

Embryology and evolutionary history of the respiratory tract

Samantha White, Melinda Danowitz, Nikos Solounias

ABSTRACT

Human respiratory embryology and anatomy often reflects the evolutionary transformation from primitive breathing apparatuses. The gills of fishes are invested with vasculature, muscles, cartilages and nerves, and function in pumping water to facilitate gas exchange. As tetrapods evolve air-breathing respiratory structures, the gills lose their breathing function. However, the associated arteries, veins, nerves, musculature, and cartilaginous support become integrated into the pharynx and head. In the *Tiktaalik*, a popular proposed transitional species between fishes and tetrapods, both gills and lungs are present. Variations in the anatomy of the larynx allow for differing methods of sound production between birds, reptiles, and mammals, and the changing position of the larynx in humans represents feeding mechanisms in infants, and voice production in adults. Comprehension of the normal embryologic development also facilitates a deeper understanding of congenital anomalies. The respiratory tree originates as a diverticulum off of the proximal endodermal gut tube; failed septation between the lung buds and digestive

tract results in an anomalous respiratory/esophageal connection seen in tracheoesophageal fistulas. Combining key features of human lung embryology with comparative respiratory anatomy reinforces the relationship between structure and function, and will facilitate a deeper comprehension of lung development.

Keywords: Anatomy education, Embryology, Evolutionary biology, Gills, Lung, Respiratory

How to cite this article

White S, Danowitz M, Solounias N. Embryology and evolutionary history of the respiratory tract. *Edorium J Anat Embryo* 2016;3:54–62.

Article ID: 100016A04SW2016

doi:10.5348/A04-2016-16-RA-8

Samantha White¹, Melinda Danowitz¹, Nikos Solounias²
Affiliations: ¹Medical Student, Anatomy, New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY, USA; ²Professor, Anatomy, New York Institute of Technology College of Osteopathic Medicine, Old Westbury, NY, USA.

Corresponding Author: Melinda Danowitz 8000 Northern Boulevard Old Westbury NY, USA, 11568; E-mail: mdanowit@nyit.edu

Received: 28 May 2016
Accepted: 28 June 2016
Published: 21 July 2016

INTRODUCTION

The study of comparative anatomy and evolutionary biology puts context to human morphology and development. Unfortunately, these courses are seldom taught in United States pre-medical and medical school curricula [1]. Comparative anatomy reinforces key concepts such as relating form to function, therefore, putting morphology into an evolutionary context. Evolutionary biology relates to medical education both at a gross and molecular level. Resistance to antibiotics is a problem plagued by hospitals worldwide; bacteria gain this virulence through natural selection [2]. The gastrointestinal tract undergoes substantial elongation in terrestrial vertebrates, allowing for enhanced water

reabsorption, therefore, reflecting the evolutionary transition from aquatic to land environments [3]. Even at the epidemiologic level, evolutionary biology explains how the sickle-cell trait became so prevalent in African countries, as this gene mutation protects against malaria. A recent review of human head embryology demonstrated how evolutionary biology fosters a deeper student understanding of head and neck development [4]. Scientists and medical educators recognize the need for comparative and evolutionary biology to be incorporated into the training of future physicians [5, 6].

The evolution of a respiratory system accommodating life on land from the gills of aquatic organisms is an essential step allowing for the development of land mammals. Without a breathing apparatus that functions outside the water, terrestrial animal life would not exist. The incorporation of evolutionary biology allows for a broader and deeper understanding of respiratory tract development by emphasizing the relationship between structure and function. In this article, we review human lung embryology and provide links to the key evolutionary events in respiratory development, therefore, providing context to the morphology of the embryologic and adult structures.

PHARYNX

The pharynx is a complex structure that connects the oral cavity to the proximal respiratory and digestive systems. The pharynx develops from a unit system of arches, clefts, and pouches. The clefts are positioned externally, and the pouches internally, with the corresponding arch in between. Each arch derives from head mesenchyme, and includes an associated artery, branchiomeric cranial nerve, muscles, cartilages, and neural crest cells. There are five pharyngeal arches, each of which include a cranial nerve (Figure 1). The cranial nerves of the pharyngeal arches (CN V, VII, IX, and X) have mixed modalities, including motor and sensory roles. These nerves also have glandular secretory functions, as they innervate the associated endocrine structures derived from their respective pharyngeal pouch. All muscles derived from a pharyngeal arch are innervated by the respective cranial nerve; for example, the muscles of facial expression derive from the second pharyngeal arch, and are therefore innervated by CN VII. The arches and cleft-pouch units comprise the wall of the pharynx, and create the pharyngeal floor and mucosal surface of the tongue [7].

Evolutionary link: Gills

Methods of gas exchange differ, reflecting the changing respiratory structures to accommodate various environmental conditions. Small, primitive aquatic invertebrates exchange gases through their entire body

surface. Vertebrates evolve specialized respiratory organs, allowing for substantial body growth, which would otherwise be limited by an inefficient surface to volume ratio for gas diffusion. In fishes, gills are structures where oxygen dissolved in water can enter the body. Each gill arch is comprised of supporting cartilages and is highly vascularized, allowing for effective gas exchange. The gills also have associated muscles and nerves; the muscles contract in an accordion-like movement, facilitating water passage, and dissolved oxygen from the water is absorbed through the gill vasculature [8].

As lungs evolve, the importance of the gills decrease, and the pharynx consequently decreases in size. Sarcopterygians are bony fishes that possess bones and musculature in their paired fins that resemble the limbs of tetrapods. Lungs are found in sarcopterygians, likely as an adaptation for survival in arid environments. Lungs would have enabled these fishes to leave small inhabitable ponds, to find larger bodies of water. The sarcopterygians

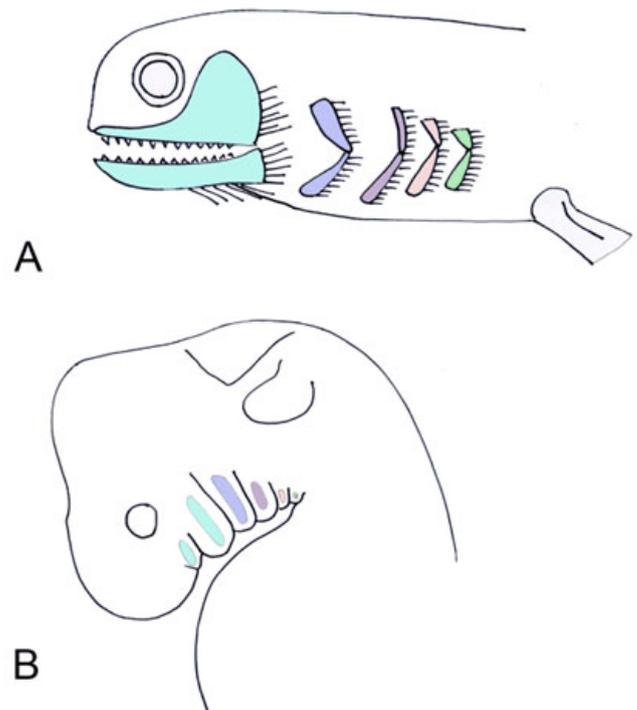


Figure 1: The pharyngeal arches in a fish and human embryo. (A) The pharyngeal arch derivatives in *Acanthodes*, an extinct spiny shark. In sharks and other fishes, the pharyngeal arches form gills, which are open externally, allowing for respiration in water. In certain species, the first arch is modified to form the jaw. (B) The pharyngeal arches around week 5 in a human embryo. Arch 1 subdivides to form the maxillary and mandibular processes, which are separated by the temporal-mandibular hinge joint. These arches are closed externally by the pharyngeal clefts, which, with the exception of cleft 1 that contributes to the formation of the tympanic membrane, are subsequently obliterated. Arch 1 is shown in turquoise, arch 2 is shown in blue, arch 3 is shown in purple, arch 4 is shown in peach, and arch 6 is shown in green.

evolved during the Devonian period (400 million years ago) during frequent seasons of drought, therefore, their survival required the presence of air breathing respiratory structures. Amphibians are transitional in respiratory evolution; the larva that develops underwater possesses external gills, whereas the adult possesses simple lung forms, allowing for air breathing on land [9].

The *Tiktaalik* is likely the species representing the transition from fish to amphibians, as it shares anatomical features seen in primitive fish as well as early tetrapods. *Tiktaalik* possesses both gills and lungs (Figure 2). Many modern fishes utilize gills for respiration, and possess a swim bladder for buoyancy in changing water depths. The majority of tetrapods, however, lose their functioning gills, and utilize the lungs for air breathing. The original gill structures become incorporated into the head and neck of land dwellers as pharyngeal arches with associated muscles, nerves, and vasculature, but lose their respiratory function. The lungs of *Tiktaalik* likely allowed the animal to spend periods of time out of the water, or in water with poor oxygen content. This animal also possesses a full set of ribs, assisting with air breathing, and providing support to its body. Typical fishes possess

dorsal and ventral sets of ribs with a different orientation of intercostal muscles from tetrapods; fishes do not rely on ribs for breathing, but rather respire with water flowing through their gills [10].

LARYNX, TRACHEA, AND BRONCHI

The complex respiratory tree originates as an outpouching, termed the respiratory diverticulum, or lung buds. This forms as a diverticulum at the proximal end of the endodermal foregut (future esophagus). The inner surface lining of the larynx therefore is endodermal. The 4th and 6th pharyngeal arches form the laryngeal cartilaginous support, including the thyroid, cricoid, and arytenoid cartilages. The musculature of the pharynx and larynx also derives from the 4th and 6th arches, and are, therefore, innervated by branches of the vagus nerve (CN X). The proximal stem of the respiratory diverticulum forms the trachea and larynx, whereas the distal portion forms the bronchi, bronchioles, and eventually, alveoli [11].

Evolutionary link

Studies have shown that the ability of a mammal to breathe, swallow, and produce sound is due to the specific positioning of the larynx. In most mammals, as well as human infants, the larynx is initially positioned high in the neck, allowing for the formation of a seal between the laryngeal epiglottis and the soft palate during feeding (Figure 3). This seal allows the infant to suckle and feed while still continuously breathing through the nasal cavity, as the proximal digestive and respiratory tracts are temporarily separated. Unlike other mammals, adult humans change the position of the larynx; the larynx is repositioned lower in the neck, and the seal between the epiglottis and soft palate is no longer possible. This descent of the larynx creates a larger supralaryngeal space in the pharynx, that likely allows for sound production and speech [12].

The larynx is an enlarged cartilaginous vestibule that is found in land tetrapods. Although many tetrapods are voiceless, the larynx is often used for sound production. Frogs produce sounds using tracheal ridges. Lizards and snakes produce hissing noises by pushing air violently through the glottis. Most mammals produce voice through a pair of laryngeal vocal cords, which are ridges of elastic tissue and ligaments that are stretched across the larynx. Birds possess a larynx but lack vocal cords; their voice production takes place through the syrinx. The syrinx is a specialized structure positioned further down the trachea than the larynx, and is positioned at the division into the two major bronchi [8].

With the exception of the sarcopterygii lungfish that possess lungs extending directly from the pharynx, many lung bearing species have a midline passageway as the

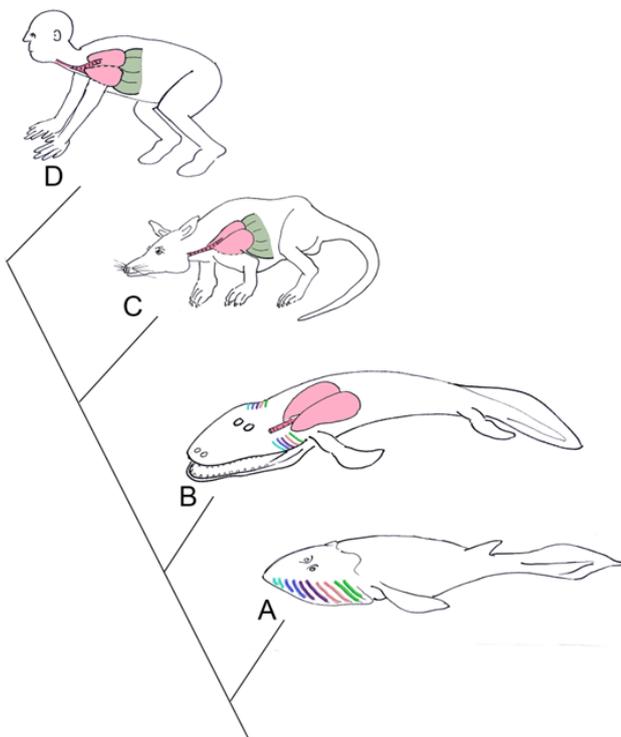


Figure 2: General evolution of respiratory structures. (A) *Cephalaspis*, a representative jawless fish that utilized gills for respiration. The mouth of this species was a circular opening without internal jaws. (B) *Tiktaalik*, a lobe finned fish that as been popularly referred to as the “missing link” between fishes and tetrapods. This fish likely had both gills and primitive lungs. (C) An early mammal, which utilized lungs and a diaphragm for respiration. (D) Human, which, like the early mammal, exhibits a complex respiratory system comprised of the trachea, lungs, and a diaphragm.

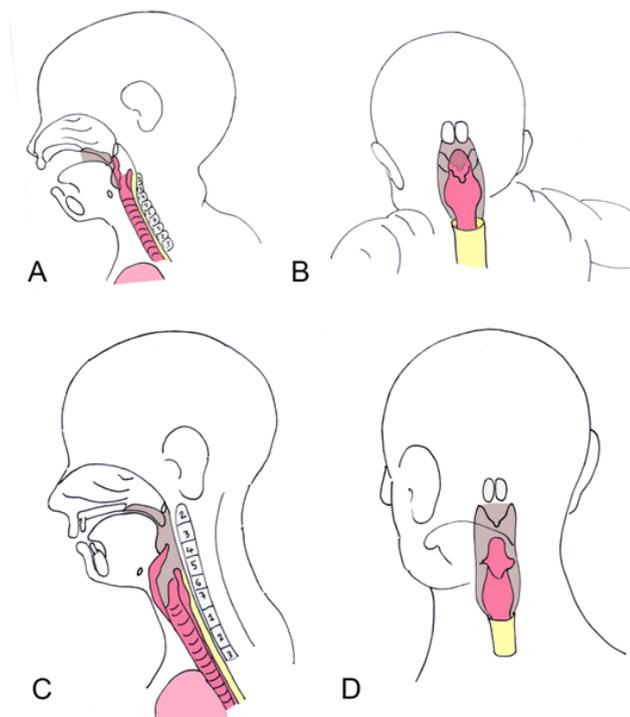


Figure 3: The position of the larynx in a human infant and adult. (A) Infant larynx/pharynx in lateral view. The larynx is positioned higher in the neck, so that the soft palate and epiglottis can form a seal during feeding, allowing the infant to feed and breathe simultaneously, (B) Infant larynx/pharynx in posterior view, (C) Adult larynx/pharynx in lateral view. The larynx descends further down the neck, thus creating a supralaryngeal region of the pharynx that allows for sound and voice production, (D) Adult larynx/pharynx in posterior view. Pharyngeal structures are shown in brown, respiratory structures including the larynx are shown in pink, and the proximal gut tube is shown in yellow.

trachea. The trachea in tetrapods extends from the larynx to the bifurcating primary bronchi. The trachea is lined with ciliated epithelium, mucous and glandular cells, and is strengthened by the surrounding cartilaginous rings [3].

Development and Maturation of the Lungs

The lung develops as a composite of endodermal and mesodermal tissues, and matures in 5 broad stages (Table 1). The endoderm of the respiratory diverticulum gives rise to the mucosal lining of the respiratory tree and to the endothelial cells of the alveoli. The supporting musculature and cartilages that surround the bronchi, as well as the visceral pleura that covers the lungs derive from splanchnopleuric (lateral plate) mesoderm. Around the end of the 4th week, the laryngotracheal diverticulum forms two lateral outpouchings, termed the lung buds. These lung buds branch into the bronchi and bronchial tree during the pseudoglandular and canalicular stages of development [13].

The primary bronchial buds undergo approximately 16 rounds of branching, therefore forming the respiratory tree (Figure 4). The branching lung endoderm becomes invested in the surrounding mesenchyme, and cellular interactions between the endoderm and mesoderm regulate the branching. The first round of branching of the primary bronchial buds around week 5 yields three secondary bronchial buds on the right and two on the left; these secondary buds give rise to the lung lobes. This round of branching forms the three lobes of the right lung and two lobes of the left lung. The secondary bronchial buds undergo an additional 14-16 rounds of

Table 1: Stages of lung development

Stage of development	Time	Morphological event
Embryonic	26 days–6 weeks	Respiratory diverticulum derives from the ventral foregut. This undergoes three generations of branching, forming the trachea, larynx, primary bronchi, and lung lobes.
Pseudoglandular	6 weeks–16 weeks	14 generations of branching occur, and form the respiratory tree through the terminal bronchioles. The term pseudoglandular derives from the fact that the earliest lung buds resemble the glandular structure seen in many endocrine organs.
Canalicular	16 weeks–28 weeks	The terminal bronchioli further divide into respiratory bronchioles. During this stage, the respiratory vasculature surrounds the developing lung, and the specialized cell types of the lungs form, including the ciliated, secretory, and type I and II alveolar cells.
Saccular	28 weeks–6 weeks	The terminal sacs, or primitive alveoli are formed.
Alveolar	36 weeks–birth	Maturation of the alveoli.

branching, and form the respiratory tree through the terminal bronchioles by the end of the canalicular stage. During the sacular stage, the bronchioles divide into the respiratory bronchioles and eventually into the terminal sacs (also termed primitive alveoli). Around week 36, the terminal sacs become invested in surrounding capillaries, allowing for future gas exchange from the respiratory to the vascular system. The alveoli continue to mature even into childhood [14].

The type II alveolar cells produce a liquid substance termed surfactant, which lines the inner surface of the alveolar endothelium. The surfactant increases the surface tension and prevents the alveolar sacs from collapsing. The developmental maturity of the lungs is a key determinant of survival in premature infants, as the lungs lack sufficient surfactant before 30 weeks, and therefore the alveoli are easily collapsible during expiration, preventing effective respiration in the newborn. During development, the fetus constantly swallows amniotic fluid produced by the kidneys. This fluid bathes the maturing lungs, and is crucial for its final maturation and expansion of alveoli [11].

There is a dual system of circulation in the lung. The lung tissue itself is supplied by the bronchial arteries, which branch off the descending aorta. The respiratory function of the lungs is supported by the pulmonary artery and branches; deoxygenated blood is transported directly to the lungs, where the blood becomes oxygenated via gas diffusion at the alveoli. The newly oxygenated blood is

returned to the heart via the pulmonary vein, where it is subsequently pumped to the entirety of the body [7].

Evolutionary link: swim bladder and air sacs

The swim bladder is a distinctive feature seen in most actinopterygian fishes. This structure is an elongated, distensible sac that originates from the anterior aspect of the gut tube. The swim bladder is a key hydrostatic organ for deep-water organisms. As the swim bladder fills with gas and therefore changes in volume, the specific gravity of the fish changes, allowing the fish to maintain a given depth in the water. The swim bladder is surrounded by elastic connective tissue fibers, and has muscles that allow for contraction and expansion [15].

Birds evolve air sacs, in addition to the typical lungs, that maximize gas exchange by modifying lung ventilation. These air sacs are located in the neck, thorax, and abdomen, and are continuous with the main respiratory tract and lungs (Figure 5). They are not highly vascularized as are the lungs, and they do not directly participate in oxygen exchange during respiration. They function as bellows that create a unidirectional flow of air, which, unlike the bidirectional mammalian system, allows for more efficient oxygen diffusion into the blood. This optimization of respiration allows birds to respire at higher elevations, and also plays a key role in thermoregulation [16].

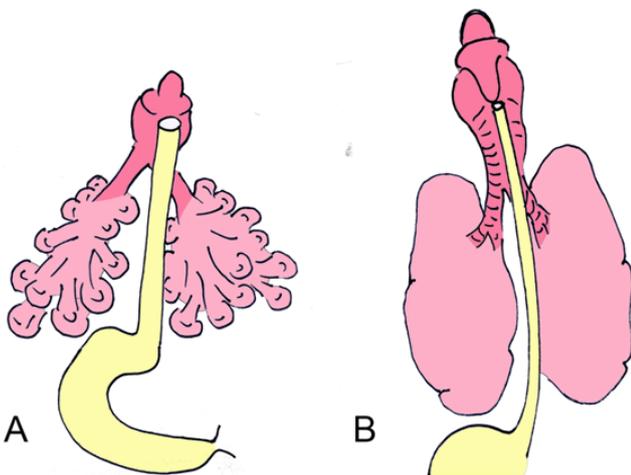


Figure 4: Development of the lungs. (A) Branching of the lung buds to form tertiary bronchial buds, around 7th week, during the pseudoglandular phase. (B) Lungs during the alveolar phase. The alveoli are formed and surrounded by dense vascular networks (not shown), and they mature from week 36 until delivery. Respiratory structures are shown in pink, and gut endoderm is shown in yellow.



Figure 5: The air sacs of a bird. The bird respiratory tract lacks a diaphragm, and instead incorporates a series of 7-9 air sacs that branch from the main respiratory tree. These air sacs function as bellows, and create a unidirectional airflow that maximizes oxygen diffusion into the blood, allowing birds to breathe at higher elevations.

DIAPHRAGM

The diaphragm originates from several embryonic structures; the septum transversum, pleuroperitoneal membranes, and body wall mesoderm. The fibrous septum transversum is originally positioned near the upper cervical somites, and therefore its innervation by the phrenic nerve (C3-C5) reflects this early positioning. The septum transversum creates the non-muscular central tendon of the diaphragm, and is the first partition between the thoracic and abdominal cavities. The bulk of the diaphragm muscle is positioned within the pleuroperitoneal membranes, and is innervated by the phrenic nerve. The peripheral rim of diaphragmatic musculature derives from body wall mesoderm, and is supplied by spinal nerves T7-T12. The crura of the diaphragm originate on the upper lumbar vertebral bodies and condense into right and left muscular bands inserting into the dorsomedial diaphragm [14].

Evolutionary link

In reptiles, breathing occurs via aspiration, and the inspiratory and expiratory motions are accomplished primarily by intercostal muscles. Reptilians lack a true partition between the pleural and peritoneal cavities, and the lungs are uniquely positioned dorsal to the heart. In many vertebrates, the diaphragm presents as a membranous partition between the thoracic and abdominal cavities. In crocodylians, the membranous separation between the abdomen and thorax is present, and they also possess a diaphragmaticus muscle that plays a role in respiration. The respiratory musculature of crocodiles functions both in assisting respiration, as in mammals, but can also change the positioning of the lungs, therefore controlling buoyancy in aquatic environments. When these muscles contract and the lungs move caudally, the animal sinks in the water, whereas when the lungs are moved cranially, the animal is able to float. In mammals, the diaphragm is invested with bulks of skeletal muscle, and therefore plays a pivotal role in mammalian respiration. Breathing in mammals is accomplished by contractions of the diaphragm as well as movements of a rib cage that circumferentially encloses the pleural cavities [15].

Congenital Abnormalities

Choanal atresia

A congenital blockage of the posterior nasal opening, due to bony abnormalities or an anomalous presence of an oronasal membrane preventing communication between the nose and pharynx. Infants classically present with cyanosis during feeding that improves during crying.

Choanal atresia is a component of a group of congenital anomalies termed CHARGE, which includes coloboma of the eye, heart defects, atresia of the choanae, retarded growth, genitourinary abnormalities, and ear defects [17].

Laryngeal webs

An incomplete separation of the vocal folds due to a retained epithelial layer extending within the lumen of the larynx. This membranous layer normally obliterates around week 10 of development. This can occur anywhere within the larynx, and is most often located at the anterior portion of the lumen adjacent to the vocal cords. This can present clinically as respiratory distress, stridor, or hoarseness, depending on the extent of airway obstruction [18].

Laryngomalacia

An abnormality of the laryngeal cartilage leading to collapse of the larynx above the glottis during inspiration. Although the etiology is unknown, this is likely due to delayed maturation of the cartilaginous support of the larynx. This presents with inspiratory stridor, which often resolves spontaneously by age 2 [19].

Vascular ring

An anomalous positioning of the aortic arch with vessels surrounding the esophagus and trachea. Tracheal compression can present as stridor, respiratory distress, and a persistent cough, and esophageal compression can lead to dysphagia and vomiting [20].

Tracheoesophageal fistula

Failure of the tracheoesophageal septum to fully separate the proximal foregut from the respiratory diverticulum. Several variations exist. The most common variant presents with the upper esophagus ending in a blind pouch (esophageal atresia), and the lower esophagus arising from the trachea. Other variations include: upper portion of the esophagus terminating in the trachea, an anomalous fistula between the esophagus and trachea without esophageal atresia, or esophageal atresia with the esophagus ending in a blind pouch but no fistula with the trachea. Since the esophagus does not connect distally with the remainder of the gastrointestinal tract, fetal swallowing of amniotic fluid is prevented, resulting in polyhydramnios. There is a greatly increased risk of aspiration after birth, and neonates commonly present with cyanosis with feeding. This is a component of the “VACTERL” association, which includes vertebral anomalies, anal atresia, cardiovascular anomalies, tracheoesophageal fistula, esophageal atresia, renal anomalies, and limb defects [21].

Kartagener syndrome (primary ciliary dyskinesia)

An autosomal recessive disorder resulting in dysfunctional ciliary function. The immotile cilia lead to chronic sinus and pulmonary disease, as cilia are necessary for mucus and bacterial clearance from the respiratory tract. During development, the dysfunctional cilia do not undergo normal rotation and thus disrupt the flow of extracellular fluid and proteins; this impairs the lateral orientation of organ development and leads to situs inversus. The flagella in male sperm are also affected, leading to infertility; fertility in females is also reduced due to impaired ciliary motion in the fallopian tubes. Other features include recurrent otitis media, hydrocephalus, and bronchiectasis [22].

Respiratory distress syndrome

A pulmonary disease commonly seen in premature infants (< 30 weeks gestation) due to insufficient surfactant production. Without adequate surfactant, the surface tension of the inner lining of alveoli is high and the alveolar sacs easily collapse during exhalation, thus reducing the surface area for respiration at birth. This ultimately leads to the development of hyaline membranes, which fill the alveolar air spaces and prevent proper gas exchange. Infantile respiratory distress syndrome can be prevented with the administration of glucocorticoids to the mother before premature delivery, as these steroids speed the production of fetal surfactant [23].

Congenital diaphragmatic hernia

Defective closure of the pleuroperitoneal folds around weeks 7–10 of development, allowing for herniation of abdominal contents into the thoracic cavity. The most common location is posterolateral (“Bochdalek hernia”), and more rarely anteriorly (“Morgagni hernia”). Herniation is most commonly left sided, as the pleuroperitoneal folds close earlier on the right, and also the large size of the developing liver likely prevents significant herniation on the right. Gut herniation into the thoracic cavity prevents the growth and differentiation of the ipsilateral or sometimes bilateral lungs, leading to pulmonary hypoplasia [24].

Pulmonary hypoplasia and oligohydramnios

Impaired pulmonary maturation due to insufficient amniotic fluid. Amniotic fluid contains several growth factors that stimulate lung differentiation and growth, and allows for proper branching of the respiratory tree. Without sufficient amniotic fluid bathing the developing lungs, the pulmonary system does not grow and mature, leading to hypoplastic lungs. This can be due to renal malformations such as bilateral renal agenesis, impairing amniotic fluid production, or due to distal blockages in

the urinary tract, preventing amniotic fluid excretion. Oligohydramnios also leads to Potter sequence, resulting in dysmorphic fetal facial and limb features due to a lack of cushioning against the uterus [25].

CONCLUSION

An understanding of the general evolutionary patterns of the respiratory tree puts lung anatomy into perspective, and reinforces the relationship of anatomical structure to its function. Comparative anatomy is a key subject for training physicians, which is often lacking in the medical curriculum, and it intimately relates to human embryologic development and adult anatomy. A deeper understanding of the embryologic processes also facilitates comprehension of congenital pathologies, as these anomalies reflect errors in development. We believe focused yet comprehensive reviews of human embryology supplemented with evolutionary biology and congenital abnormalities will broaden the medical student knowledge of development.

Acknowledgements

We thank the Department of Anatomy at New York Institute of Technology College of Osteopathic Medicine. We also thank Wolfgang Gilliar and Jerry Balentine for their continued support and assistance.

Author Contributions

Samantha White – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Melinda Danowitz – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Nikos Solounias – Substantial contributions to conception and design, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

Copyright

© 2016 Samantha White et al. This article is distributed under the terms of Creative Commons Attribution License which permits unrestricted use, distribution and reproduction in any medium provided the original

author(s) and original publisher are properly credited. Please see the copyright policy on the journal website for more information.

REFERENCES

1. Miller SA, Perrotti W, Silverthorn DU, Dalley AF, Rarey KE. From college to clinic: reasoning over memorization is key for understanding anatomy. *Anat Rec* 2002 Apr 15;269(2):69–80.
2. MacCallum CJ. Does medicine without evolution make sense? *PLoS Biol* 2007 Apr;5(4):e112.
3. Wake MH. Hyman's Comparative Vertebrate Anatomy, 3ed. Chicago: The University of Chicago Press; 1979. p. 1–768.
4. Danowitz M, Zheng H, Guigova A, Solounias N. A combined approach of teaching head development using embryology and comparative anatomy. *J Anat Embryo* 2016;3:17–27.
5. Nesse RM, Schiffman JD. Evolutionary Biology in the Medical School Curriculum. *BioScience* 2003;53:585–7.
6. Downie JR. Evolution in Health and Disease: The Role of Evolutionary Biology in the Medical Curriculum. *Bioscience Educ* 2004;4:1–18.
7. Standring S. Gray's anatomy: The anatomical basis of clinical practice, 41ed. Philadelphia: Churchill Livingstone; 2015. p. 1–15843.
8. Romer AS, Parsons TS. The Vertebrate Body, 5ed. Philadelphia: W.B. Saunders Company; 1986. p. 1–624.
9. Feduccia A, McCrady E. Torrey's Morphogenesis of the Vertebrates, 5ed. New York: John Wiley & Sons; 1991. p. 1–528.
10. Daeschler EB, Shubin NH, Jenkins FA Jr. A Devonian tetrapod-like fish and the evolution of the tetrapod body plan. *Nature* 2006 Apr 6;440(7085):757–63.
11. Sadler TW. Langman's Medical Embryology, 13ed. Philadelphia: Lippincott Williams & Wilkins; 2014. p. 1–400.
12. Laitman JT, Reidenberg JS. Specializations of the human upper respiratory and upper digestive systems as seen through comparative and developmental anatomy. *Dysphagia* 1993 Fall;8(4):318–25.
13. Hamilton WJ, Mossman HW. Human embryology, 4ed. Baltimore: The Williams and Wilkins Company; 1972. p. 1–646.
14. Schoenwolf GC, Bleyl SB, Brauer PR, Francis-West PH. Larsen's human embryology, 4ed. Philadelphia: Churchill Livingstone; 2009. p. 1–687.
15. Young JZ. The life of vertebrates, 3ed. Oxford: Clarendon Press; 1981. p. 1–645.
16. O'Connor PM, Claessens LP. Basic avian pulmonary design and flow-through ventilation in non-avian theropod dinosaurs. *Nature* 2005 Jul 14;436(7048):253–6.
17. Myer CM 3rd, Cotton RT. Nasal obstruction in the pediatric patient. *Pediatrics* 1983 Dec;72(6):766–77.
18. Milczuk HA, Smith JD, Everts EC. Congenital laryngeal webs: surgical management and clinical embryology. *Int J Pediatr Otorhinolaryngol* 2000 Jan

- 30;52(1):1–9.
19. Belmont JR, Grundfast K. Congenital laryngeal stridor (laryngomalacia): etiologic factors and associated disorders. *Ann Otol Rhinol Laryngol* 1984 Sep-Oct;93(5 Pt 1):430–7.
20. Backer CL, Mavroudis C, Rigsby CK, Holinger LD. Trends in vascular ring surgery. *J Thorac Cardiovasc Surg* 2005 Jun;129(6):1339–47.
21. Kovesi T, Rubin S. Long-term complications of congenital esophageal atresia and/or tracheoesophageal fistula. *Chest* 2004 Sep;126(3):915–25.
22. Ferkol TW, Leigh MW. Ciliopathies: the central role of cilia in a spectrum of pediatric disorders. *J Pediatr* 2012 Mar;160(3):366–71.
23. Clark RH, Gerstmann DR, Jobe AH, Moffitt ST, Slutsky AS, Yoder BA. Lung injury in neonates: causes, strategies for prevention, and long-term consequences. *J Pediatr* 2001 Oct;139(4):478–86.
24. Bohn D. Congenital diaphragmatic hernia. *Am J Respir Crit Care Med* 2002 Oct 1;166(7):911–5.
25. Thomas IT, Smith DW. Oligohydramnios, cause of the nonrenal features of Potter's syndrome, including pulmonary hypoplasia *J Pediatr* 1974 Jun;84(6):811–5.

Suggested Reading

- Moore KL. The Developing Human: Clinically Oriented Embryology, 9ed. Philadelphia: W.B. Saunders Company; 2012. p. 1–560.
- Kardong KV. Vertebrates: comparative anatomy, function, evolution, 7ed. Boston: McGraw-Hill; 2014. p. 1–816.
- Cochard LR. Netter's atlas of human embryology, updated ed. Philadelphia: Saunders; 2012. p. 1–288.

Access full text article on
other devices



Access PDF of article on
other devices

