ESSENTIAL PULMONOLOGY

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Motto:

*Breath is the bridge which connects life
to consciousness, which unites your body to your thoughts.
Whenever your mind becomes scattered, use your breath
as the means to take hold of your mind again.*

Thich Nhat Hanh
(Vietnamese Zen Buddhist monk,
writer and peace activist)

*Dedicated to my co-workers
and our successors*

PREFACE

Dear colleagues, dear foreign students,

with pleasure, we introduce this new textbook of pulmonary medicine to you. As you should know, pulmonology is one of the oldest members of the many specialties of internal medicine. It is remarkable due to its complexity and its social and medical importance as well as of its history and the dynamics of its evolution.

Pulmonology has grown from the roots of historical medical specialty of "phtisiology" which has been devoted to diagnostics and therapy of one of most widespread and pernicious disease affecting the human race – tuberculosis. Let me remind some of the founders of phtisiology and pneumonology which are respected worldwide: Sir John Crofton, Karel Stýblo, Ladislav Šula, Severin Daum, Cyril Šimeček, and, recently, Peter Barnes or Sally E. Wenzel.

Pulmonologists use many special diagnostic and therapeutic methods and take care about wide spectrum of patients sufferring from diseases of lungs, bronchi, pleura and of some mediastinal lesions on several levels of health care system. Contemporary pulmonology is rapidly developing in many directions, gradually evolving into separate subspecialties – therapy of inflammatory diseases, COPD, asthma, interstitial lung diseases or sleep respiratory disorders. There are departments of acute pulmonology and specialized intensive care units, highly specialized centers of cystic fibrosis, brittle asthma, idiopathic pulmonary fibrosis, and pneumooncology centres providing care for patients with pulmonary and thoracic malignities. Inevitably, this includes the area of functional examinations and bronchology, which has become one of the very foundations of the field. Even the lung transplantation gradually shifted from clinical experiments to a nearly routine medical procedure.

I believe that you will find our textbook of pulmonology interesting and useful for your future medical career.

Miloš Pešek

Left to right: assoc. prof. Milan Teřl, M.D., Ph.D., prof. Miloš Pešek, M.D., Ph.D., Olga Kirchnerová, M.D., Ph.D., Gabriela Krákorová, M.D., Ph. D., and David Havel, M.D., Ph.D.

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I.

BASIC AND GENERAL PART

1 DEVELOPMENT, STRUCTURE AND FUNCTION OF THE RESPIRATORY SYSTEM

Jaroslav Slípka†, Pavel Fiala†, František Vožeh, Milan Teřl

1.1 DEVELOPMENT OF THE RESPIRATORY SYSTEM

From the phylogenetic and ontogenetic point of view, the entire respiratory system is a derivative of the digestive system, thus it is of endodermal origin. In evolution, its mother's area was a cranial, side-perforated, short area of the pharynx that appeared to serve as a mechanical sieve to capture food particles from the incoming water in the first chordates. These small animals (of the type of today's lancelet) with a thin skin covering originally breathed through the entire body surface. Only later, in the course of the tribal development and with the enlargement of the body, the skin respiration was not enough and thus the area of the pharynx gained, in addition to its nutritional function, also a respiratory function.

1.1.1 Phylogenesis of the Respiratory System

Gills (branchiae) were formed from the mechanical sieve, trapping food. The entire gill area, that is, branchial region, specialized in gas exchange already in the first vertebrates, i.e., fish and amphibian larvae. The gills are preferably located in an exposed and strategically important cranial area.

In terms of **fish**, four gill slits are mostly created, communicating directly with the pharynx. Among the slits there are five gill arches, projecting outward in fine gill lamellae. In higher bony fish, the entire gill area is covered with a special operculum that protects fine gills. The gills are richly vascularized structures, covered with thin epithelium, allowing gas exchange. However, they do not only have a respiratory but also an excretory function complementing renal function, which is particularly important in marine animals having additional salt management tasks. Some fish and amphibian larvae also have various other accessory respiratory organs in the form of external gills, growing above the internal gills. Also, skin breathing is maintained in many fish and amphibians with rich-blooded skin and is almost as important as pulmonary respiration.

For lung evolution, an important developmental intermediate is the existence of the so-called **gas bladder**. It is known in most fish species as a non-paired dorsal diverticulum of the front part of the digestive tube.

It is a hydrostatic organ filled with air or similar gas and allowing the fish to keep its position even in depth. In lungfish, the bladder is already paired, which descends ventrally, i.e., to the same position as the lungs of terrestrial animals, and it serves these fish to breathe atmospheric oxygen similarly to the lungs.

Only in the postlarval stages of **amphibians**, the right lungs develop as paired, simple, thin-walled and translucent sacs without internal folds. Because the ribs are missing, the frog lungs are filled by a special mechanism using throat and tongue muscle movement.

In **reptiles** (snakes and lizards), the lungs are still in the form of sac-shaped structures with small internal folds. In many reptiles, only one lung is developed, but the trachea is usually extended into the so-called tracheal lung. In the chameleon, both lungs protrude into long, digit-shaped protrusions that serve as an air reservoir and allow the animal to benefit from less frequent breathing movements. Reptiles, however, have well-formed ribs (that also play a great role in locomotion in the snakes) and thus also intercostal muscles, significantly involved in respiratory movements. In turtles, however, the respiratory mechanism is dependent on the movements of cingulum membri thoracici and cingulum membri pelvini.

In **birds**, the lungs are relatively small and compact, that is, little extensible, and so some of the bronchi expand into paired air sacs (usually four) that penetrate into all parts of the body and bone.

From the anterior air sacs (expiratory sacs), the protrusions penetrate into the bones of the wings and into the skin (e.g., "rattle" skin of pelicans). From the posterior air sacs (inspiratory sacs), the protrusions penetrate into the bones of the lower limbs and pelvis.

In birds, the bronchioles pass into a rich network of air capillaries that communicate with each other and also with the sacs. Thus, blind alveoli are not formed as in mammals, but air circulates through all open airway sections, and gas exchange occurs in passable air capillaries.

Generally speaking, in the evolutionary series of vertebrates, especially in **mammals**, the internal surface of the lungs is increased by folding walls or rich branching of the bronchi which branches in ever finer branches – the bronchioles which end in the thin-walled hollow cavities – the pulmonary alveoli. The walls of these hollow cavities are surrounded by a network of capillaries which are the site of gas exchange.

1.1.2 Ontogenesis of the Respiratory System

The development of respiratory organs in terrestrial animals begins at the distal end of the branchial region. The developmental processes, which the entire gill area undergoes in the early embryonic period, correspond with the adult condition of similar organs in lower animals (just according to the rules of recapitulation of phylogenetic structures in the ontogenesis of the evolutionary higher organisms – phylogenesis is recapitulated during ontogenesis).

Thus, in the case of early human embryos, four gill slits are also formed but they do not open and do not develop in gills such as in fish. Instead of a respiratory function, they have other important homeostatic tasks, such as immunological or endocrine function. To accomplish these tasks, the organs such as thymus, thyroid gland, tonsil, and parathyroids develop from the gill slits.

Embryonal development of the lungs cannot be separated from the development of the airways, which develop just behind the last gill slit in the endodermal area of the pharyngeal bottom. In humans, in the third week of development, a longitudinal furrow – a laryngotracheal groove is here formed in the midline. This is deepened in a groove-like manner and then closes in a laryngotracheal tube lined with mesenchymal plicae. This mesenchyme is joined together from both sides and forms a tracheoesophageal septum, separating gradually the respiratory tract from the digestive tract. The larynx develops from the upper part of the tube, the trachea is formed from its next part, and from the caudal end of the tube, a lung bud is formed, which is the basis for future lungs. In lung bud, an elevated alkaline phosphatase concentration as evidence of proliferation activity can be demonstrated. From this endodermal structure, the epithelium lining of the larynx, trachea, bronchi and alveoli is formed. Connective tissue, skeleton, smooth muscle and vessels are developed from surrounding mesenchyme. It should be remembered that in the laryngeal region, this is mostly a material derived from gill arches, in which the ectomesenchyme of origin from the neural crest predominates.

The development of the lungs and especially of their bronchial trunk occurs in humans in four main phases.

During the first phase so-called **early embryonic stage** (between the 4^{th} and the 7^{th} week of development), the pulmonary basis is detached from the closing laryngotracheal groove and divided into a smaller left and larger right bronchial buds. Both of these buds are already suggesting future lung asymmetry at this time. From these buds, the main bronchi of the lung lobes are formed, two bronchi on the left and three bronchi on the right. These are further branched and give rise to the segmental bronchi.

The second phase – **pseudoglandular phase** – begins at approximately the 5^{th} week and continues until about the 17^{th} week. A richly branched bronchial trunk resembling the tube-alveolar gland develops during this phase.

It is an epigenetic process in which, under the influence of induction of surrounding mesenchyme, the epithelial basis for the bronchi is branched dichotomically, mostly unevenly, so one bronchus is stem bronchus and the other one forms a lateral branch.

At the end of this phase, over a period of about 15–20 generations, the entire bronchial trunk is definitely formed, including the terminal bronchioles. Proximal bronchi are lined with a cylindrical epithelium, which gradually differentiates into the ciliary epithelium and is supplemented with cup cells. Distally, the lining decreases to cubic epithelium.

Tracheal cartilages develop at the 7th week, and cartilages of segmental bronchi are formed at the 12th week of ontogenesis.

The third phase – **canalicular phase** – takes place approximately from the 13th week to the 26th week and is, after the previous phase of the formation of basic conductive structures, the phase with the development of the respiratory part of the bronchial trunk. Short canaliculi corresponding to future ducti alveolares grow from the terminal bronchioles. In the 24th–26th week, the respiratory part of the bronchial trunk is constructed and terminated by distal buds as the basis for future sacculi alveolares.

This phase is followed by the fourth phase – **alveolar phase**, which begins in approximately 23th–24th week by the development of alveoli distally from the respiratory sections of the bronchial trunk. At the same time, the development of interalveolar and interlobular septa occurs by differentiating elastic and collagen fibre bundles in mesenchyme.

Development of interalveolar septa begins at approximately week 24 of ontogenesis but continues in the first years of postnatal life. After 24 weeks of prenatal life, respiratory bronchioles are surrounded by a dense network of elastic and collagen fibres, and after the 30th week, the proliferating epithelial buds of other alveoli protrude into the meshes of network. As early as the 24th week, the cubic epithelium of the future *ductus et saccus alveolares* begins to become thinner.

The first squamous epithelial cells develop and differentiate into type I pneumocytes. They occur in places where they are closely attached to the epithelium of the blood capillary. Some lining cells retain cubic shape, differentiate into type II pneumocytes and form surfactant phospholipids.

A baby is born in the middle of the alveolar phase. Before the 7th month of his/her development, the lungs cannot perform respiratory tasks, although respiratory movements have already been proved in spontaneously aborted fetuses in the 3rd month of development. As a result of these movements, aspiration of a portion of the amniotic fluid into the bronchial trunk occurs. Fetal lungs resemble a water-soaked sponge. The fluid must be removed before the air is breathing, by absorbing it into the blood and lymph vessels, and then by mechanical squeezing of the fetal body during passage through the birth canal. Aeration of the lungs, therefore, lies primarily in exchanging fluid for air and not in the expansion of the collapsed lung with the air, as is often interpreted. At birth, the entire bronchial trunk is already branched and terminated by very flat temporary alveoli. The epithelium of these alveoli becomes thinner, surfactant secretion is increased and intimate contacts with the capillary network are formed.

After the birth, the completion of alveoli continues and ends in the early years of postnatal life (usually at age 3–4 years; it should be ended no later than 6–8 years of age). The number of alveoli in the newborn is approximately 50 million and increases to about 300 million alveoli in the adult human lungs.

The question of whether the formation of new alveoli can occur even in adulthood is still not fully answered. However, it has been found that after resection of parts of the lungs or under hypoxic conditions new formation occurs in young experimental animals.

Histogenetically, at 28 weeks of prenatal development, type I pneumocytes with scattered type II pneumocytes are formed in the alveolar lining. Capillary networks are formed parallel to the development of pneumocytes (also when alveoli are re-forming) and this image does not differ much from the microstructure of adult lungs. The mesenchyme between the alveoli thickens during development and produces gradually very thin interalveolar septa. The originally two-layered capillary network turns into a single-layer network. Elastic and collagen fibre systems arise around the entrance to the alveoli at around 30 weeks, and at the time of birth, they are well-constructed in the newborn.

Generally in most mammals, the entire process of alveolar development, thinning of the alveolar wall, surfactant formation, and contact with the capillary network, i.e., functional maturation of the lungs, is achieved after approximately 80% of the total length of pregnancy has elapsed. Of course, a human is extraordinary among mammals by developing the alveolar phase much earlier, even after 60% of the total length of pregnancy has elapsed.

This developmental shortening in humans is most likely related to prolonging the total length of gestation during its evolution. The development of the lungs has not yet been adapted to this prolongation, which is probably related to the massive and complicated development of the brain. This is evidenced by the situation in our closest animal relative – the chimpanzee – in which the alveolar phase occurs, as in other animal species of mammals, in 80% of the length of pregnancy.

1.2 ANATOMY OF THE RESPIRATORY SYSTEM AND MEDIASTINUM

1.2.1 Trachea

The trachea is an approximately 10–12 cm long and a 12–15 mm wide tube that is attached to the larynx at the level of the C6 vertebral body. It descends through the superior thoracic aperture (*apertura thoracis superior*) into the chest, where at the level of the Th4 vertebra is branched (*bifurcatio tracheae*) into two bronchi – the right and the left main bronchus (*bronchi principali*). Two trachea sections – the cervical part (*pars cervicalis*) and the thoracic part (*pars thoracica*) are approximately the same lengths. The trachea has a cylindrical shape and is flattened at its dorsal part. The base is formed by 15–20 horseshoe-shaped cartilages (*cartilagines tracheales*) that are linked together by ligaments (*ligamenta anularia*). At the back, there is the elastic wall (*paries membranaceus*) that is made up of connective tissue and smooth muscle. The elastic wall allows the esophagus to dilate when swallowed. The trachea is connected by loose connective tissue (*tunica adventitia*) with surrounding structures. Inside, the trachea is lined with a mucosa covered with a pseudostratified ciliated columnar epithelium. In the mucous membrane and especially in the tela submucosa (*tunica submucosa*) there are numerous seromucinous glands (*glandulae tracheales*).

Topographic relationships

Pars cervicalis tracheae is a section from the cricoid cartilage (*cartilago cricoidea*) to the upper edge of the manubrium sterni. The cranial part is located more superficial than its caudal part. In front of the trachea, there are the infrahyoid muscles (*mm. infrahyoidei*), the cervical fascia (*lamina superficialis et lamina praetrachealis fasciae cervicalis*), the thyroid isthmus, and the thyroid veins. Behind the trachea. there is the esophagus, and along the sides of the trachea, there are thyroid lobes. The right and left recurrent laryngeal nerves (*n. laryngeus recurrens dexter et sinister*) come out in the space between the trachea and the esophagus. ***Pars thoracica tracheae*** descends in the superior mediastinum (*mediastinum superius*). The thymus, *vena brachiocephalica sinistra* and *truncus brachiocephalicus* are located in front of the trachea. Under the tracheal bifurcation (*bifurcatio tracheae*), the lymph nodes (*nodi lymphatici tracheobronchiales*) are located. There are large vessels on the sides of the trachea – on the left: *arcus aortae*, on the right: *vena cava superior*. The esophagus descends dorsally.

The vascular and lymphatic system, innervation

The trachea is fed by branches (*rami tracheales*) of *a. thyroidea inferior* which originates from the thoracic aorta. Small veins divert blood into the veins of the esophagus, *venae brachiocephalicae* or *venae thyroideae inferiores*. The lymph is drawn through *nodi lymphatici tracheales* and *nodi lymphatici tracheobronchiales superiores* into *truncus bronchomediastinalis*. Tracheal innervation is ensured by *n. vagus* and *sympathetic ganglion stellatum* and periarterial nerve plexuses.

1.2.2 Bronchi

The bronchi are made up of a system of tubes that gradually branch and form the bronchial tree (*arbor bronchialis*). The trachea is branched into two main bronchi (the main bronchi, *bronchi principales*). Both main bronchi divide into lobar bronchi (*bronchi lobares*) and enter the lungs where branch into segmental bronchi (*bronchi segmentales*). Another branching is described in the section "Lungs".

Bronchus principalis dexter (the right main bronchus) is shorter (about 3 cm) and wider (15 mm) and runs more vertically (therefore, the inhaled foreign body gets easier into the right bronchus), whereas ***bronchus principalis sinister*** (the left main bronchus) is longer (4–5 cm) and narrower (less than 11 mm) and runs more horizontally. The main bronchi depart from the trachea at an angle of 70°–80° and have a similar structure as the trachea. Within the trachea, there is a ridge of cartilage called the carina of the trachea (*carina tracheae*) which occurs between the division of the two main bronchi.

Topographic relationships

The right main bronchus is eparterial (located above *a. pulmonalis*), whereas the left main bronchus is hyparterial. Pulmonary veins lie caudally from the bronchi.

The vascular and lymphatic system, innervation

The bronchi are fed by branches of the thoracic aorta (2–3 *rami bronchiales* which can sometimes also originate from *a. thoracica interna* or some intercostal arteries).

Venous blood flows into *v. azygos* (on the right) and into *v. hemiazygos* (on the left) through *vv. bronchiales*.

The lymphatic vessels collect the lymph and flow into the lymph nodes around the bronchi (*nodi pulmonales*), then into hilar lymph nodes (*nodi bronchopulmonales*) and ultimately into mediastinal lymph nodes so-called tracheobronchial lymph nodes. These are divided into the lower nodes – subcarinal lymph nodes located centrally under the tracheal bifurcation (*nodi tracheobronchiales inferiores*) and the upper tracheobronchial lymph nodes, located cranially and laterally in the angles between the trachea and the tracheal bifurcation (*nodi lymphatici tracheobronchiales superiores dextri et sinistri*).

The innervation is ensured by the vagus nerve (*n. vagus*) and sympathetic periarterial nerve plexuses.

(*Note:* Anatomical nomenclature of lymph nodes differs from the clinical one, used in the TNM classification.)

1.2.3 Lungs – Pulmones

The lungs are the paired organs located in the pleural cavities. The space between them is a mediastinum (*mediastinum*). The pleural cavity is lined with the pleura – the outer pleura or the parietal pleura (*pleura parietalis*) that passes around the root of the lung (*radix pulmonis*) into the pulmonary pleura – the inner pleura or the visceral pleura (*pleura visceralis*).

The topography of pulmonary hila is different in both lungs. In the **right radix pulmonis (*radix pulmonis dextra*)** there are: cranially – *bronchus principalis dexter*, in the middle – *a. pulmonalis dextra*, and ventrocaudally – *venae pulmonales*. In the **left radix pulmonis (*radix pulmonis sinistra*)** there are: in the upper part: *a. pulmonalis sinistra*, in the middle: *bronchus principalis sinister*, and in the front lower part: *venae pulmonales*.

On the medial surfaces of the lungs there are the visible **impressions caused by adjacent organs:** in front of the hilus pulmonis of the **right lung** there are the impression of superior vena cava (*vena cava superior*) and the cardiac impression (*impressio cardiaca*), above the hilus pulmonis there is the impression of *v. azygos* and *a. subclavia dextra*, and dorsally there is the impression of the esophagus. On the medial surface of the **left lung** there is a deep impression (*impressio cardiaca*) in front of the hilus, *sulcus aorticus* behind the hilus, and an impression of *a. subclavia sinistra* and a shallow impression of the first rib under the hilus. The surfaces of the lungs meet in the margins – *margo inferior pulmonis*, *margo posterior pulmonis* and *margo anterior pulmonis* which has the cardiac notch (*incisura cardiaca pulmonis sinistra*) and *lingula pulmonis* (under *incisura cardiaca*) on the left lung.

A division, the structure and properties of the lungs

Lungs are divided into the lobes (*lobi pulmonis*) by fissures (inter-lobe fissures – *fissurae*).