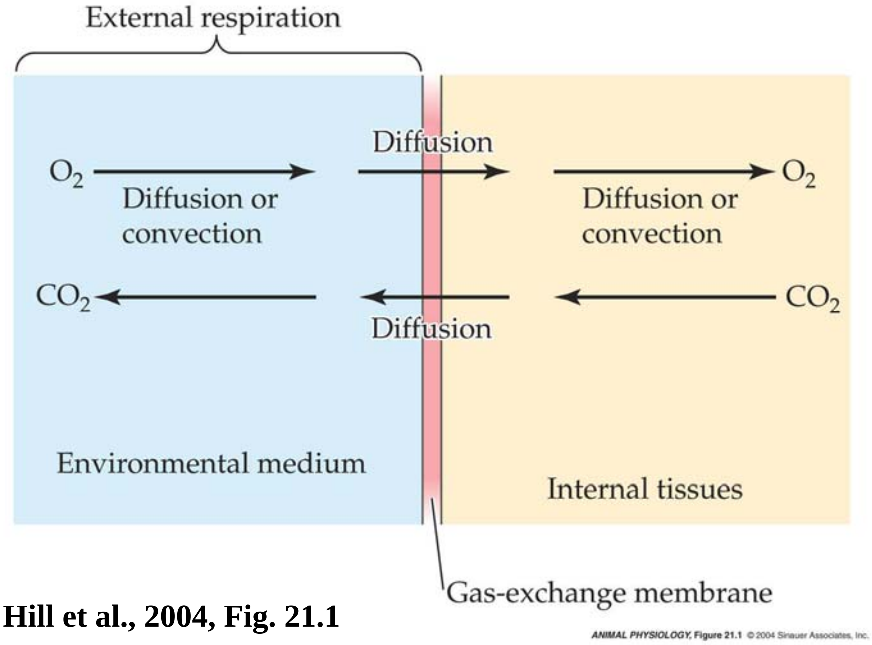
Ribaya JD & Gershoff SN (1982). Factors affecting endogenous oxalate synthesis and its excretion in feces and urine in rats. *J Nutr* **112**, 2161–2169.

Schaechinger TJ & Oliver D (2007). Nonmammalian orthologs of prestin (SLC26A5) are electrogenic divalent/chloride anion exchangers. *Proc Natl Acad Sci U S A* **104**, 7693–7698.

Shcheynikov N, Wang Y, Park M, Ko SB, Dorwart M, Naruse S, Thomas PJ & Muallem S (2006). Coupling modes and stoichiometry of Cl^-/HCO_3^- exchange by slc26a3 and slc26a6. *J Gen Physiol* **127**, 511–524.

Vertebrate
Respiration

Respiration… (Ch20-21, then 22&23)



Hill et al., 2004, Fig. 21.1

ANIMAL PHYSIOLOGY, Figure 21.1 © 2004 Sinauer Associates, Inc.

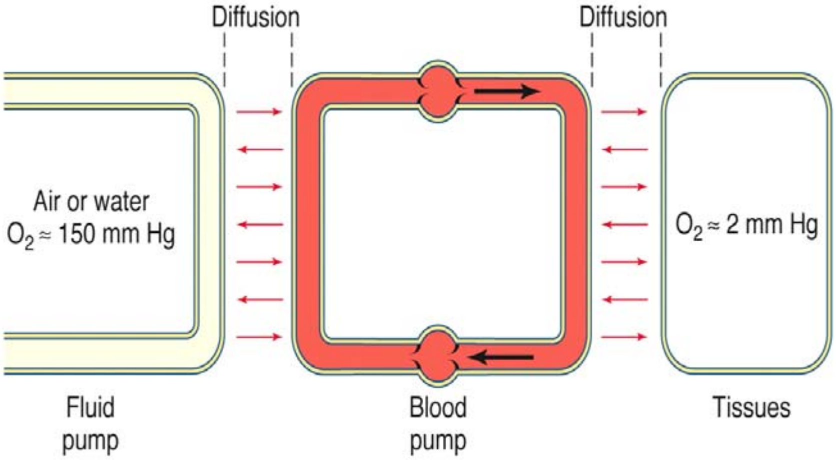
Gas transfer

1. **Breathing** **(supply air or water to respiratory surface)**

2. **Diffusion** **of O_2 & CO_2 across resp. epithelium**
(humans = 50-100^2 m SA)

3. **Bulk transport** **of gases by blood**

4. **Diffusion** **across capillary walls (blood → mitochondria)**

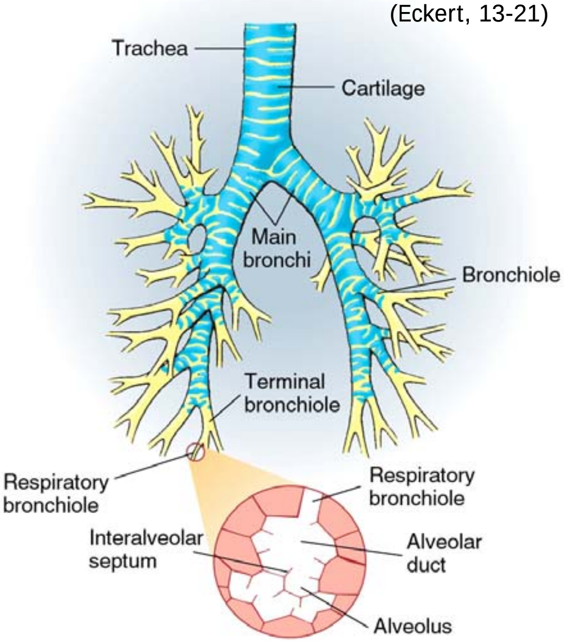


Lung Anatomy

<u>Nonrespiratory</u>
-Trachea ->
-Bronchi ->
-Bronchioles ->

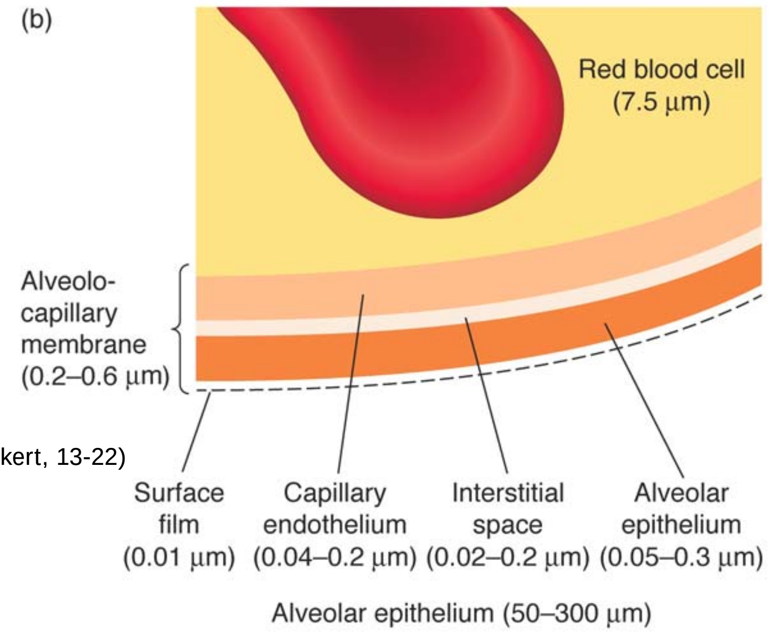
<u>Respiratory</u>
-Terminal bronchioles ->
-Respiratory bronchioles ->
-Alveoli

-Cilia and Mucus

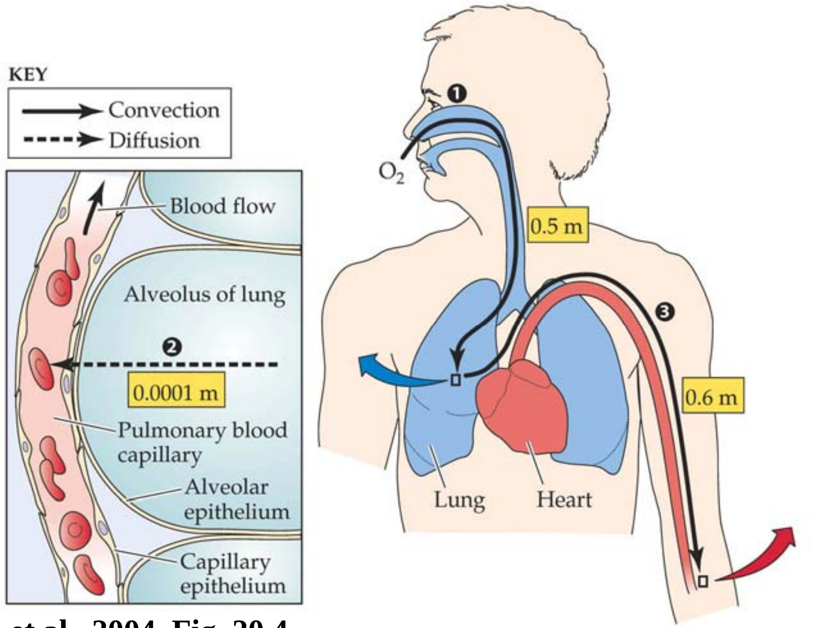


(Eckert, 13-21)

-Gas Diffusion Barriers:

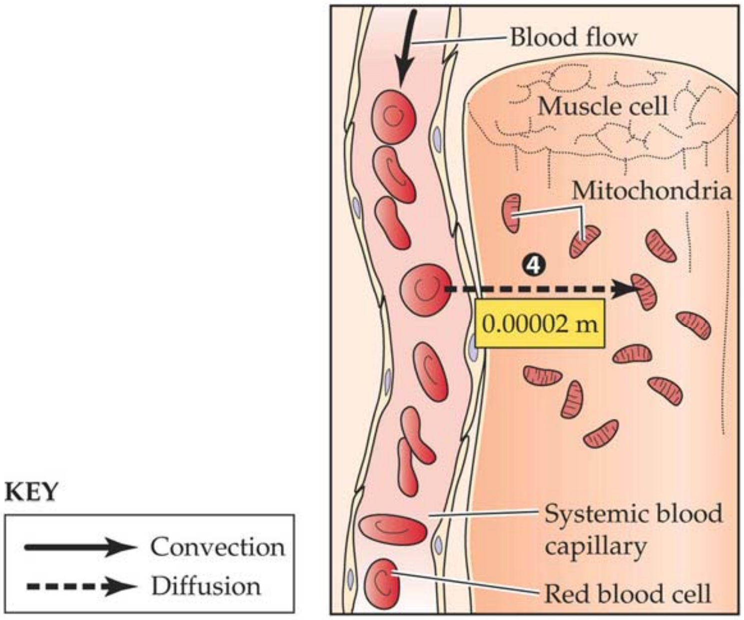


(Eckert, 13-22)



Hill et al., 2004, Fig. 20.4

ANIMAL PHYSIOLOGY, Figure 20.4 (Part 1) © 2004 Sinauer Associates, Inc.



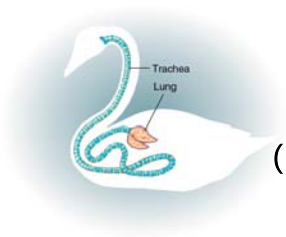
Hill et al., 2004, Fig. 20.4

ANIMAL PHYSIOLOGY, Figure 20.4 (Part 2) © 2004 Sinauer Associates, Inc.

Lung Ventilation

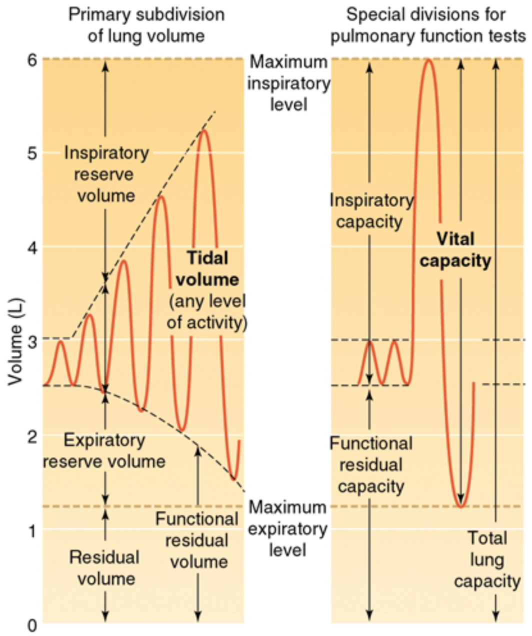
-Small mammals with greater per gram O_2 needs and therefore greater per gram respiratory surface area?

-Dead Space (anatomic and physiological)



Swan
(Eckert, 13-24)

Lung Ventilation



(Eckert, 13-23)

Mammalian Ventilation

-lungs are elastic bags

-suspended in pleural cavity within thoracic cage (ribs and diaphragm define, fluid lines)

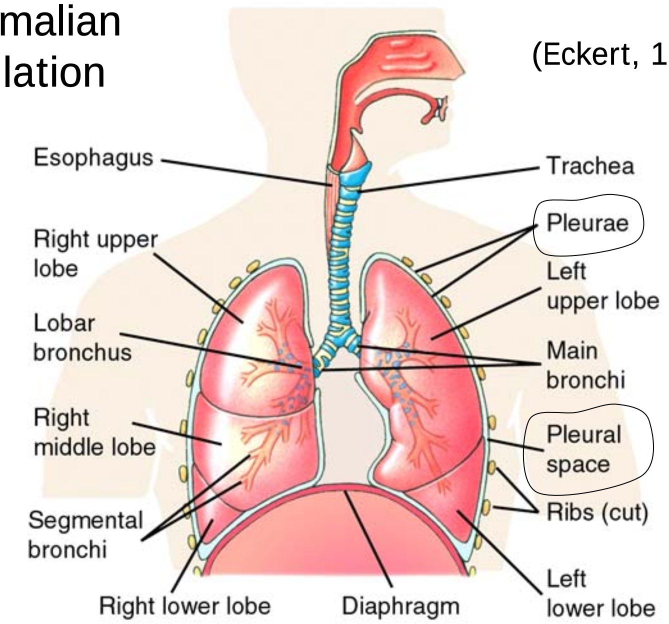
-low volume pleural “space” between lung and thoracic wall

-negative pressure to inflate lungs
(increase volume)

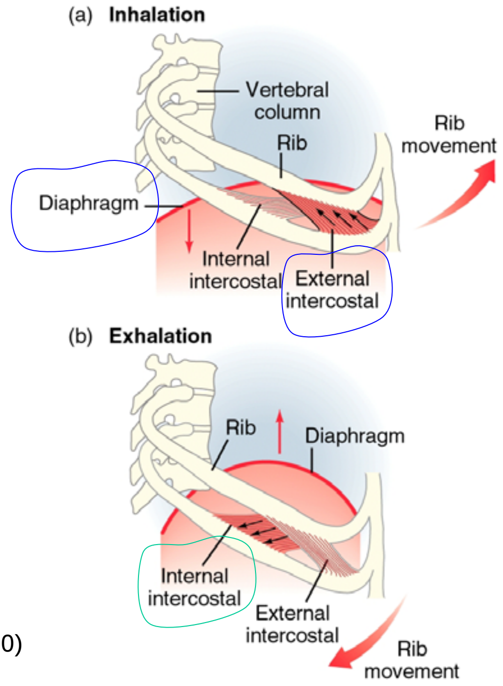
-pneumothorax

Mammalian Ventilation

(Eckert, 13-28)

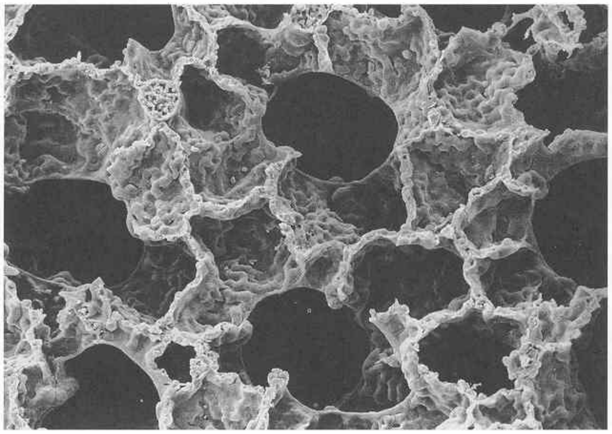


Mammalian Ventilation



-expiration usually passive

(Eckert, 13-30)



MAMMALIAN LUNG Scanning electron micrograph of the lung structure of a wildebeest (*Connochaetes taurinus*). The capillaries, filled with red blood cells, are visible as a bulging network in the alveolar walls. The distance across the photograph corresponds to about 0.5 mm in the lung. [Courtesy of Ewald Weibel, University of Berne, Switzerland]

Mammalian Lung

RED BLOOD CELL A human red blood cell caught in the meshwork of fibrin in a blood clot. The cell, whose diameter is about 8 μm, has the biconcave shape characteristic of

Alveoli and Capillaries

RBC (not to scale)

Knut Schmidt_Nielsen 1997

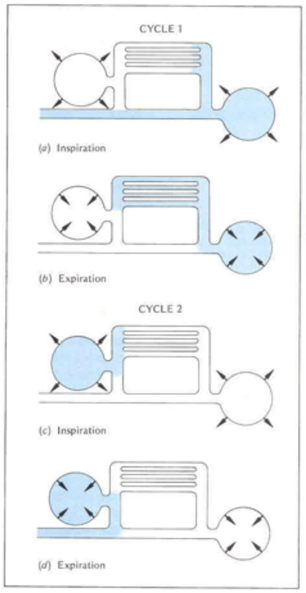


Figure 1.26 The movement of a single inhaled volume of gas through the avian respiratory system. It takes two full respiratory cycles to move the gas through its complete path. [Bretz and Schmidt-Nielsen 1972]

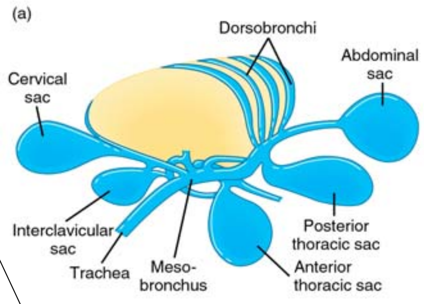
Bird Lung Ventilation

Unidirectional!!

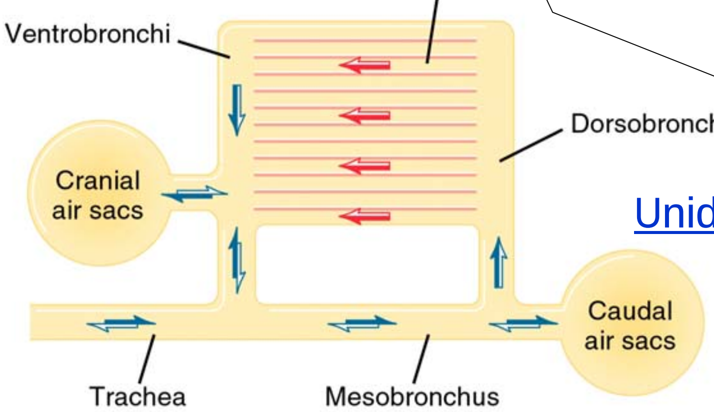
Knut Schmidt_Nielsen 1997

Bird Ventilation

-lung volume changes very little, air sacs instead



(Eckert,13-32)



(Eckert,13-32)

Unidirectional

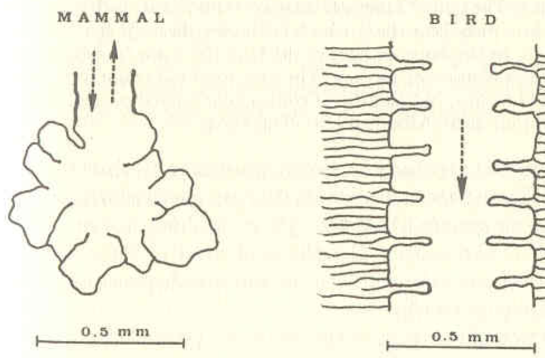


Figure 18. The smallest units of the lung of mammals end in blind sacs, alveoli. In birds the finest branches of the bronchi (the parabronchi) are tubes which are open at both ends and permit through-flow of air.

Knut Schmidt_Nielsen 1972

Mammal Lung
Alveoli

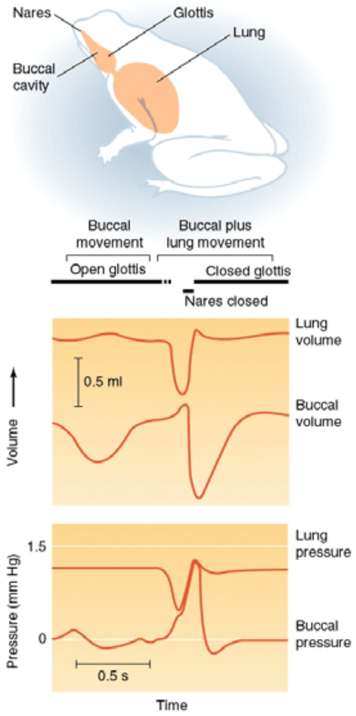
Bird Lung
Parabronchi

Frog Ventilation

-Positive pressure ventilation

1. Into mouth (buccal cavity)

2. Close nares, open glottis and force air into lungs by raising buccal floor



(Eckert, 13-33)

Pulmonary Surfactants

-Reduce liquid surface tension in alveoli

-Allows for compliance and low-cost expansion of lung

-Lipoproteins

-keep alveoli from getting stuck closed

Atelectasis = collapsed lung

-premature babies may need artificial surfactant

Panting Dogs?

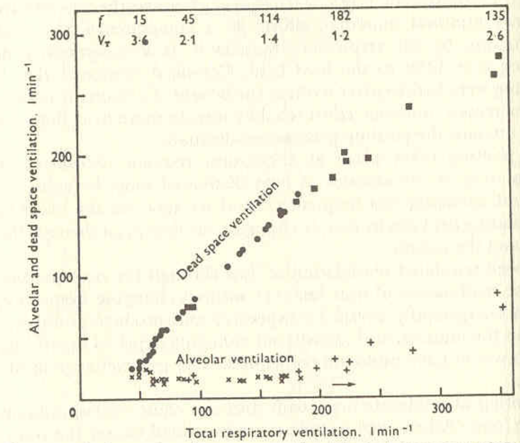
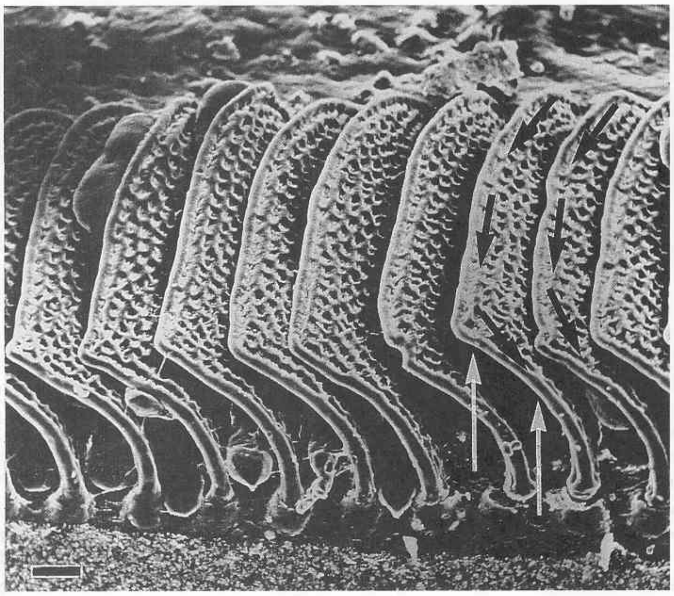


Figure 17. As the total respiratory ventilation (abscissa) increases in the panting ox, the dead space ventilation increases steadily. The alveolar ventilation, however, does not increase until the total ventilation exceeds about 200 liters per minute. In extreme panting the respiratory frequency (f) is decreased as tidal volume (V_T) is increased (figures at top of graph). (From Hales, 1966.)

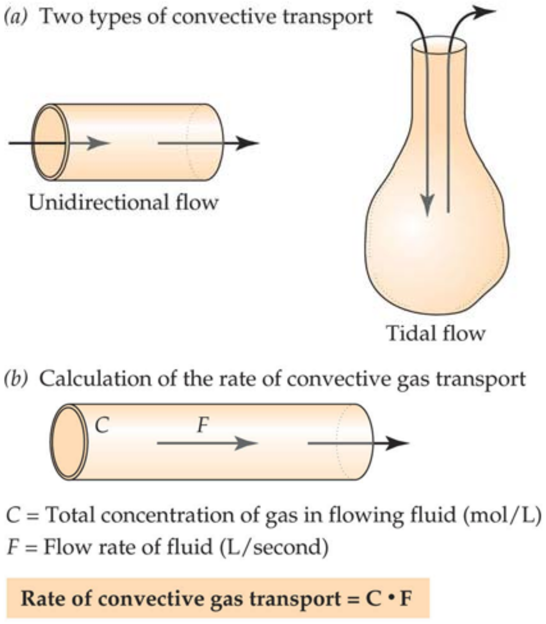
Knut Schmidt_Nielsen 1972



FISH GILL Scanning electron micrograph of gill filaments of a sturgeon (*Acipenser transmontanus*). White arrows show the direction of water flow and black arrows the direction of blood flow. The bar in the lower left corner represents 0.05 mm. [Burggren et al. 1979; courtesy of Warren W. Burggren, University of Massachusetts]

Fish Gill

Knut Schmidt_Nielsen 1997



Hill et al., 2004, Fig. 20.3

ANIMAL PHYSIOLOGY, Figure 20.3 © 2004 Sinauer Associates, Inc.