LOUIS BOLK INSTITUTE

Physiology

Organphysiology from a Phenomenological Point of View

Christina van Tellingen MD

BOLK'S COMPANIONS FOR THE STUDT OF MEDICINE

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LOUIS BOLK
INSTITUTE

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Christina van Tellingen MD

About the Author

Christina van Tellingen MD (1949) has been a general practitioner since 1982. She has educated medical students, physicians, and therapists in the United States, Canada, and Europe. She teaches medical students and physicians at the University of Witten/Herdecke, Germany. She is a member of the Medical Section of the School of Spiritual Science at the Goetheanum, Dornach, Switzerland.

About the Project

The project *Renewal of Medical Education* aims to produce Companions that demonstrate how the insights of current biomedical science can be broadened by using the Goethean phenomenological method. This method innovates current concepts and expands the understanding of biochemical, physiological, psychological, and morphological factors in living organisms and their development in time and space, and in health, illness, and therapy. The project is commissioned by the Kingfisher Foundation, which aspires the development, application, and publication of the Goethean phenomenological research method in the widest sense, to complement and innovate the accepted scientific view and research method.

BOLK'S COMPANIONS FOR THE STUDY OF MEDICINE complement current medical education, specifically disclosing human qualities in the fundamental biomedical sciences of today.

BOLK'S COMPANIONS FOR THE PRACTICE OF MEDICINE contribute to a scientific phenomenological basis for integrative medicine and integral psychiatry.

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Christina van Tellingen, Driebergen, November 2002.

*An originator of this approach to science is the author and scientist Wolfgang von Goethe. For further information on this method we recommend the book by Henri Bartoft, 1986 and the Companion Wholeness in Science by Guus van der Bie, 2012.

Preface

This module of **BOLK**'S COMPANIONS FOR THE STUDY OF MEDICINE is presented in an effort to aid medical and other science students in their study of the physiology of functioning organisms and to help them remember it better in later study and work.

It is meant as a supplementary text in physiology and aims at gaining an overview by using an innovative study and research method: the Goethean method*. At the Louis Bolk Instituut, Holland where this work was written, this method is used extensively in research in agriculture, nutrition, and medicine, since it brings details in connection with one another. Since the detailed knowledge we have of physiology comes from coherent organisms, we can bring the details together again to augment our understanding of functioning organisms as a whole.

In the Goethean method the known facts are *listed* and then *evaluated*. Demonstrating where certain processes are typical in the living world and *characterizing* them is the next step. Then we may *compare* a typical process with others within the organism or living nature, which enables us to draw conclusions as to its role or meaning in the whole of the organism. Thus a greater overview of the subject is gained. Therefore, next to studying the details of physiology texts, the study of this module will aid in finding the coherence between organs, organisms, and living nature.

We dedicate this work to all students who need to learn the facts of physiology and who also want to gain a greater understanding. We want to emphasize that this module does not replace studying a physiology textbook. The information contained in this module is compact and presupposes the knowledge contained in such textbooks. But it hopes to make studying and remembering the texts (ever) more interesting.

1. Introduction

How can we do justice to life itself when studying the life sciences?

In his book, *Lifelines,* Steven Rose states: "The challenge to the opponents of biological determinism is that, while we may have been effective in our critique of its reductionist claims, we have failed to offer a coherent alternative framework within which to interpret living processes." (Rose 1998)

This module offers an alternative framework. In trying to remedy the problem, we have striven for two goals: first, to introduce a new coherent framework in physiology, and second, to show that this framework opens up new possibilities for interpreting physiological processes. We achieve the characterization of a new framework by using a phenomenological approach to physiology. Phenomenology approaches life from the point of view of the whole, such as the whole organism or the whole of an ecological system. This allows the facts of physiology to be placed in a different relation to each other. The new insights that evolve from this approach can be interpreted with the methods of Goethean science, which places the facts in a context, as is described in the foreword. Physiology is typically concerned with *living* organisms. Organisms function as a whole, and physiological processes in organisms are interrelated as a consequence.

Four organ systems will be examined: the lung and respiratory tract, the liver and digestive tract, the kidneys and urinary tract, and the heart and circulation. We will try to find where and how their physiological processes fit into the whole of the organism, and at the same time if they have a *prototypical* place and function in it. We chose these four organ systems because they allow us to see that organs are subject to *different formative principles* in their formation and physiology. These underlying principles are themselves related to forces in nature and appear in a definite order wherever they are at work. All mammals and humans have hearts and lungs; we will demonstrate where in the human organism and in living nature the principles underlying heart and lung have been perfected and play a special role. This will augment our understanding of the function of organs as well

as of the organism as a whole. We will do this by first looking at:

- the **physiological morphology** of organs: their gross anatomical characteristics (shape), their inner structure (histology) and the embryological processes that led to these
- an overview of the **blood supply**
- the relevant **physiological facts**
- the way the organ physiology is **regulated** in the organism and itself regulates the organism
- the **function** of the organ for the organism as a whole
- followed by the **conclusions** regarding the physiology of this organ from a phenomenological point of view.

The **last chapter** (Chapter 6) presents a review and puts the four organs in relation to each other. This offers the possibility to interpret the facts in context and gain a larger view of the role of these organs and the formative principles that underlie them.

Fig. 1.1. These four Egyptian canopical jars were found in the graves of pharaos. They each contained one of four organs of the deceased. The Egyptians often buried the organs separately next to the mummified body (private slide series)

2. The Lung and Respiratory Tract

2.1. Introduction

The respiratory tract allows gaseous substances from the surrounding air (chiefly oxygen - O_2) to enter the aqueous milieu of the organism, and metabolically generated gases (chiefly carbon dioxide - CO_2) to pass from the blood into the surrounding air. Air from the environment enters the respiratory tract when we inhale, and oxygen is taken up into the blood in the lungs. The O_2 is transported mainly by the hemoglobin in red blood cells to every cell of the organism. In the mitochondria of all cells of the organism oxygen becomes involved in the metabolic breakdown of substrate. The CO_2 that is formed in this process is subsequently taken to the lungs dissolved in the blood and carried by the hemoglobin. In the lungs, it leaves the fluid phase and enters the respiratory tract as gas. Exhaling expels the carbon dioxide into the air. *Breathing* takes place in the respiratory tract; *respiration* occurs in every cell of the organism when metabolites are oxidized. The circulating blood insures the transport of gases between the respiratory tract and the cells of the organism.

We will subsequently consider the physiological morphology (the shape and structure) and embryology, the blood supply, the physiology, the regulation, and the function in the organism of the respiratory tract to gain a view of its characteristic place in the organism.

2.2. The Physiological Morphology of the Respiratory Tract

2.2.1. The Shape of the Respiratory Tract

The respiratory tract is divided into an upper and a lower respiratory tract.

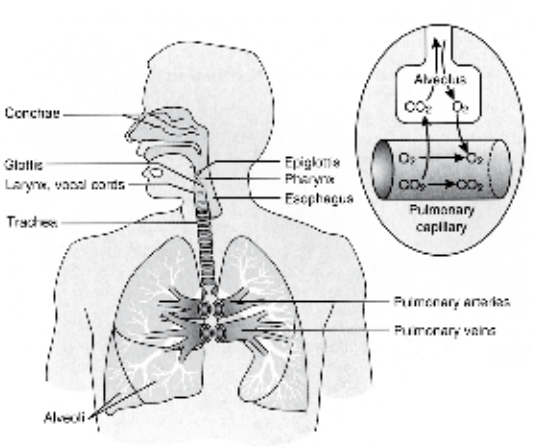


Fig. 2.1. The upper and lower respiratory tract (from Guyton 2000)

The Upper Respiratory Tract

The upper respiratory tract consists of nose, pharynx, and larynx (fig. 2.1.). Several other air-filled spaces in this area, the paranasal sinuses and the middle ear, which directly connect to the nose, pharynx, and larynx, are closely related to the upper respiratory tract. In disease of the upper respiratory tract, the sinuses and middle ear (including the mastoid air cells) may be involved. We will also consider the paranasal sinuses and the middle ear when we discuss the upper respiratory tract. Together they form all the air-filled spaces of the head. Most of the nasal passages, sinuses, and middle ear are embedded in bone. A cartilaginous wall suspends the Eustachian tube. The pharynx is suspended from the base of the skull.

The entire upper respiratory tract, including the paranasal sinuses and middle ear, is embedded in or suspended from either bone or cartilage.

The Lower Respiratory Tract

The lower respiratory tract is mostly tubular in shape.

- Proximally:
  Proximally, the lower respiratory tract consists of the larynx, trachea, and bronchial system (fig. 2.1.), which all have cartilage in their walls. The cartilages of the larynx hold the vocal cords. The larynx is an intricate system of cartilage and muscular cords that form the central organ for speech in humans.
- Distally:
  Distally, the lower respiratory tract consists of the respiratory bronchioles (fig. 2.1.).

The alveolar ducts and the alveoli form respiratory units, where the actual gas exchange occurs. The trachea, bronchial system, and the respiratory units together form the lung. There is no bone or cartilage in the tissue of the respiratory units that keeps these essential areas open to the flow of air. They are kept open with the help of the pleura and the chest wall, and the action of "surfactant".

- Pleura:
  A layer of visceral pleura covers the lung, and a layer of parietal pleura covers the inside of the thoracic wall. The viscous fluid in the pleural cavity between them permits the lung to glide along the thoracic wall as it is expanding at *inhalation*. The negative intrapleural pressure ensures that the two layers of pleura hold together as the chest expands, and thus enables lung expansion along with chest expansion during inspiration.
- Surfactant:
  Surfactant is a surface tension-lowering compound inside the alveoli that prevents the alveoli from collapsing at *exhalation*. The forces that hold together a drop of water would also collapse the alveoli in a gesture of imploding if the surface tension locally were not drastically lowered up to 1/12th of its value by a surface active agent in water, such as surfactant (see also section 2.2.2.).
- Other factors influencing the shape of the lower respiratory tract:
  The heart is spared out in lung tissue, or rather the lungs grow around the heart phylogenetically. The bronchial tree has special bronchi-associated lymphoid tissue (BALT), which deals with incoming pathogens, since the bronchial tree interfaces directly and intensively with the surroundings.

The upper part of the lower respiratory tract is held open by cartilage. The respiratory units are kept open by the pull of the thoracic wall during inspiration and by the action of surfactant during expiration. The respiratory units are suspended in the bones and muscles of the thoracic wall. (For further thoughts about the morphology of the respiratory tract see also the Anatomy Module of ***BOLK****'S COMPANIONS FOR THE STUDY OF MEDICINE)*

➔ *The outer shape of the entire respiratory tract is to a large extent dependent on the surrounding structures of skull, spine, ribcage, mediastinum, and diaphragm.*

2.2.2. The Structure of the Respiratory Tract

The respiratory tract is mostly a membranous structure that allows the passage and diffusion of air when the processes described above keep it open to the surrounding air.

The membrane-like structure of the respiratory tract repeats itself in the structure of surfactant. Surfactant molecules line the alveolar walls (fig. 2.2.). Surfactant consists mainly of the phospholipid dipalmitoylphosphatidylcholine and some specific proteins. The lipid molecules, which are mostly hydrophobic, arrange themselves such that their hydrophobic tails stick out into the air of the lumen of the alveoli. The specific proteins of surfactant form channels in the lipid layer for the passage of substances. Thus surfactant structure has similarities to the structure of the layers of the membranes in the body.

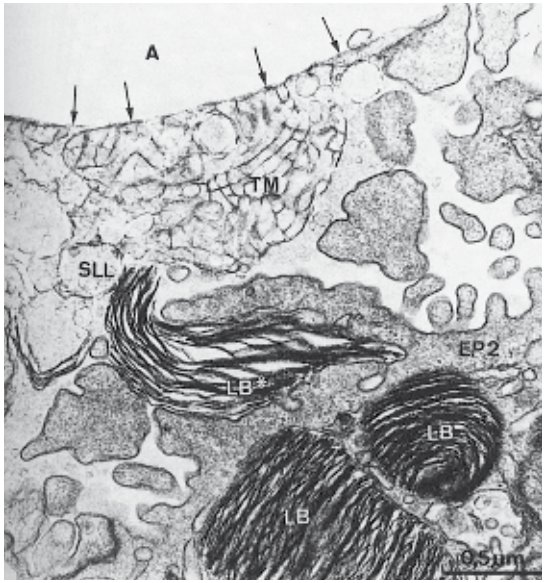


Fig. 2.2. The apical part of a type II cell with lamellar bodies (LB) being excreted into the surface lining layer (SLL). The alveolar space (A) is lined with a thin black film of dipalmitoylphosphatidylcholine (arrows) (from Fishman 1988)

The type II cells lining the alveolar walls secrete the surfactant. The membrane-like structure of surfactant is replenished when we sigh every few minutes or so, when we yawn, or when the membrane is otherwise stretched out. A special feature of

surfactant is that it allows the surface tension in the alveoli to change in relation to the changes in the alveolar surface area during breathing. Surfactant is a characteristic substance of the respiratory tract and is essential for the mechanics of allowing air to enter the fluid phase. Underneath the surfactant membrane lie intra-alveolar macrophages, which constantly remove surfactant molecules.

The structure of the respiratory tract is characteristically membrane-like. Also, surfactant, a prototypical substance of the lungs, has a membrane-like structure.

➔ *The membrane-like structure is characteristic of the respiratory tract.*

2.2.3. Embryology and Development

Macroscopic Development

The development of the upper respiratory tract starts from a different point of origin than the lower respiratory tract. They will be described separately.

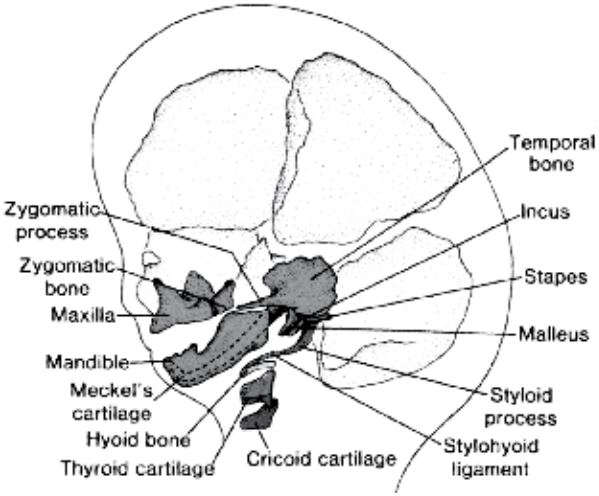


Fig. 2.3. Embryological development of the head in a 4 week old embryo. The darker shaded area originates from the pharyngeal arches (from Sadler 1995)

Upper respiratory tract

The *nose and paranasal sinuses* develop during the first years of life from and in the plate bones of the head, which have their origin in the neural crest (fig. 2.3.). The sinuses start out as diverticulae of the lateral wall of the nose after birth. The nose and sinuses are not full-grown until after puberty. Then they contribute substantially to the definitive shape of the face.

The area of the *pharynx, larynx, and ear* is almost completely derived from the pharyngeal (or branchial) arches and clefts. This area is phylogenetically related to the gill system in fishes and amphibians. For these, the gas exchange takes place in the area of the gills.

Lower respiratory tract

The lower respiratory tract develops from a diverticulum in the primitive foregut (see also section 3.2.3.). This lung bud forms dichotomous branches in up to 24 generations (fig. 2.4.). The two buds that are formed each time do not have the same diameter. Branching in the pulmonary tree is not a matter of chance but happens according to a definite ordering principle (Goldberger et al 1985).

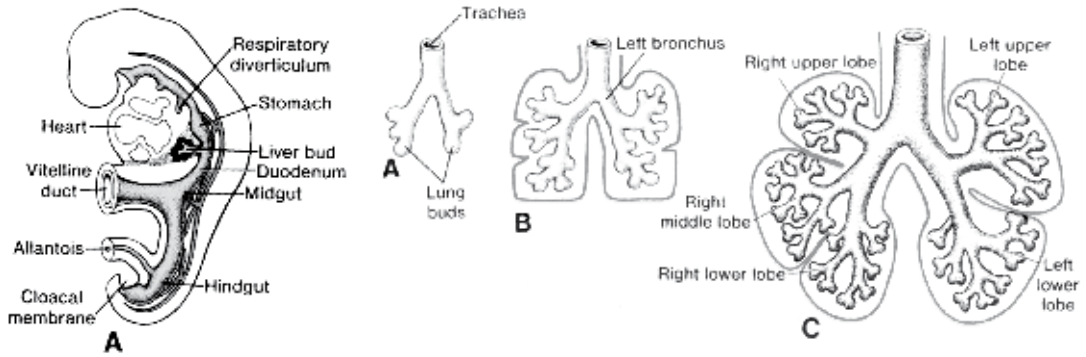


Fig. 2.4. Embryological development of the lower respiratory tract. The development of respiratory diverticulum to lung (from Sadler 1995)

The splanchnic mesoderm surrounding the foregut also surrounds the future trachea and bronchi. It develops into the smooth muscle and cartilage that allows and at the same time restricts the expansion and contraction of this system independently of the pressure in the lungs.

The *larynx* develops where the lung bud is connected to the primitive foregut. The laryngeal cartilages and muscles develop, however, not from splanchnic mesoderm, but originate

from mesenchyme of the 4th and 6th pharyngeal arch. Their innervation and blood supply develop from the innervation and blood supply to these pharyngeal arches.

During the first 10-14 years of life, the *lung* continues a maturation process consisting of further branching of the bronchial system, formation and growth of new alveoli, and thinning of the blood-air barrier. The alveolar surface is about 70 m^2 in adults. In the newborn it is 2.8 m^2. The lung is not full-grown until after puberty.

The respiratory tract, including sinuses and middle ear, originates in all 3 different embryological layers:

- *the nose and sinuses develop from **ectoderm** from the neural crest*
- *the middle ear, pharynx, and larynx develop from the **mesoderm** from all 6 pharyngeal arches, covered on the one side by a layer of ectoderm, on the other by a layer of endoderm, whereby the larynx develops at the point of transition between the primitive foregut and the respiratory diverticulum*
- *the bronchial system and respiratory units develop from **endoderm** from the respiratory diverticulum of the foregut*

Development of the Epithelium of the Lower Airways

In the 3rd-4th week after fertilization, during the time that all organs first develop (see also the *Embryology Module* of **BOLK**'S COMPANIONS FOR THE STUDY OF MEDICINE), the budding lung is lined with primordial epithelium that is undifferentiated and cylindrical. It is of endodermal origin, since the respiratory diverticulum buds out from the primitive foregut.

From the 10th-12th week onwards, the trachea and main bronchial system can be easily differentiated from the future respiratory units by the epithelium that lines the walls. It is cylindrical in the main bronchial system; in the respiratory bronchioles it has become cuboidal. The cylindrical cells in trachea and bronchi develop into ciliated cells and mucus producing cells, which will assist the lung in clearing away undesirable particles upward and outward. The lung will be in direct contact with the outside world!

At the end of the 6th month, the cuboidal epithelium includes type II alveolar cells, which produce alveolar surfactant. In the last two months of pregnancy and during the first years of postnatal life, some cuboidal cells become more and more flattened (type I cells), which minimizes the blood-air barrier between the alveoli and the lung capillary network and thus facilitates the transport of gases. The red cell hemoglobin/air distance is only approximately 1.5 mm in the adult.

The epithelium becomes more and more membrane-like in the respiratory units, where effective air exchange has to occur.

➔ *The embryology of the respiratory tract shows how it originates from all three embryological layers. In the respiratory units of the lung the epithelium differentiates to allow for its function in gas exchange.*

2.3. Blood Supply to the Lung

The lung has two sources of blood circulation, the bronchial and the pulmonary vessels. The pulmonary system is much larger than the bronchial system.

Bronchial System

The bronchial system supplies the structures of the larger airways and the large pulmonary vessels with oxygen saturated arterial blood. It also warms and humidifies the incoming air. Sympathetic nerves regulate blood flow in the bronchial system.

Pulmonary System

The pulmonary system develops from the artery of the right 6th pharyngeal arch, and supplies the capillary network around the alveoli where the gas exchange occurs. The pulmonary vascular resistance of vessels decreases markedly after birth and is eventually only 10% of the vascular resistance in the systemic circulation. With it the wall thickness of this system decreases also. The capillary network looks more like a thin film of blood, spread out over the outside surface of the alveoli. The film is just thick enough to allow

the passage of red blood cells. The low vascular resistance in the large capillary bed results in a low-pressure system locally.

Pulmonary artery blood is arterial blood with a low oxygen saturation that comes directly from the right ventricle (see also section 5.2.1.). The pulmonary veins take the oxygenated blood from the lungs directly into the left atrium. 10% of the total blood volume is pooled in the pulmonary circulation. The fraction of blood in the lung is 40-50% of its *total weight*. This is higher than in any other organ.

➔ *The lung contains the largest amount of blood by relative weight.*
Most of the blood that enters the lungs has low oxygen saturation.
Most of the blood that leaves them has high oxygen saturation.

2.4. Physiology of the Respiratory Tract

2.4.1. The Movement of Air

Physiologically, the respiratory tract can be divided into three areas, which each have a different relation to the *flow* of air. There are areas where the air is mainly absorbed, those where the air is mostly only conducted, and there is the area where the air is exchanged in a process of diffusion.

Air Absorption

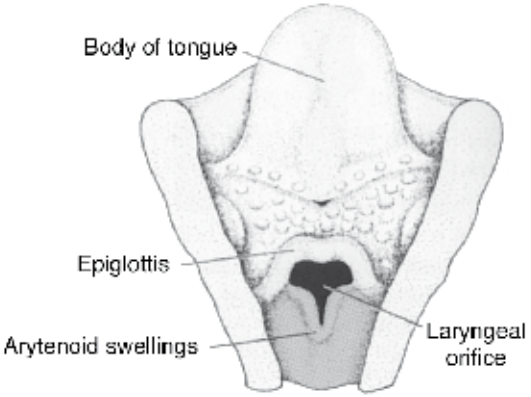
In the sinuses, the air hardly moves. Air enters the sinuses passively from the nose through a narrow opening in the lateral nasal wall. A small amount of air in the sinuses is absorbed into the bloodstream. This may result in a negative pressure in the sinus during sinusitis, since the air cannot be replenished from the nose due to swelling of the membranes in the opening between nose and sinus. It may cause much pain in sinusitis.

The middle ear also contains air that does not move much. The air in this area is passively replenished from the pharynx through the Eustachian tube. We may become aware of this phenomenon when we pop our ears. There is some resorption of air from the middle ear, which becomes visible in the retracted tympanic membrane in chronic middle ear infection, when the swollen Eustachian tube does not permit air to enter the middle ear space.

In the sinuses and middle ear, the air becomes rather static, and some ***absorption of air*** *into the blood takes place.*

Air Conduction and Speech

The nose, pharynx, larynx, and bronchial tree conduct the air. Physiologically, they form a middle area in which the air streams rhythmically back and forth with the breathing. This is the area of the anatomical "dead" space, which comprises 30% of the volume of each breath. Contraction or relaxation of the smooth muscles in the trachea and bronchial system can influence airflow. These smooth muscles are involuntary, and may be influenced by subconscious thoughts and feelings related to stress or anxiety, for example in asthmatic diseases. Clearing the throat, coughing, sneezing, or crying move the air in the respiratory tract too.



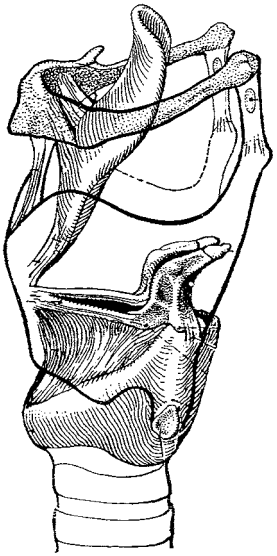


Fig. 2.5. The laryngeal opening in a 12 week old embryo (from Sadler 1995) and the adult larynx

In the middle of the ventilatory dead space, the larynx is situated, which needs the rhythmical movement of the air to function (fig. 2.5.). The vocal cords in humans, with their very specific, mostly muscular structure, influence the flow of air by interrupting it partially or bringing it to a total standstill in many varied and refined ways. The vocal cords are the area where the resistance against the flow of air in the respiratory tract is greatest. The normally inaudible inhaling and exhaling of air then becomes audible in speech. The pharynx is also part of the speech apparatus, and further expands the possibilities of speech. This happens as a result of the descent of the larynx, which results in a lengthening of the pharynx and a position of the tongue that is more dorsal and caudal than in the higher primates. Also the pelvic floor, abdominal muscles, diaphragm, and neck musculature participate in the speech process.

The vocal cords in lower primates are only membranous. In higher primates there is some muscular tissue in the vocal cords (Verhulst 1999).

Speech is an active, conscious process in humans that occurs during expiration in the middle of a part of the respiratory tract where the air is moved passively, rhythmically, and mostly unconsciously.

The ***conduction of air*** *is predominant in the nasal passages, pharynx, larynx, and bronchial tree. The air current moves continuously and rhythmically on the inbreathing and outbreathing and allows the possibility of speech.*

Air Diffusion

The lower respiratory tract contains the respiratory units where the actual gas exchange occurs. Gas exchange is by diffusion. Diffusion is a *passive* process, whereby the substrates move by way of a pressure gradient, in this case between the gas pressure of the alveolar air and of the blood in the capillary bed. Oxygen and carbon dioxide are gases, and are lipid soluble. This makes their diffusion through the surfactant layer and the alveolar and capillary membrane easy. To assure adequate gas exchange, the capillary surface area of the lung is the greatest of any organ in the body.

*The **diffusion of air** is predominant in the lungs' respiratory units. The air again becomes almost static, but only for the moment between inhaling and exhaling, as the current of air turns around.*

2.4.2. Breathing

Breathing has two phases, inspiration and expiration.

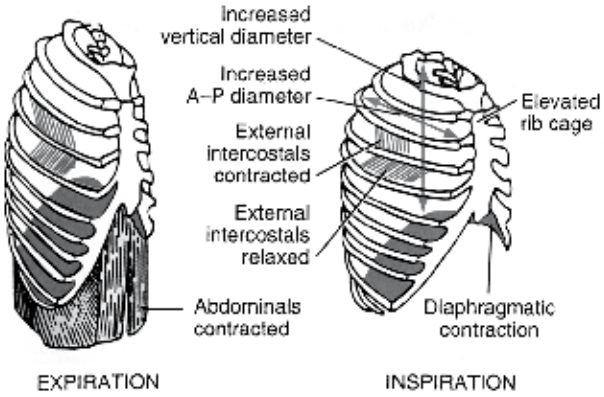


Fig. 2.6. The thoracic cage in inspiration and expiration (from Guyton 2000)

Inspiration

Airflow in the respiratory tract during inspiration is effected by contraction of the muscles of the chest wall (internal and external intercostals, and the diaphragm), and, in case of need, the accessory muscles of breathing (scalenes and sternocleidomastoids). All muscles are voluntary, striated muscles. They enlarge the chest cavity in a caudal as well as in the fronto-dorsal direction (fig. 2.6.). By means of the existence of a negative intrapleural pressure, the lungs are forced to move along with the chest wall. Chest wall expansion causes an increase of the negative intrapleural pressure and a negative pressure in the respiratory tract and consequently a flow of air from the surroundings via the upper respiratory tract into the lungs.

The inhaling of air is an active process. Muscles surrounding the respiratory tract perform the work. The tissues of the respiratory tract follow the chest wall movements passively.

Expiration

The movement of air in the expiratory phase is largely dependent on the elastic recoil or elasticity of the lungs (80%) and surrounding tissues (20%). That the lungs do not

collapse during deflation is in part due to the rigidity of the ribcage and the cartilage around the larger airways and the negative intrapleural pressure. When this pressure becomes positive, for example in pneumothorax as a result of a perforation trauma in the thoracic wall, the lung collapses. The pleura holds the lung connected to the chest wall. Alveolar surfactant molecules play a major role in this phase, assuring that the alveoli do not collapse (see also section 2.2.2.).

The exhaling of air is an overall passive process.

2.4.3. The Rate of Breathing

The rate of breathing in humans varies as a function of the respiratory needs of the tissues. At rest the rate is 16-18 breaths per minute. In walking or running, the rate may vary from one breath for 4 or more steps to one for every 2 steps. The vertebrates in general have to take one breath with each step as they move. This is related to the fact that their thorax muscles and bones also serve as padding against the impact to the spine and nervous system of the contact of the front legs with the ground. They also need the breathing to get rid of excess warmth produced in movement. In humans the eccrine sweat glands take over this function, which frees the lungs further from functions other than breathing (Verhulst 1999). In humans, the lungs are freed from all functions except breathing, which creates the further possibility to develop speech.

➔ *Airflow in the respiratory tract as a whole is not caused by the respiratory tract itself, but by surrounding muscles and the elastic recoil of tissues. Airflow itself is a passive event. Only in the larynx we find muscles that actively and voluntarily control the flow of air against the flow of normal breathing. This forms the basis for the capacity of speech, which is only present in humans.*

2.4.4. Digestion and the Respiratory System

The air that passes through the respiratory tract is *physically* warmed up, partially cleaned, and humidified in the nose, pharynx, and bronchi to match the temperature and humidity level in the alveoli, where gases from the air will enter the bloodstream. This process of equilibration happens very rapidly, and, even when the air is inhaled through the mouth, is accomplished by the time the air reaches the distal bronchi.

We could compare this to the activity of the digestive tract, which has to transform food rather than air such that it can enter the bloodstream. In order to do this, enzymes are formed and secreted at different levels to break down the foodstuffs *chemically* and bile is secreted to allow the hydrophobic lipids to be taken up in the aqueous milieu of the blood. In addition the food is physically warmed up, partially cleaned, and liquefied.

The epithelium in the alveoli of the lung produces surfactant actively (section 2.2.2.). The epithelium of the bronchi, trachea, larynx, pharynx, and nose produces mucus. The capillary endothelium in the lung metabolizes some substances, the most important of which is angiotensin I from the liver. It converts angiotensin I into its active metabolite angiotensin II, which is a strongly vasoactive hormone (see also sections 3.5.2. and 4.5.).

The physical warming, cleaning, and humidifying of air before it enters the bloodstream in the respiratory tract, and its secretion of mucus, is a relatively passive occurrence compared to the production and activity of digestive secretions and the movement of food in the intestines.

➔ *The physiology of the respiratory tract is characterized by relatively passive events. The exception to this is the active production of surfactant in the alveoli.*

2.5. Regulation of Respiration and Pulmonary Circulation

Respiration is mainly regulated through different centers of the central nervous system and the vagus nerves (fig. 2.7.). Excess carbon dioxide or excess hydrogen ions (low pH) in the blood directly affect the respiratory center to increase the breathing rate. Stretch receptors in the walls of the airways affect the breathing through respiratory centers in the central nervous system via afferent fibers of the vagus nerves.

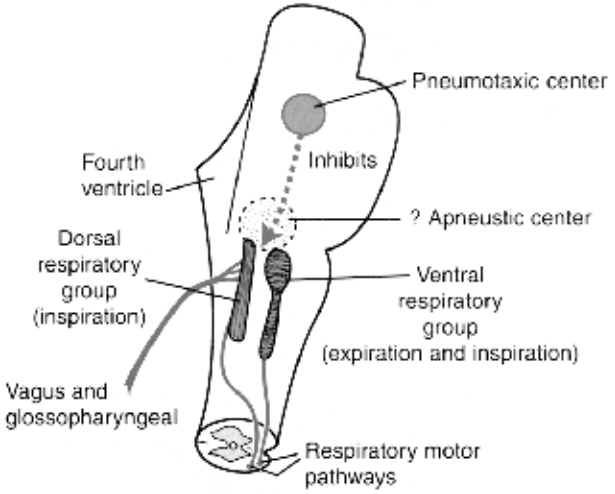


Fig. 2.7. The respiratory centers in the brain stem (from Guyton 2000)

Oxygen saturation affects peripheral chemoreceptors in carotid and aortic bodies in the respective arteries, which in turn transmit the signal to the respiratory center.

Alveolar circulation is diminished when oxygen saturation in the alveolus falls. Increased cardiac output, as in exercise, increases the pulmonary circulation up to sevenfold by opening extra capillaries so that the total volume of the capillary bed increases. Local pressure in the capillaries changes very little with increased cardiac output.

➔ *The regulation of respiration comes chiefly from outside the respiratory tract, via the nervous system.*

2.6. The Function of the Respiratory Tract and the Lung

The function of the respiratory tract is to facilitate the streaming of air into and out of the organism. Oxygen and carbon dioxide are essential in metabolism. Oxygen plays an important role in the catabolic processes of cells as it allows the energy of hydrogenated molecules such as the reduced form of nicotinamide adenine dinucleotide (NADH) to be transferred to energy carriers like adenosine triphosphate (ATP). This is accompanied by the formation of water. Carbon dioxide is the most abundant end product of catabolism.

2.7. Conclusion

The respiratory tract is able to fulfill its function, supplying the organism with the necessary oxygen for (catabolic) combustion processes and excreting gaseous waste products (chiefly carbon dioxide), mainly by creating the conditions to make this possible rather than by actively pursuing its goals.

- Morphology:
  The membrane-like respiratory tract is largely supported and shaped *passively* by surrounding bone, muscle, or cartilage. The alveoli keep their *passive* shape in expiration through the action of surfactant. *The respiratory tract is membrane-like in structure and completely supported from without. This is the most characteristic feature of the respiratory tract.*
- Blood supply:
  The pulmonary artery blood supply contains blood low in oxygen saturation. Up to 50% of the lung weight is blood.
- Physiology:
  The physiology of the respiratory tract is dominated by *passivity* on the part of the respiratory tract: the necessary movement of air is effected by surrounding muscles for the inhaling, and by the elastic recoil of the lung tissue for the exhaling. Gas exchange takes place through the *passive* process of diffusion on the basis of pressure gradients in the upper respiratory tract as well as in the alveoli. The modification that the air

	Lung + Respiratory Tract	Liver	Kidneys	Heart
Morphology	Shape from without, tubular organ, **membranous structure**			
Blood supply	50% of *weight* is blood, largely O_2 unsaturated, capillary blood in thin film			
Physiology	Passive diffusion			
Regulation	Mainly from without, via the central nervous system			
Function	Passive supplying			
Characteristic	Membrane-like structure, *diffusion of gases* (O_2 and CO_2) and water			

undergoes in the respiratory tract is very mild compared to the changes the food has to undergo before it can enter the blood stream in the digestive tract.

- Regulation:
  The respiratory tract ventilation and perfusion are regulated mainly *from without* through the nervous system via the carbon dioxide- and oxygen-concentrations, the pH of the blood, and the cardiac output.
- Function:
  The function of the respiratory tract is *passive* in that it supplies the organism with needed gases, without doing much with them itself directly.

➔ *The respiratory tract is an overall passive system. It is constantly in movement but it is moved along, rather than actively moving itself. Its membrane-like structure is its most characteristic feature.*

The passivity in the respiratory tract is overcome in the **larynx**, especially in humans. The human larynx actively shapes the air to become the carrier of sound by bringing it to a relative standstill. This is refined by the action of the muscular activity of the vocal cords and the pharynx, including the tongue, and is supported by many other muscles in the body. The speech apparatus develops in the part of the respiratory tract that is considered physiological and anatomical "dead" space.

3. The Liver and Digestive Tract

3.1. Introduction

The intake of nutrients into the organism takes place in the digestive tract. Food is broken down in the intestines, becomes water-soluble, and is taken up into the bloodstream. The venous circulation from the intestines (the portal circulation) subsequently takes most of the nutrients to the liver, where they undergo further conversions, and finally enter the venous bloodstream of the liver to be transported to their final destinations.

We will consider the physiological morphology and embryology, blood supply, physiology, regulation, and function, of the liver and digestive tract to gain a view of their characteristic place in the organism.

3.2. Physiological Morphology

3.2.1. Shape of the Liver and Digestive Tract

Intestines

The intestines have a tube-like shape, like the lower respiratory tract as described in section 2.2.1. The lower respiratory tract and the intestines both originate from the primitive gut, but the intestines are not fixed in cartilage or being passively moved like the airways. The intestines are in constant, slow movement, which is mostly active and autonomous, again unlike the movement of the respiratory tract (section 2.4.2.). The shape and position of the different parts of the intestines in the abdominal cavity is dependent on outside influences, such as the tone of the abdominal muscles and the diaphragm, the shape of the spine, the filling of the large abdominal vessels. Surgeons may reposition the intestines after surgery more or less at random. How much this affects the function of the intestines is unknown.

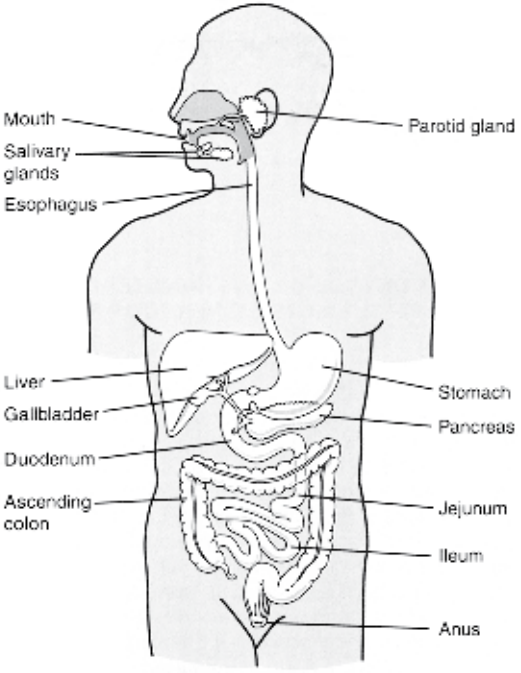


Fig. 3.1. The liver and intestines (from Guyton 2000)

The intestines are connected through and surrounded by peritoneum, which also carries the blood vessels and autonomic nerves.

Liver

The external form of the liver is determined by its surrounding structures. The liver is a large organ, which has impressions of the right kidney, gallbladder, and vessels on its lower surface. The diaphragm determines the shape of its upper surface. The liver is situated on the right side of the abdominal cavity.

The liver is a large, expandable organ that contains more than 10% of the total volume of blood at any moment. It is one of the largest organs of the body, contributing just short of 2.5% of the total body weight, about the same amount as the brain.

➔ *The external shape of the liver and intestines is like the surface of a body of water: everything around it makes an impression on it and the environment determines its form.*

3.2.2. Structure of Liver and Intestines

The Intestines

The intestines have a membrane-like quality with an inner layer of mucosa through which the nutrients enter the organism via the blood vessels just underneath the mucosal

surface. Several layers of smooth muscle cells surround the mucosa of the intestines. In the walls of the intestines lies a plexus of the autonomic nervous system with both sympathetic and parasympathetic fibers, the intramural plexus (fig. 3.7.).

The intestines, like the lower respiratory tract, have special mucosa-associated lymphoid tissue (MALT), which deals with incoming pathogens, since, like the respiratory tract, they interface directly and intensively with the surroundings.

The Liver

The liver is a parenchymatous organ. The main type of functional cell is the hepatocyte. Hepatocytes all appear similar to one another. They make the liver parenchyma look homogenous, and are structured into lobes and lobules. The liver lobule is hexagonal in shape.

The structure of the liver lobule allows a constant, slow stream of blood (both venous and arterial) to pass by each hepatocyte directly. The incoming blood flows from the periphery of the liver lobule into large sinusoids, and slowly moves toward a central venule (fig. 3.4.).

The sinusoids of the hepatic lobule are lined by hepatocytes, endothelial cells, and Kupffer cells. Kupffer cells are cells from the reticuloendothelial system that act as phagocytic macrophages. They are instrumental in removing from the portal blood, among others, a detectable number of coli bacilli from the intestines. A culture of systemic blood does not normally grow any bacteria. The interface of the liver with the outside world becomes visible in such a phenomenon!

Between the hepatocytes originate the bile canaliculi. They lead the bile that is secreted by the hepatocytes to the common bile duct, via the terminal bile ducts and hepatic bile duct. From there the bile either flows directly into the duodenum or is stored in the gallbladder.

The liver parenchyma has a high threshold to pain. Cells in the liver and digestive tract have a strong regenerative capacity.

➔ *The intestines have a membrane-like structure that is more muscular than the respiratory tract and exhibits autonomous motility. The liver is a parenchymatous organ that consists mainly of one type of cell, the hepatocyte.*

3.2.3. Embryology of Liver and Intestines

The intestines develop from the primitive gut. The primitive gut forms in the 4th week after fertilization, when the embryo goes through its lateral folding. Lateral folding results in the formation of the ventral wall of the embryo. Through cranio-caudal growth, a tube is formed which runs through the embryo from top to bottom: the primitive gut, which is lined by parts of the yolk sac (fig. 3.2.). At its cranial end, the lung buds off from the

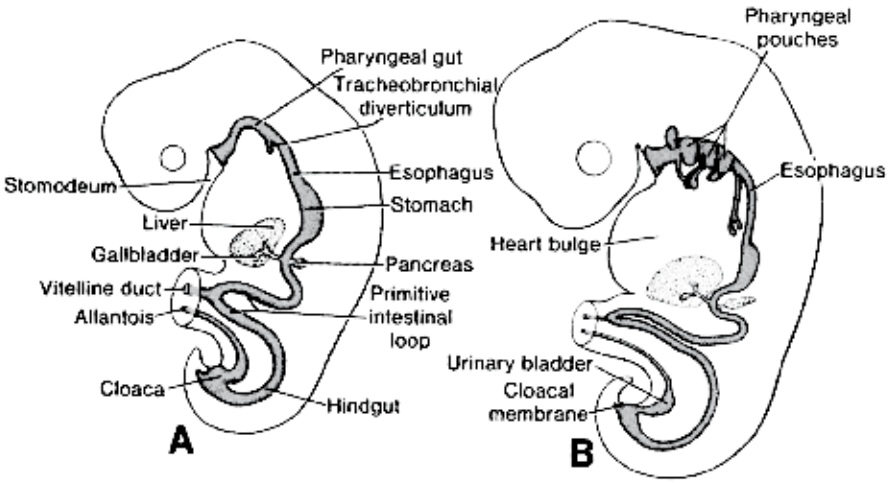


Fig. 3.2. The gastrointestinal tract and liver in the 4th (A) and 5th (B) week of embryological development (from Sadler 1995)

primitive gut; about midway, the liver bud develops into a parenchymatous organ.
During the second trimester of pregnancy, the liver is the main organ for the synthesis of red blood cells. There is also some red cell production in the spleen and lymph nodes at that time. During the first trimester, red blood cells are formed in the yolk sac. During the third trimester, red blood cell development is taken up by the bone marrow. During embryological development, the liver is relatively much larger as compared to the total size of the body.

➔ *The primitive gut gives rise to the lower respiratory tract as well as the intestines and the liver. The latter becomes a parenchymatous organ.*

3.3. Blood Supply to Liver and Intestines

The liver has an ample blood supply. Around one quarter of the cardiac output (27%) is directed toward the liver. This means that 1350 ml of blood flows through the liver each minute. Three quarters of the blood flow through the liver is venous blood that comes from the portal vein, one quarter is arterial blood from the hepatic artery. The two types of blood flow into the liver sinusoids and mix there. Consequently most of the blood flowing through the liver is venous blood, which is low in oxygen saturation.

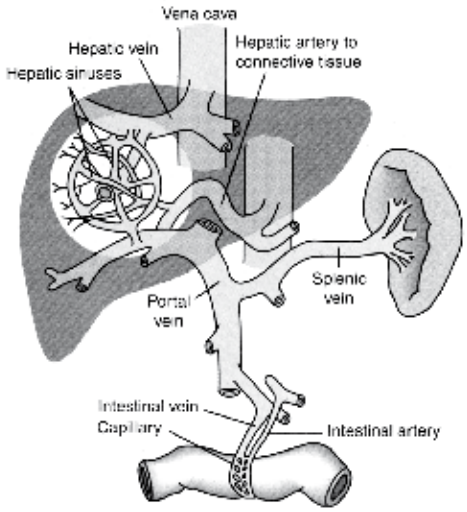


Fig. 3.3. Blood supply to the liver and intestinal tract (from Guyton 2000)

The Intestinal Blood Supply and the Portal Vein

Blood in the portal vein comes from the intestines, spleen, and pancreas (fig. 3.3.).

It carries with it broken-down mostly non-fat nutrients (chiefly carbohydrates and proteins). These have been rendered water-soluble in the intestines and are absorbed into the blood. The countercurrent exchange system between the intestinal arteries and veins allows the portal vein to carry extra oxygen that comes directly from the intestinal arterioles, especially at low flow rates. The *specialized venous blood supply* of the liver through the portal system is unique in the body. There is only one other place where this occurs, namely in the pituitary gland.

The Hepatic Artery

The hepatic artery carries blood that is fully saturated with oxygen from the aorta to the liver. About three-quarters of the oxygen the liver uses comes from the hepatic artery. The liver maintains a nearly constant oxygen consumption level.

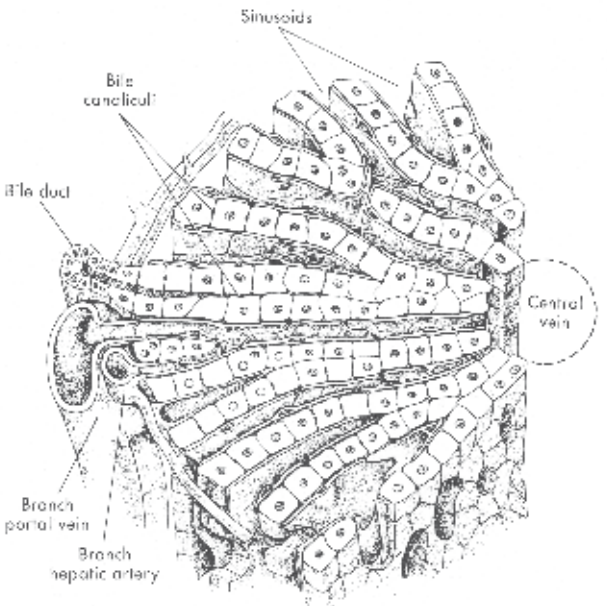


Fig. 3.4. Blood flow in the liver (from Berne 1998)

Blood Flow in the Liver

The two blood streams that flow into the liver empty into the large sinusoids in the liver lobules (fig. 3.4.). They form a thin layer of blood around the hepatocytes. The portal system blood supply and that from the arterial hepatic system vary reciprocally, so that the blood flow to the liver cells is near constant. Only the blood flow in the hepatic artery can be auto-regulated to achieve this.

Under the low pressure-gradient between the sinusoids and the liver veins (the vascular resistance in the liver bed is very low), the nutrients are taken up into the hepatocytes. There are large pores or fenestrae in the

sinusoids, which allow the formation of lymph in the liver in the spaces of Disse. Half of all lymph arises in the liver.

The liver is a large, expandable venous organ and acts as a blood reservoir. In bleeding or in shock, when there is a shortage of intravascular fluid, the liver can expel several hundred milliliters of blood, which it keeps stored. The liver contains 10-15 % of the total blood volume at any one time. The spleen is also a blood reservoir; it can store up to 100 cc of blood at a time. The large abdominal veins may store another 300 cc. Thus the intestinal system may store 650 cc of blood or more. By comparison, the heart and lung only store 75 and 150 cc respectively.

➔ *The liver has the greatest perfusion of blood of all the organs in the body. Its blood supply consists for three-quarters of blood that has low oxygen saturation, which flows to the liver in a specialized venous system (the portal circulation), and one quarter of blood that has high oxygen saturation. The liver capillaries form a thin layer of blood in the sinusoids. The intestines have a specialized countercurrent exchange system. The intestinal organs act as a blood reservoir.*

3.4. Physiology of the Liver and Intestines

3.4.1. Physiology of the Intestines

The different parts of the intestines are specialized in different physiological processes related to digestion, such as moving the food stream along (esophagus), absorption of nutrients in addition to moving the food stream along (small intestines), or excretion in addition to moving the food stream along and absorption (large intestines).

Movement in the intestines is initiated by stretch. The smooth muscle layers of the intestine form a functional syncytium that contracts rhythmically, and normally moves the food in

peristaltic waves from mouth to anus. Stretch makes the unitary smooth muscle cells more excitable, so that superimposed action potentials are generated on top of continuous, spontaneous slow waves. Action potentials are based on the influx of calcium ions, along with some sodium ions, into the cell. They accompany the contraction of the smooth muscle layers (see also section 5.4.2.).

The mucous membrane of the small intestines allows for *passive diffusion* and *active absorption* of nutrients into the blood stream, as well as possibly allowing a *passive* solvent drag (solvents carrying dissolved substances along).

- *Carbohydrate* components like glucose and galactose are absorbed *actively* with the help of Na^+/K^+ ATPase.
- *Protein* constituents are mainly absorbed *actively* by means of a variety of carrier systems, depending on the types of amino acids; mostly this is also a sodium co-transport mechanism. Some amount of whole protein uptake also normally takes place, especially in infancy. When whole protein absorption is increased in adults, it relates to the development of food allergies (Linder 1997).
- *Lipids* are absorbed by *passive* diffusion through the mutual cell membrane since they are soluble in the cell membrane. Lipids are transported in the intestine and disposed of locally by the micelles. Most lipids enter the lymph stream of the thoracic duct in the form of chylomicrons via the endoplasmic reticulum of the mucosal cells. They are deposited into the blood stream where the thoracic and lymphatic ducts empty into the subclavian veins. Some lipids are absorbed directly into the portal blood.

The intestines also play an *active* role in the secretion of myriad local digestive enzymes and hormones that influence the motility of the digestive tract and prepare the foodstuffs for absorption into the body by breaking them down and making them water-soluble. Some important enzymes are pepsin, trypsin, lipase, and amylase. Some important local hormones are gastrin, cholecystokinin, and secretin.

The intestinal tract allows for the nutrients to be taken up into the organism from outside through its membrane-like mucosal structure. It actively moves the food along in peristaltic waves of contraction of its muscular layers, and excretes waste products. Absorption of the

nutrients across the intestinal mucosa is both active and passive. The intestinal tract actively secretes enzymes and hormones for the digestion of nutrients and to increase the motility of relevant parts of the intestinal tract.

3.4.2. Physiology of the Liver

The hepatocytes are a large pool of chemically reactant cells. They have a high rate of metabolism and effect a large number of chemical conversions of the nutrient compounds. The chemical conversions render many compounds more water-soluble and give them the form that is most usable for the body at the time. This may be either a storage form or as an active metabolite. They temporarily absorb and store one half to three-quarters of all absorbed water-soluble nutrients.

Carbohydrates

Much of the metabolic activity of the liver is directed towards carbohydrate (glycogen) storage and reactions like glycogenolysis and gluconeogenesis. The liver has a glucose buffer function for the serum of the blood. It plays an important role in glucose homeostasis since it can convert glucose to glycogen, lipids, or amino acids, as well as vice versa except the direct conversion of lipids to carbohydrates (fig. 3.5.).

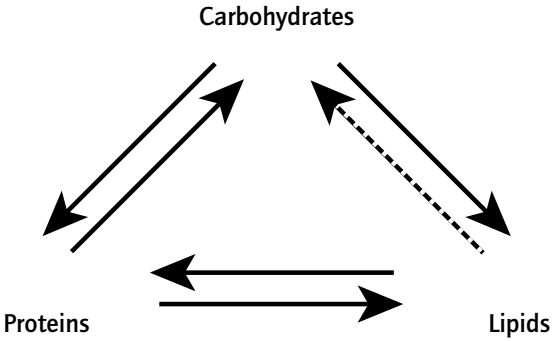


Fig. 3.5. The liver converts carbohydrates to proteins or lipids and vice versa.

Proteins and Amino Acids

Amino acids from the diet are not stored as free amino acids, but as rapidly exchangeable proteins, specifically in the liver. The free amino acid levels of the blood are replenished by the degradation of proteins in the liver. The liver plays a central role in homeostasis by regulating amino acid metabolism.

The liver cells form all plasma proteins, including albumin. One third of the amino acid required in the diet can be accounted for by the synthesis of albumin and other plasma proteins in the liver. Albumin may be a temporary amino acid store and act as a vehicle for transporting amino acids to peripheral tissues to replace daily losses (Linder 1996). The processes of transamination and deamination allow the liver to convert amino acids into other amino acids, glucose, or lipids (fig. 3.5.). Deamination leads to NH_4^+ formation, which is converted to urea for excretion in the kidneys. Essentially, all urea in the body is formed in the liver. Decreased liver function results in high ammonia levels, which impairs consciousness.

The liver is the site where the hemoglobin of the blood is broken down to bilirubin and excreted in the bile.

Lipids

The liver is the site of several specific reactions in lipid metabolism. The liver can synthesize lipids from proteins or carbohydrates. The liver synthesizes phospholipid, cholesterol, and many lipoproteins. Around 80% of synthesized cholesterol is converted by the liver into the more water-soluble bile salts. At the same time, this is the major route of excretion for cholesterol. Thus the liver plays a central role in regulating the serum cholesterol level.

Through ß-oxidation of fatty acids, the liver can supply the organism with energy in the form of ketone bodies. The liver is essential in maintaining lipid homeostasis through its central role in lipid synthesis and catabolism (fig. 3.5.). (For further information on the biochemistry of carbohydrates, proteins, and lipids see also the *Biochemistry Module* of **BOLK**'S COMPANIONS FOR THE STUDY OF MEDICINE)

Bile

The hepatocytes excrete bile. Bile salts account for about half of the solutes in bile. They are the degradation product of cholesterol, and can help both to emulsify the lipids in the gastrointestinal tract as well as aid in their absorption through the formation of micelles. Through the bile, the liver can also directly excrete excess cholesterol as well as bilirubin, the metabolite of hemoglobin. Other constituents of the bile include lecithin and

electrolytes. The gallbladder mainly stores and concentrates the bile. Part of the bile, including cholesterol, is resorbed from the gastrointestinal tract into the portal circulation and thus enters the *enterohepatic cycle* (fig. 3.6.).

Other Physiological Activity of the Liver

The hepatocytes also play a role in storing iron and some vitamins (A, D, B_{12}), excreting calcium through the bile, as well as inactivation, degradation, and excretion of drugs, toxins and hormones.

The liver is characteristically active in physiological processes in metabolic cycles. It plays a role in storage and in maintaining homeostasis.

➔ *The physiology of liver and intestines consists of many active processes.*

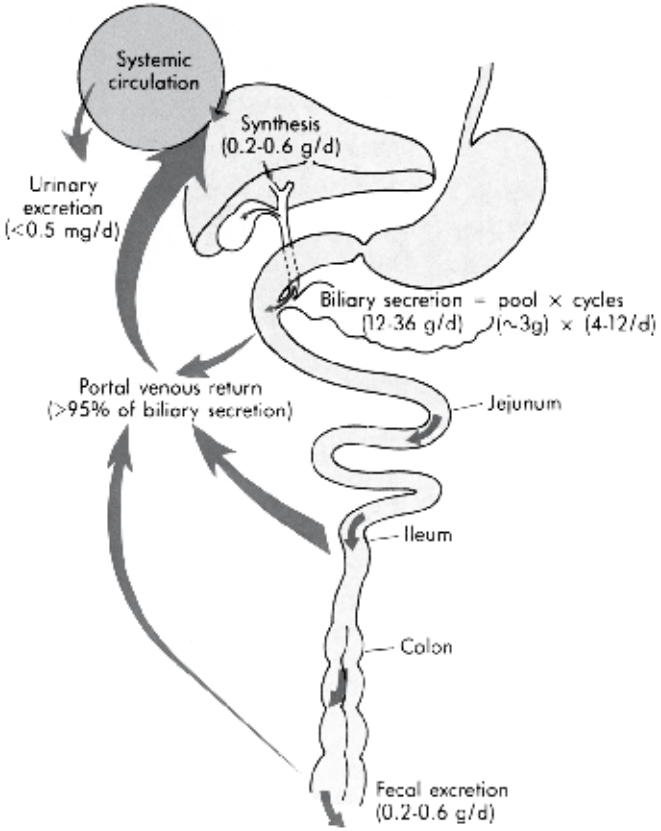


Fig. 3.6. The enterohepatic circulation of bile acids (from Berne 1998)

3.5. Regulation in Liver and Intestines

3.5.1. Intestines

Hormones

Autonomous intestinal functions are regulated locally by the secretions of hormonal substances from the glands in the mucosa through mechanical pressure of the food that enters a particular part of the intestines. Intestinal organs such as the pancreas add digestive hormones such as secretin and cholecystokinin, which stimulate the secretion of bile into the duodenum. Three hormones from the pancreas, glucagon, insulin, and somatostatin, are important in regulating the metabolic functions in the liver. The internal secretion of the pancreas of insulin and glucagon regulates the metabolism of, especially but not exclusively, the carbohydrates in the whole organism. Intestinal hormonal substances are all peptides or derivatives of peptides.

Autonomic Nervous System

Autonomic stimulation and inhibition play an important role in intestinal function. The autonomic nervous system of a particular segment is stimulated by direct contact with the food. The intramural plexus (fig. 3.7.) consists of two systems of plexuses, which both have sympathetic as well as parasympathetic innervation: the *myenteric* plexus mainly regulates movement, the *submucosal* plexus mainly regulates the secretions. The neurons of these plexuses con-

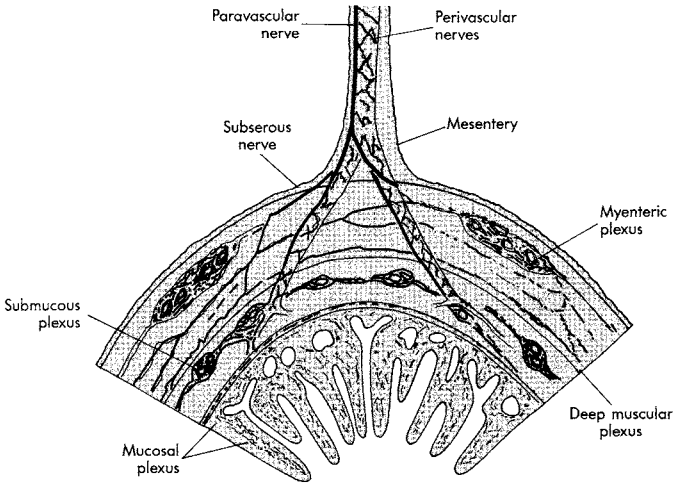


Fig. 3.7. Autonomic innervation of the intestines. (from Berne 1998)

tain many of the neuropeptides (gut-brain peptides) that are found in the central nervous system.

- Parasympathetic stimulation:
  Parasympathetic stimulation mostly stimulates peristalsis, relaxes the sphincters, and stimulates the secretions. Without parasympathetic stimulation, the movement of the intestines becomes very slow. Parasympathetic stimulation can be enhanced by brainstem activity in the *cephalic phase* of regulation at the sight or thought of food. Brainstem activity in the central nervous system is transmitted to the gastrointestinal tract through the vagus nerves. The cephalic phase stimulates salivation and the secretion of gastric and pancreatic juices.
- Sympathetic stimulation:
  Sympathetic stimulation mostly slows the propulsion of food, tightens the sphincters, and inhibits the secretions.

3.5.2. Liver

Mainly local hormones from the gastrointestinal tract such as insulin, glucagon, and somatostatin regulate liver activity. The liver secretes *angiotensinogen*, which can be converted by renin from the kidneys into angiotensin I (see also section 4.5.), which in turn is converted in the lung endothelium to angiotensin II (section 2.4.4.). Angiotensin II is an important regulator of blood pressure.

➔ *Regulation in the liver and intestines is mainly local. The local autonomic nervous system plays an important role as well as local hormonal substances. Some intestinal hormones have a general metabolic function. There is also a cephalic regulatory phase in the stimulation of the vagus nerves by the sight or thought of food.*

3.6. Function of the Liver and Intestines in the Organism

The function of the liver and intestines is to *supply* the organism with nutrients. The physiological processes that underlie this function are active processes, but the function of supplying is itself mainly passive. The intestines facilitate the intake of nutrients and the excretion of fecal matter. The liver *maintains* homeostasis in the metabolic functions of the organism. It *stores* mainly glycogen itself. Also maintaining and storing are basically passive functions (an active process is, for instance, regulating). Liver and intestines also contribute to homeostasis by pooling a significant amount of blood, which can help *maintain* the extracellular volume.

➔ *The function of liver and intestines in the organism is to supply, maintain, and store. These are mainly passive functions.*

3.7. Conclusion

- Morphology:
  In its overall shape, the liver is a large organ that is *passively* formed by its surroundings, like the lungs. The intestines are membrane-like in structure, like the lungs, but are not rigid and exhibit *active* autonomous movements. The liver structure is that of uniform, homogenous parenchyma.
- Blood supply:
  The blood supply of the liver is *the largest* in the body. It has low oxygen saturation like in the lungs, but has mixed arterial and venous blood through the presence of the specialized and *unique venous portal system*. Both lung and liver have a large capillary net that forms a thin layer of blood. The pressure gradient that moves the blood in the capillaries is even lower in the liver than it is in the lungs.
- Physiology:
  The liver and intestines are *active* physiologically, contrary to the lungs, even though all three come from the same embryological tissue (the primitive gut). The liver and intestines transform metabolites to render them suitable for use by the body.

	Lung +	Liver + Respiratory Tract	Kidneys Intestinal	Heart Tract
Morphology	Shape from without, tubular organ, **membranous structure**	Mostly shaped from without, uniform parenchyme, tubular organs		
Blood supply	50% of *weight* is blood, largely O_2 unsaturated, capillary blood in thin film	Largest *flow*, special *venous portal system*, ¼ is O_2 saturated, ¾ has a low O_2 saturation, capillary blood in thin layer		
Physiology	Passive diffusion	**Great activity in metabolic cycles**		
Regulation	Mainly from without, via the central nervous system	Both through local hormones and local autonomic plexuses, some via central nervous system		
Function	Passively supplying	Passively supplying, maintaining, and storing		
Characteristic	Membrane-like tubular structure, *diffusion of gases* (O_2 and CO_2) and water	Physiologically active in metabolic cycles, diffusion and *absorption of fluid nutrients* in tubular part		

- Regulation:
  The liver and gastrointestinal tract are mainly regulated autonomously. Regulation is mostly local, by local hormones and the local autonomic nervous system.
- Function:
  The function of liver and intestines is mostly *passive,* since their function is to supply the organism with the compounds needed in metabolism, store them, and aid in maintaining homeostasis.

➔ *Characteristic for the liver and intestines is that they are active physiologically. The hepatocytes are active in the cycles of metabolism. In structure, blood supply, and function liver and intestines are passive, similar to the lungs. The tubular, membranous structure of the lungs and respiratory tract manifests again as the tubular structure of the intestines, where diffusion and active absorption takes place of fluid nutrients, rather than gases. The parenchymatous nature of the liver is not found in the respiratory tract.*

4. The Kidneys and Urogenital Tract

4.1. Introduction

The kidneys take in large quantities of blood, filter it, and then *reabsorb* most of the ultrafiltrate. A small part of the ultrafiltrate is excreted as waste in the urine. Some substances are actively secreted out of the plasma into the urine. The kidneys secrete hormones and are regulated by hormones.

We will consider the physiological morphology and embryology, blood supply, physiology, regulation, and function of the kidneys and urogenital tract to gain a view of their characteristic place in the organism.

4.2. Physiological Morphology

4.2.1. The Shape of the Kidneys and Urogenital Tract

The kidneys have a characteristic shape, which impresses itself on the surroundings. The caudal surface of the liver carries an imprint of the right kidney, the spleen from the left kidney.

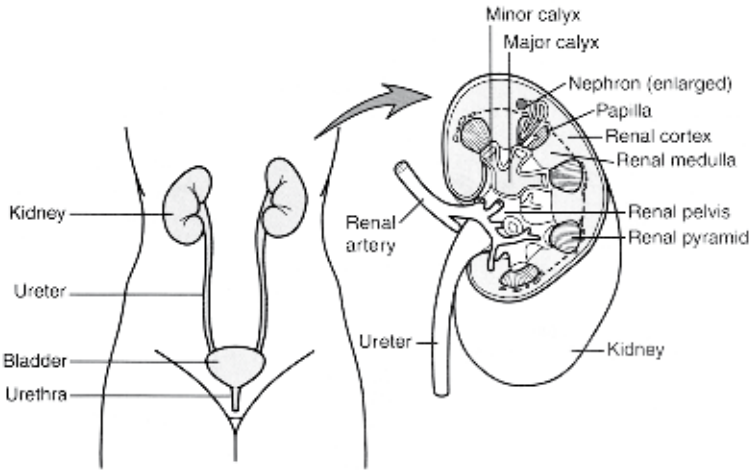


Fig. 4.1. The kidneys and urinary tract (from Guyton 2000)

The kidneys are parenchymatous organs. The

parenchyme is not uniform, but differentiated. Morphologically, two areas may be distinguished on the cut surface of the kidneys: the cortex and the medulla (fig. 4.1.). The outer layer is the cortex. The inner layer of medullar tissue surrounds the renal calyces, where the urine is collected to pass from there to the renal pelvis and then through the ureters to the bladder. From the bladder, unconscious reflexes and conscious relaxation of the bladder neck musculature allow the urine to pass through the urethra and be excreted. The urinary tract is a tube-like organ (fig. 4.1.).

The kidneys are paired and more or less symmetric, and are situated in the upper dorsal abdominal cavity. Liver, pancreas, gallbladder, stomach, and intestines, the prototypical digestive organs of the abdominal cavity, are neither paired nor at all symmetric. They also do not have the differentiation into a cortex and medulla. The adrenal glands, which are situated on top of the kidneys, are also paired organs and have a cortex and a medulla. The other symmetric abdominal organs with a cortex and medulla are the genital organs. The genital organs, like the kidneys, have a differentiated duct structure that allows excretion. Together with the kidneys and adrenals, the genital organs are not situated inside the peritoneum, which surrounds the prototypical digestive organs. The kidneys, adrenals, and genitals lie retroperitoneally, in contradistinction to most of the "typical" abdominal organs.

The clear differentiation of tissue into a cortex and a medulla that we see in kidneys, adrenal tissue, and ovaries and testes, is a characteristic feature of the brain. The brain and the organs of the head and nervous system are paired and/or display symmetry like the kidneys, adrenals, and genitals. In the heart and lung, both organs of the rhythmically active middle area of the body, we find a reminiscence of symmetry, but no differentiation of tissues into a cortex and a medulla. The phenomenon of symmetry is decreasingly present from cranial to caudal. Yet, we find paired, symmetric organs such as the kidneys and genitals in the abdominal region. This may raise questions as to how kidneys, adrenals, and genital organs got there (see section 4.2.3.).

➔ *The kidneys and adrenals (and genital organs) are more similar to the nervous system of the head in their shape than to the other abdominal*

organs. They are retroperitoneal, paired, symmetric organs and display a cortex and medulla in their parenchyme. The firm outer shape of the kidneys impresses itself on neighboring abdominal organs.

4.2.2. The Inner Structure of the Kidneys

The kidneys have a rather complicated and intricate inner structure (fig. 4.1. and 4.3.). The renal functional units, more than a million nephrons, are located partly in the cortex, partly in the medulla. The nephrons have four structural and functional parts. The *glomerulus* is the place where the filtration occurs to form the ultrafiltrate (180 L/day). The other three parts, the *proximal tubule*, *Henle's loop*, and the *distal tubule with collecting ducts*, mainly serve the reabsorption of constituents from the ultrafiltrate. The secretion of compounds from the plasma directly into the urine takes place in the tubules. Urinary output is approximately 1.5 L/day.

The Renal Cortex

The cortex is the place where the glomeruli are located. Glomeruli consist of a tuft of capillaries inside the bowl- or vessel-shaped end of the urinary tubules: Bowman's capsule. The filtration barrier between blood vessels and urinary tubules has three constituents:

- the capillary membrane with fenestrae (=holes, windows), similar to the sinusoidal pores or fenestrae in the liver
- the basement membrane with large spaces
- the podocytes of Bowman's capsule with large slits between them.

The filtration barrier allows the passage of small compounds, which includes water and electrolytes, and somewhat larger compounds such as glucose and urea. The negative charge of the proteins in the capillary membrane, the basement membrane, and the podocytes of Bowman's capsule repels compounds which are themselves also charged negatively. It prevents many proteins from passing the filtration barrier, even when they are small enough. The filtration barrier in the kidneys filters 100x more water and solutes than usual capillary membranes.

The juxtaglomerular apparatus is also situated in the cortex. It consists of:

- mesangial cells, which provide structural support, secrete extracellular matrix, and may act as phagocytes. The phagocytes indicate that the kidneys also have an interface with the world outside the organism
- granular cells, which produce renin, prostaglandins, and cytokines
- the macula densa, which registers changes in the NaCl concentration in the distal tubule.

The juxtaglomerular apparatus plays a major role in the auto-regulation of the blood flow to the kidneys (see also section 4.5.).

In the glomeruli an intricate passive filtration system has developed, as compared with the basic diffusion capability of the lungs. The juxtaglomerular apparatus in the cortex regulates blood flow to the kidneys.

The Medulla

Proximal tubules, Henle's loops, and distal tubules with collecting ducts are chiefly situated in the medulla.

The epithelium lining the renal tubules has specialized membrane proteins on the urinary side and/or the blood side that allow active transport of specific compounds in specific areas (see also section 4.4.). In the proximal tubules, $^2/_3$ of the filtered sodium and water is reabsorbed. In Henle's loop, the urine is concentrated and another $^1/_4$ of sodium and $^1/_6$ of water is reabsorbed. In the distal tubules and collecting ducts, the fine-tuning of the consistency of the urine and of the plasma is achieved. Secretion of substances from the plasma into the urine occurs in the proximal and distal tubules. These processes result in an inner structure of the medulla in which the fluid osmolality changes from the area close to the cortex to the area close to the renal calyces. The osmolality in the medulla increases fourfold from the cortex side (300 mOsm/L H_2O) towards the calyx (1200 mOsm/L H_2O) (see section 4.4.3).

In the highly specialized cells of the tubular system in the medulla of the kidneys, selective reabsorption takes place. This is more developed and has a reverse direction of the substrate stream as compared to the absorption in the intestines. A physiological differentiation of the medulla in the form of a fourfold increase in fluid osmolality is present.

➔ *The inner kidney parenchymatous structure has become more differentiated as compared to the liver. The differentiation is anatomical as well as actively physiological.*

4.2.3. Embryology

Pronephros

The kidneys are formed from intermediate mesoderm, which is dorsally situated, next to the developing nervous system. The first beginnings of the kidneys appear early in the 4th week of embryological development in the *cervical* region. The so-called pronephros obliterates after a few days, before it is ever functional as an excretory organ (fig. 4.2.).

Mesonephros

The next kidney system, the mesonephros, is formed in the area of the *thoracic* vertebrae. It includes glomeruli and excretory ducts, and may function for a brief period. The excretory ducts develop from

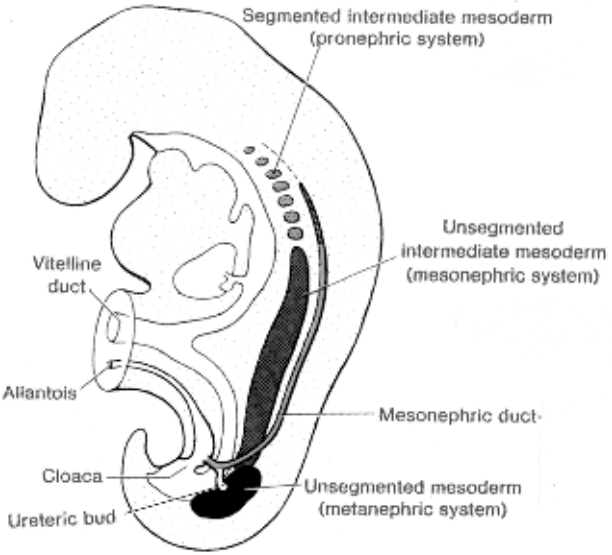


Fig. 4.2. Development of the kidneys in a 5 week old embryo (from Sadler 1995)

outgrowths of the intraembryonic coelom, which grow toward the developing glomeruli. The gonads develop directly medially to the mesonephros on either side of the body on the urogenital ridge. During the second month, the mesonephros also obliterates, except for some of its duct system. The Wolffian ducts persist in males to form some of the excretory system of the male genital tract. The Müllerian ducts form main components of the female genital system.

Metanephros

The third embryological kidney system is the metanephros, and it is permanent. It forms in the *lumbosacral* region of the intermediate mesoderm from the 5th week onward. It starts to develop when the ureteric buds, bilateral outgrowths from the mesonephric ducts, grow towards the metanephrogenic mesoderm, forming the renal pelvis, the calyces, and the collecting tubules. The ureteric buds *induce* the formation of the glomerulus, specifically Bowman's capsule, in the metanephrogenic mesoderm. The bowl- or vessel-shaped Bowman's capsule and a tuft of capillaries together develop into the glomerulus. The metanephros, or definitive kidney, becomes functional at the end of the first trimester.

This phylo- and ontogenetical "descent" of the urogenital tract is followed by an embryological "ascent", in which the kidneys move cranially from a low lumbosacral (pelvic) location to their final location, high up and dorsal in the abdominal cavity at the level of the lower thoracic vertebrae. Their retroperitoneal position indicates that they are not part of the "typical" abdominal organs.

The kidney and genital systems are originally (also phylogenetically) formed much more cranially than their final location in humans. A descent takes place, followed by a partial ascent of the kidneys. The ureteric buds actively induce the formation of glomeruli.

➔ *The cervical onto- and phylogenetic origin of the kidneys, adrenals, and genital systems close to the nervous system goes hand in hand with their similarity to the brain in structure and symmetry.*

4.3. Renal Blood Supply

The renal artery from the aorta supplies the kidneys with oxygen saturated blood. The blood flows through afferent arterioles to the glomeruli, and from there through efferent arterioles to the rest of the nephrons (fig. 4.3.). From there it collects in the venous system. Renal blood flow is 1100 ml/min, or 22% of cardiac output. The kidneys constitute only 0.4% of total body weight.

Renal blood flow is normally constant in spite of differences in arterial pressure between 90 and 180 mm Hg. This is the result of autoregulation by the juxtaglomerular apparatus and a pressure-sensitive, myogenic mechanism in the afferent arterioles. Different hormonal substances influence renal blood flow, such as epinephrine and angiotensin II.

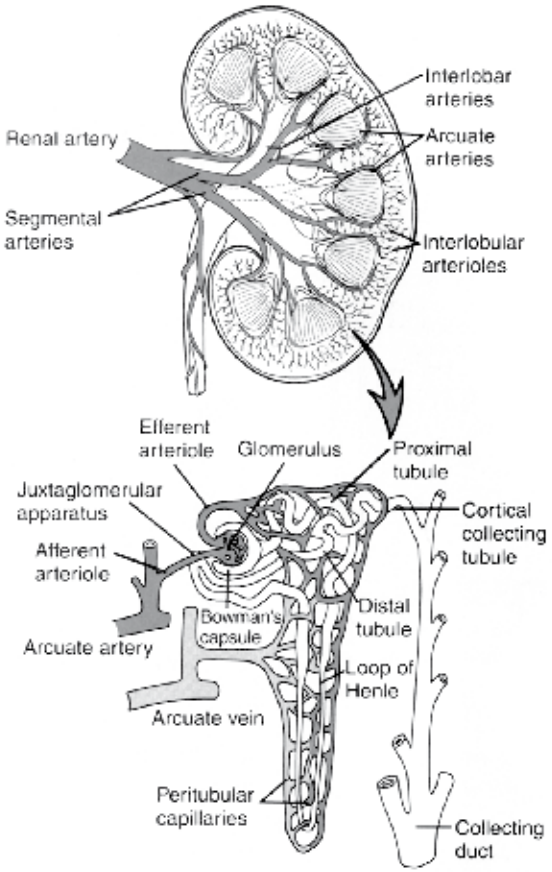


Fig. 4.3. The blood supply of the kidneys (from Guyton 2000)

➔ *The kidneys have the second greatest perfusion of blood in the body after the liver. They have a specialized arterial system, which forms afferent and efferent arterioles to and from the glomeruli. In contradistinction to the lungs and liver, blood supply to the kidneys is saturated with oxygen. Blood flow is regulated by autoregulation as well as by hormonal influences.*

4.4. Physiology of the Kidneys

Each tubular segment has various subsegments that differ anatomically and/or functionally from one another. The effect is that tubular fluid composition varies at different locations in the nephron. The resorption of every substance is linked in some way to the activity of the sodium-potassium ATPase system (see section 4.4.2.). The activity of active resorption consumes much ATP, which is supplied from metabolic energy. Therefore tubular activity requires a large supply of oxygen, which is provided by the blood in the efferent arterioles.

4.4.1. The Glomerulus

The blood is filtered in the glomerulus. The glomerular filtration rate follows renal blood flow, and is 20% of renal plasma flow or approximately 180 L/day. Most of this is obviously reabsorbed, since urine output averages 1.5 L/day. Resorption takes place in the tubular system. Ultrafiltration in the glomerulus happens under the influence of Starling forces, namely hydrostatic and oncotic pressure differences between the blood and the lumen of Bowman's capsule. Ultrafiltration is principally a *passive* process and does not take much energy. The oxygen from the oxygen-saturated blood in the afferent arterioles does not get used up and is available for physiological processes in the medulla.

Glomerular filtration is a passive process.

4.4.2. The Proximal Tubule

Resorption

- Sodium, bicarbonate, chloride, and water:
  In the proximal tubule, Henle's loop, and the distal tubule, 99.5% of Na^+ is resorbed, mainly through the action of sodium-potassium ATPase, an enzyme in the basolateral membrane of tubular cells. This is an *active* transport mechanism, which is accompanied

by the *passive* movement of other compounds such as $HCO3^-$, Cl^-, and water. Sodium and water are the two substances that are resorbed most abundantly in the tubular system. Almost all of the sodium is resorbed *actively*, all of the water is resorbed *passively*. The hormone angiotensin II stimulates Na^+ resorption, dopamine release from the local dopaminergic nerves inhibits Na^+ resorption in the proximal tubules.

- Albumin:
  The ultrafiltrate contains 7 grams of albumin/day (out of 50,000 g/day that pass through the glomeruli), which is *actively* reabsorbed in the proximal tubule, almost none is excreted with the urine.
- Glucose:
  Glucose is normally completely reabsorbed in the proximal tubule. An *active* transporter brings it into the cell, it leaves the cell passively to enter the blood again.
- Lactate and inorganic phosphate:
  Lactate and inorganic phosphate are also *actively* resorbed in the proximal tubules. Most of these resorption mechanisms are co-transport systems with Na+.

Secretion

Organic end products of metabolism and exogenous organic compounds, such as drugs and pollutants that were not filtered, are selectively secreted from the plasma into the urine in the proximal tubule. This is an *active* process.

In the proximal tubules the active resorption of sodium allows many other substrates to be resorbed in co-transport systems or to diffuse passively. Sodium resorption is actively regulated through hormones here. There is some active secretion.

4.4.3. Henle's Loop

The Countercurrent Mechanism

Henle's loop may span the whole depth of the medulla. Here the urine is concentrated by an ingenious countercurrent mechanism (fig. 4.4.). This may concentrate the urine from the normal plasma osmolality of 300 mOsm/L in the area close to the cortex, fourfold to 1200 mOsm/L in the medullar area close to the calyces. This is coupled with the fact that the ascending limb of Henle's loop is impermeable to water, and sodium and potassium can be further *actively* resorbed, along with *passive* diffusion of other solutes such as calcium and magnesium. This may effectively decrease the concentration of the filtrate to 100 mOsm/L. *The intricate structure of Henle's loop allows for regulation of the concentration of the urine.*

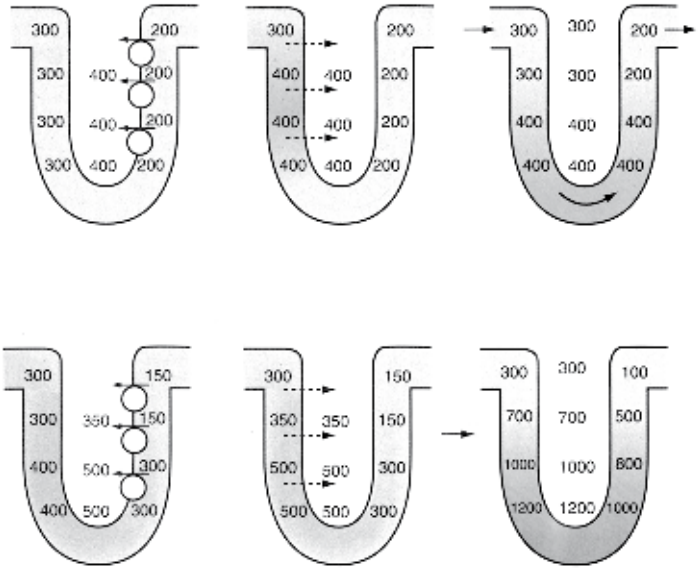


Fig. 4.4. The principle mechanisms of the countercurrent multiplier system in Henle's loop (from Guyton 2000)

Urea

The concentrating ability of the urinary system is highly enhanced by the presence of urea in the ultrafiltrate. Urea contributes about 40% of the osmolality of the medulla (fig. 4.5.). Urea is *passively* reabsorbed, mostly in the collecting ducts. The thick ascending limb of Henle's loop and the distal tubule are impermeable to urea, whilst the collecting ducts are quite permeable for urea and the thin descending and ascending limb sections are somewhat permeable to it. The subsequent high concentration of urea in the medulla allows for its recirculation and high urea concentrations in the urine. Consequently,

individuals on a high-protein diet have a greater ability to concentrate their urine.

The concentrating ability in Henle's loop is achieved by differentiated permeability to various substances, especially water and urea. The osmolality of the medulla, and consequently the concentrating ability of the kidneys, is dependent on the concentrations of sodium and urea.

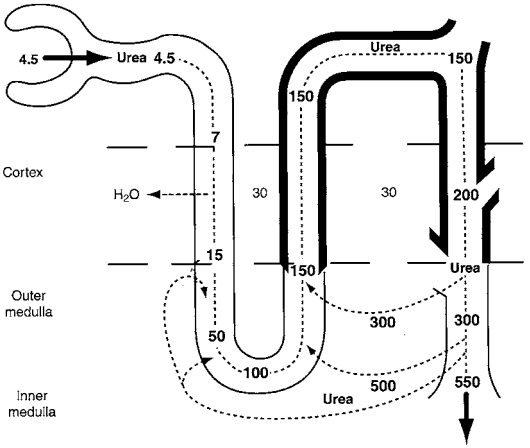


Fig. 4.5. Urea recirculation contributes to the osmolality of the medulla and the urea concentration in the urine (from Guyton 2000)

4.4.4. Distal Tubules and Collecting Ducts

Hormonal Regulation

The resorptive capacity is more limited in the distal and collection ducts, but a fine-tuning of the urine concentration and composition can be achieved here with the help of hormonal regulation, which is specifically *active* in this area. Different hormones regulate sodium reabsorption, including adrenal aldosterone and atrial natriuretic peptide from the heart. Hypothalamic antidiuretic hormone (ADH) is the major factor in regulating water resorption in the distal tubules and collecting ducts. The concentrating capacity of Henle's loop is indirectly influenced by the action of ADH on the distal tubules and collecting ducts, since it determines the amount of water resorption into the medullary interstitium. Sodium and water resorption mechanisms regulate the extracellular volume of the organism. Quantitatively, the selective reabsorption of substances is the major activity of the kidneys that uses up most of the oxygen in the efferent arterioles.

Hormonal regulation in the distal tubules and collecting ducts achieves fine-tuning of the consistency of the urine and blood plasma.

4.4.5. Acid-Base Balance

The kidneys also play a major role in maintaining the acid-base balance in extracellular fluids. The acid-base balance is maintained with the help of extensive buffer systems. The most important buffer is the CO_2/HCO_3^- (bicarbonate)-system.

Plasma buffer systems react immediately, for instance to a lowering of the pH, but do not have the ability to get rid of excess hydrogen ions. The *lungs* can excrete CO_2 to influence a return of the pH to normal. The respiratory response is just a bit slower than the immediate response of the buffer systems, and only partial, since it cannot return the pH to normal when the cause of the acid-base imbalance lies outside the respiratory tract (effectiveness is 50-75%). The *kidneys* respond most slowly, over days by supplying extra buffering capacity to the plasma and excreting H^+ ions, but are 100% effective. Thus the kidney system is by far the most powerful regulator of the pH of the blood in chronic acid-base imbalances.

HCO_3^- formation in the kidneys is stimulated by the enzyme *carbonic anhydrase*, and occurs when there is excess CO_2 in the circulating blood (fig. 4.6.). With the excretion of an H^+ ion to the urine, an HCO_3^- ion is added to the plasma, increasing its buffering capacity. The H^+ is added to ammonia and excreted as $NH4^+$ in the urine (the ammonia buffer system). This is the most important route for excreting excess acid. An increase in plasma H^+ stimulates the renal metabolism of glutamine to release NH_3.

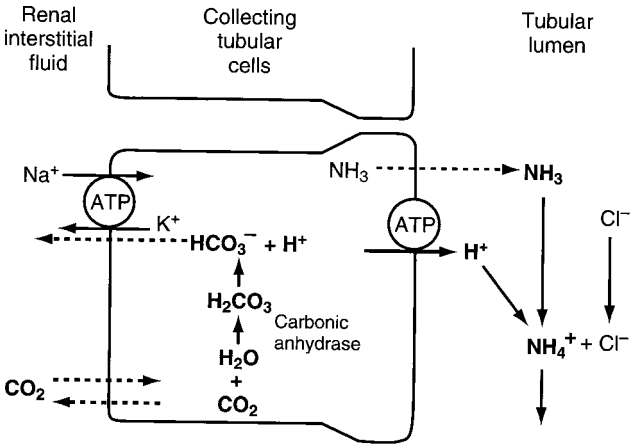


Fig. 4.6. The buffering of hydrogen ions by the bicarbonate buffer system in the collecting duct cell and ammonia io the urine. For each hydrogen ion in the urine a bicarbonate molecule enters the plasma (from Guyton 2000)

The pH of the blood is maintained primarily by the activity of the kidneys, with the help of the release of ammonia from amino acid breakdown and, through the same process and at the same time, HCO_3^- is added to the plasma for extra buffering capacity. The regulation of the pH of the blood is strongly dependent on the production of ammonia.

➔ *Kidney physiology consists of both active and passive processes. These regulate the extracellular volume of the organism and the pH of the blood. Kidney physiology is closely connected to the metabolism of proteins and amino acids.*

4.5. Regulatory Activity in the Kidneys and Adrenals

4.5.1. Regulation of Kidney Activity

Autoregulation in the Kidneys and Sympathetic Control

Renal blood flow is not normally regulated by arterial blood pressure but through the *activity* of various local and systemic hormones. Yet an acute increase in blood pressure of 30-50 mm Hg will increase sodium excretion 2-3 times by means of the phenomena of *pressure diuresis* and *pressure natriuresis*. These two processes are key to the kidneys' regulatory function in regard to body fluid volume and arterial pressure. This basic regulatory mechanism, which is also present in some of the lowest of vertebrates, is expanded in the human organism to include hormonal control for greater precision.

The *juxtaglomerular apparatus* plays a major role in basic regulation of kidney activity. It *perceives* kidney functioning through the macula densa, which registers changes in the NaCl concentration in the distal tubule, and effects *auto-regulation* of the blood flow to the kidneys through the hormones produced in its granular cells: renin, prostaglandins, and cytokines.

The blood vessels in the kidneys have a rich innervation by sympathetic autonomic nerve fibers. They only play a role in regulating kidney activity for a brief period following severe,

acute disturbances such as ischemia of the brain or severe hemorrhage. The sympathetic nerves in the kidneys secrete dopamine as well as norepinephrine. Norepinephrine release from sympathetic nerves stimulates NaCl and water reabsorption; dopamine from dopaminergic nerves has the opposite effect and inhibits NaCl and water resorption.

Hormonal and Enzymatic Control in the Kidneys

- The renin-angiotensin system:
  An especially powerful mechanism is the renin-angiotensin system (fig. 4.7.). A fall in arterial pressure causes the release of renin from the juxtaglomerular cells. Renin is an enzyme that acts on a liver produced substance, angiotensinogen, and splits off the

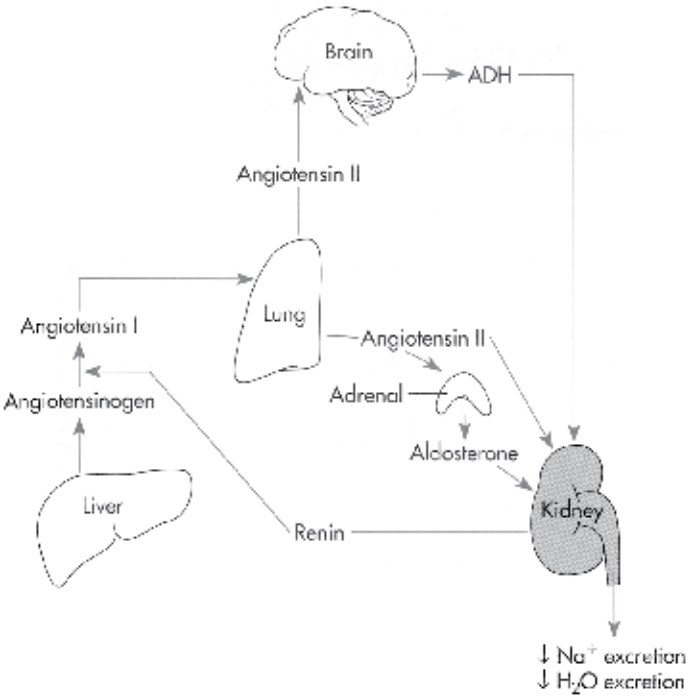


Fig. 4.7. The renin-angiotensin-aldosterone system (from Berne 1998)

decapeptide angiotensin I. In the endothelium of mainly the lung capillaries, angiotensin I is converted to the octapeptide angiotensin II by the angiotensin converting enzyme (ACE) that is present there. Angiotensin II acts on the proximal tubules, increasing the resorption of salt and water, as well as having a direct powerful vasoconstrictive effect on the arterioles. Both mechanisms act to increase arterial pressure back to normal. Conversely, an increase in sodium intake in the diet will lower the level of renin secretion and thus of angiotensin II, which will effect a decrease of the sodium and water reabsorption and a subsequent increased sodium loss through the urine.

- Aldosterone:
  Angiotensin II also stimulates the release of aldosterone from the glomerulosa cells of the adrenal cortex (fig. 4.7.). Aldosterone is a powerful stimulator of NaCl reabsorption in the thick ascending limb of Henle's loop, the distal tubules, and the collecting ducts.
- Atrial natriuretic peptide (ANP):
  Atrial natriuretic hormone is secreted by the cardiac atria. A rise in blood pressure and an increase in effective circulating volume stimulate its secretion by stretching the atrium. It enhances the excretion of NaCl and water in the collecting ducts, and thus has an opposite effect from angiotensin II and aldosterone.
- Antidiuretic hormone (ADH):
  Antidiuretic hormone is the only major hormone that directly influences the amount of water that is excreted by the kidneys. It is produced in neuroendocrine cells in the hypothalamus, and a stimulus from osmoreceptors in the hypothalamus effects their release by the posterior pituitary. The osmoreceptors act in response to an increase in the osmolality of the plasma or a decrease in effective circulating volume.
- Carbonic anhydrase:
  The passive buffer system for maintaining the acid/base balance is activated by the enzyme carbonic anhydrase (fig. 4.6.).
- Erythropoietin:
  Erythropoietin stimulates red blood cell formation. The kidneys produce 90% of circulating erythropoietin, the other 10% comes mainly from the liver. Hypoxia is the principal factor stimulating erythropoietin production. When the kidneys are dysfunctional or absent, patients will be anemic.

Regulation of volume control by the kidneys is basically internal and is fine-tuned by hormones that arise in the kidneys and adrenals, or come from outside, like angiotensin II, ADH, and ANP. The pH is regulated by the local enzyme carbonic anhydrase. Erythropoietin stimulates erythropoiesis.

4.5.2. Adrenal Hormones

In the adrenal cortex, the corticosteroids are produced, including the mineralocorticosteroids, cortisone, and sex hormones. In the adrenal medulla, epinephrine is produced. These hormones have a regulating function, not only with regard to the kidneys and genital tract, but also for many vegetative functions in the body such as are influenced by the vegetative nervous system. The adrenal hormones cortisone and epinephrine help us deal with stress. Embryologically, the cells of the adrenal medulla originate in neural crest cells. Hormones from the pituitary gland of the central nervous system (ACTH and the gonadotropic hormones) stimulate cortisone and sex hormone production in the adrenal cortex.

The adrenal hormones regulate the functions of organs in the abdomen that are morphologically related to the adrenal gland (section 4.2.1.), such as kidneys and genitals. They also influence vegetative nervous system functions in the whole organism, and are regulated in part by hormones from the pituitary gland in the central nervous system.

➔ *Regulation of kidney activity is both internal and through hormones, which come from outside. The kidneys also produce hormones that affect related activities and erythropoiesis. The adrenal hormones regulate the activity of the kidneys and genitals and are related to nervous system functions.*

4.6. Kidney Function in the Organism

The function of the kidneys is to *actively* contribute to homeostasis in the organism by regulating the effective circulating volume and its osmolality as well as the pH of the extracellular fluids. The kidneys have an *active* auto-regulation system in the tubulo-glomerular feedback system to effectuate this, as well as an extensive hormonal control system that fine-tunes the volume and osmolality of the plasma, and an extensive buffer production system to regulate the plasma pH.

➔ *Kidney function in the organism is characteristically active, and is influenced through hormones partly from inside, partly from outside the kidney system.*

4.7. Conclusion

- Morphology:
  The kidneys have their *own strong form*. Their differentiated inner structure (cortex and medulla), as well as their pairedness and symmetry, reminds us of the structure of the brain. This becomes understandable from their phylo- and ontogenetic origin in the cervical region.
- Blood supply:
  Blood supply to the kidneys is *abundant and saturated with oxygen* to support their activity of reabsorption in the tubular part of the nephrons. The kidneys have a *unique arterial supply* in the afferent and efferent arterioles of the glomerulus.
- Physiology:
  Glomerular filtration is a *passive* process. The *active* tubular reabsorption processes are centered around sodium, water, and urea. Protein metabolism plays an important role in kidney physiology.
- Regulation:
  A broad scale of *active* regulating mechanisms is available to effect kidney activity. Plasma volume control is effectuated through regulation of sodium and water

	Lung + Respiratory Tract	Liver + Intestinal Tract	Kidneys + Urogenital Tract	Heart
Morphology	Shape from without, tubular organ, **membranous structure**	Mostly shaped from without, uniform parenchyme, tubular organs	Own active form, differentiated parenchyme with cortex and medulla, tubular parts specialized	
Blood supply	50% of *weight* is blood, largely O_2 unsaturated, capillary blood in thin film	Largest *flow*, special *venous portal system*, 1/4 is O_2 saturated, 3/4 has low O_2 saturation, capillary blood in thin layer	Second largest flow, *unique arterial system*, high O_2 saturation, capillaries in tufts	
Physiology	Passive diffusion	**Great activity in metabolic cycles**	Both active and passive processes	
Regulation	Mainly from without, via the central nervous system	Both through local hormones and local autonomic plexuses, some via central nervous system	Both local and external hormones and buffering processes, kidneys secrete regulatory hormones for functions in organism	
Function	Passively supplying	Passively supplying, maintaining, and storing	**Actively regulating the internal milieu of the organism**	
Characteristic	Membrane-like tubular structure, *diffusion of gases* (O_2 and CO_2) and water	Physiologically active in metabolic cycles, diffusion and *absorption of fluid nutrients* in tubular part	Active regulatory function in the organism, diffusion and *resorption of blood constituents* in tubular parts	

reabsorption by the combined action of brain, liver, lung, and heart with the kidneys. Acid-base balance in plasma is regulated through enzymatic activity.

- Function:
  Kidney function is characteristically *active in regulating* volume, osmolality and pH of the extracellular fluid. Hormones fine-tune the regulatory activity of the kidneys.

➔ *The kidneys are active in their morphology, physiology, and function. Morphology and physiology are supportive of kidney function. Most characteristic of the kidneys is their active, hormone regulated function. The tubular functions are highly specialized as compared to the functions of the respiratory tubular-shaped areas and the tubular shaped intestines. The kidney parenchyme is differentiated as compared to the homogenous liver parenchyme. The capillaries in the kidneys form tufts.*

5. The Heart and Circulation

5.1. Introduction

The heart and vessels contain the moving blood. The heart and vessels are in rhythmic motion. They contribute to the movement of blood. The vessels are distributed over the whole body. At the same time they are a very differentiated system, which is formed differently in different organs and areas, related to the needs of the tissues in question and their function.

We will consider the physiological morphology and embryology, blood supply, physiology, regulation, and function, of the heart and circulation to gain a view of their characteristic place in the organism.

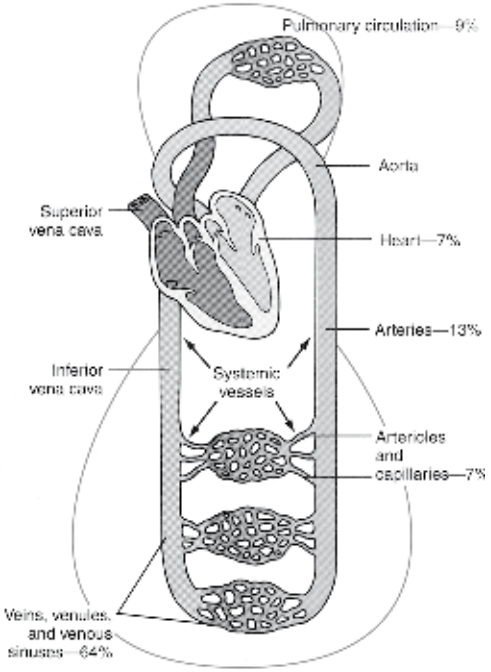


Fig. 5.1. The heart and the pulmonary and systemic circulation. The two circulations with the heart at the center together form a lemniscate (adapted from Guyton 2000)

5.2. Physiological Morphology of the Heart and Circulation

5.2.1. The Shape of Heart and Circulation

The heart and vessels are hollow, tubular-shaped organs. However, their tubular shape does not result from folding the disc-shaped embryo into a tubular shape, which is the basis of respiratory and digestive tract development, nor from outgrowths of the intraembryonic coelom like in the kidney system, but the tubular

lumen arises anew during embryological development (see section 5.2.3.).

The Circulation

The vessels build an intricate branching system, becoming ever smaller the closer they come to the functioning tissue. In the tissue itself, the three billion capillaries of the human body become so small that the blood content (especially the blood cells) can only just move through them. In the capillaries, the vessels have their smallest diameter. There are a great number of capillaries in every body tissue. The blood flow to the capillaries is supplied by the arterial system and leaves the tissue by way of the venous system.

Two separate circulations may be distinguished in the circulation, which each originate in the heart, go to the target organ(s), and then return back to the heart (fig. 5.1.):

- The oxygenated blood in the *systemic circulation* flows from the left side of the heart to all tissues of the organism. From there, the blood, which is now low in oxygen saturation, flows back to the right side of the heart
- The blood that has low oxygen saturation flows from the right heart via the *pulmonary circulation* through the lungs, where the blood is oxygenated, and from there the blood flows back to the left side of the heart.

The circulation could be seen to have two foci: one of the foci is in the capillaries, which are supplied by arterial blood and from whence the venous blood leaves. The heart is the other circulatory focus. The circulation consists of two circuits, the systemic and pulmonary circulations.

The Heart

In the heart, the vessels have their largest diameter, both internally and externally. The heart is approximately as big as our fist, and the vessels are arranged such that the two circulations meet there. The vessels of the two circulations lie alongside each other near the heart and cross each other (see fig. 5.1.).

The heart has four chambers, two atria and two ventricles (fig. 5.2.). The four chambers are separated by the interatrial and interventricular septa between atria and ventricles

respectively, and a fibrous skeleton (the base of the heart) between the atria and the ventricles that holds the four valves and is suspended from the large vessels, aorta and pulmonary artery. The tricuspid and mitral valves, on the right and left side of the heart respectively, are in the outflow tracts of the atria into the ventricles. The ventricles also have valves in their outflow tracts, on the right side the pulmonary valve to the lung circulation, on the left the aortic valve to the systemic circulation. The muscle fibers of the ventricles arise from the fibrous skeleton such that the ventricles are suspended from the large vessels.

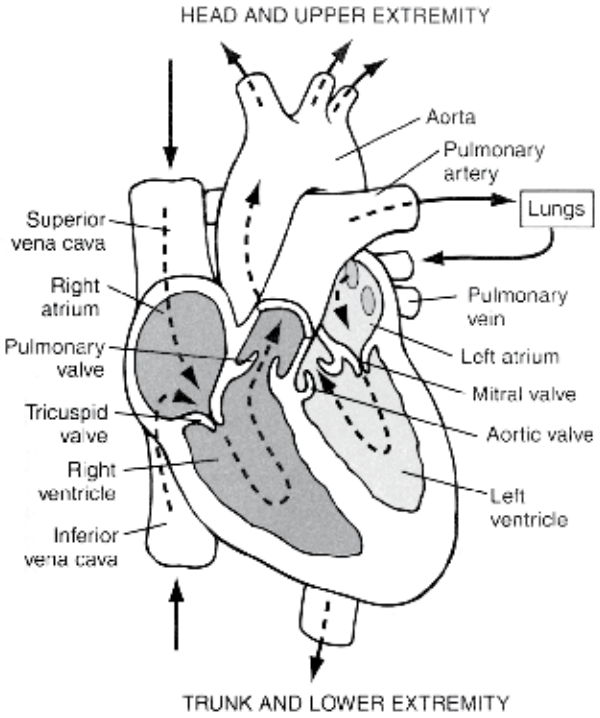


Fig. 5.2. Blood flow in the heart (from Guyton 2000)

In the systemic circulation, blood flows through the superior and inferior caval veins to the right atrium and leaves the right ventricle through the pulmonary artery of the pulmonary circulation. The pulmonary circulation empties through the right and left pulmonary veins into the left atrium and the blood leaves the left ventricle through the aorta to the systemic circulation. This means that these two circulations intersect and that the blood flow makes a somewhat complicated *figure-eight or lemniscate* shape as it passes from the one into the other circulation (see fig. 5.1.).

The shape of the heart is actively formed; the lungs develop around it. The heart is suspended from the large vessels and rests on the diaphragm.

5.2.2. Structure of the Heart and Vessels

Blood in the vessels is contained in endothelium. True capillaries are devoid of smooth muscle fibers. In the larger vessels, one or more smooth muscle layers surround the endothelium. These are especially developed in the arterial circulation and culminate in the heart, where, instead of smooth muscle cells, more differentiated heart muscle tissue develops. The heart muscle cells actually form a functional syncytium of branching and interconnecting striated muscle fibers. The smooth muscle cells and heart muscle cells in heart and circulation are arranged in spiraling or circular layers. Cardiac muscle forms a double spiral that has fibrous septa between the spiraling layers (fig. 5.3.). Ventricular muscle is thicker than atrial muscle, and the left ventricle is thicker than the right. The muscle layers in the ventricles are thickest at the base of the heart, where the outflow tracts are located. At the apex of the heart the layers are very thin. The heart is surrounded by the epicardium and pericardium. The coronary vessels are situated in subepicardial tissue. *Phylogenetically*, the heart develops from two types of heart muscle tissue, trabecular and compact myocardium. In fish, we find only trabecular tissue. It receives its blood supply from sinusoids, and there are no coronary vessels. From the amphibians

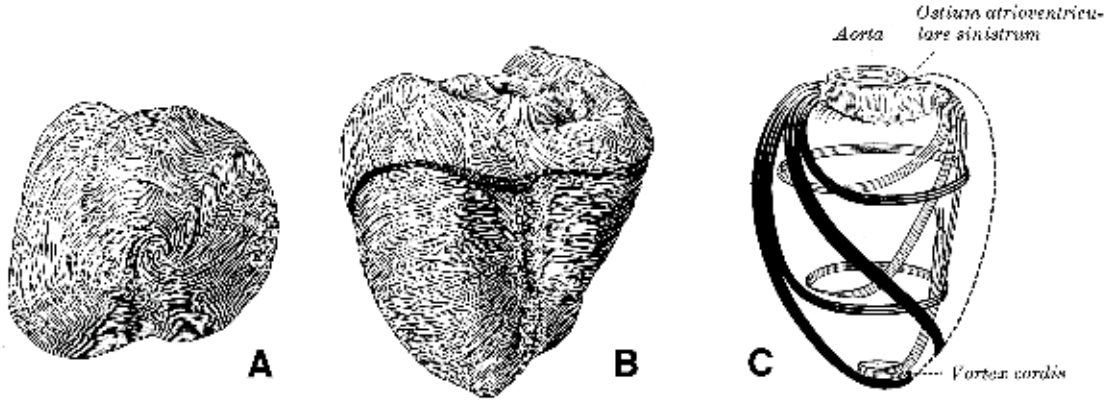


Fig. 5.3. The double spiral layers of heart musculature from the apex (A) and from a dorsal view in which the superficial spiral layer is partially removed (B), and a schematic representation of the spiral layers of the left ventricle (C) (from Benninghoff-Goerttler 1967)

onwards, compact myocardial tissue starts to develop around the trabecular tissue and with it coronary vessels form. The thebesian vessels (section 5.3.) are leftovers from the sinusoids. In vertebrates that move more actively and in those that are larger in size, the thickness of the compact layer becomes relatively greater. This allows a greater blood pressure and more tone in the circulation. Only humans have just compact myocardium.

The valves in the fibrous skeleton at the base of the heart are made up of endothelium covered fibrous tissue and move *passively*. The fibrous skeleton with the fibrous heart valves and the fibrous septa between the spiraling layers in the heart form a structural basis and create areas of relative rest in this organ that is constantly moving. The heart is not a tubular organ in the true sense of the word, neither is it a parenchymatous organ in the true sense of the word. The tubular-shaped lumen develops *de novo* (section 5.2.3.) and the "parenchyme" consists of actively moving muscular tissue.

The smooth muscle cells of the circulation and the morphologically more differentiated heart muscle cells have a spiral or circular configuration. The heart muscle cells form a functional syncytium of striated heart muscle fibers that is in constant, rhythmic motion. The fibrous parts are passively moved along and give the heart a structural basis.

5.2.3. Embryology

Angioblasts

At the start of the 3rd week of embryological development, the pericardial cavity becomes visible above the cephalic area of the embryo (fig. 5.5.). Capillary-size vessels are the first to appear in the embryo from day 17 on. They originate from angioblasts that are also the forerunners of blood cells.

Angioblast cells develop in the mesenchyme of the wall of the yolk sac, and the lateral sides of the splanchnic mesoderm layer. They initially form islands of isolated cell clusters, which soon begin differentiating (fig. 5.4.). The central cells of the blood islands become round and give rise to the primitive blood cells; the peripheral cells flatten and form the

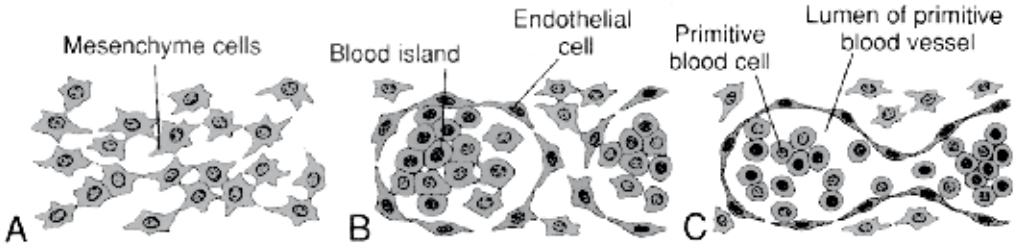


Fig. 5.4. The differentiation from mesenchyme cells (A), to angioblasts (B), and blood and vessel formation (C) (from Sadler 1995)

endothelial lining around the blood cells. The endothelial cells of different blood islands grow towards each other, fuse, and form the lining around the newly created lumen of first capillaries.

Blood and vessels originate from the same angiogenic tissue in much the same way that the embryo and its surrounding sheaths develop from the same tissue during the morula stage (see also the *Embryology Module* of **BOLK**'S COMPANIONS FOR THE STUDY OF MEDICINE). Then too, the compaction of the peripheral cells and their eventual flattening designates them as trophoblast cells, which are the forerunners of the *surrounding* embryological sheaths, in contradistinction to the *central, round* embryoblast cells. The embryoblast cells are the last ones to differentiate, and become the developing embryo itself. The central blood cells in the angiogenic areas also differentiate later and slower than the vessel walls.

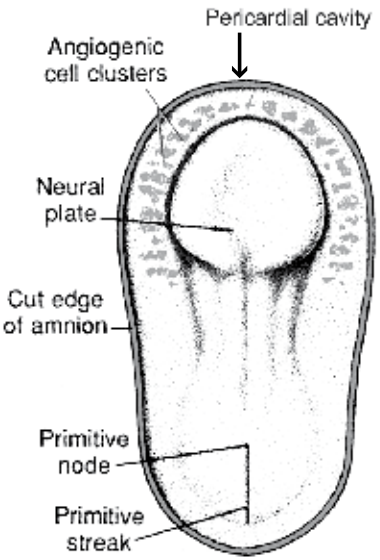


Fig. 5.5. The horseshoe shaped plexus of angiogenic cells and the position of the pericardial cavity (adapted from Sadler 1995)

In a next phase, blood islands also start to form on the cephalic end of the embryo. The capillaries on the lateral sides of the embryo and the cephalic capillaries grow to form a horseshoe-shaped plexus of small vessels around the developing embryo (fig. 5.5.). Blood is already moving in this plexus, possibly aided in its movement by the factors that also influence the slow, rhythmic vasomotion in adult vessels (see section 5.4.1.). At the cephalic bend of the horseshoe the plexus is called the cardiogenic area. The rapid growth of the central nervous system over the cardiogenic area in a cephalic direction results in the *relative descent* of this area from a location above the future head (fig. 5.5.) to the cervical and finally the chest region (see figure 5.6. and also section 4.2.3.). It becomes enclosed in the

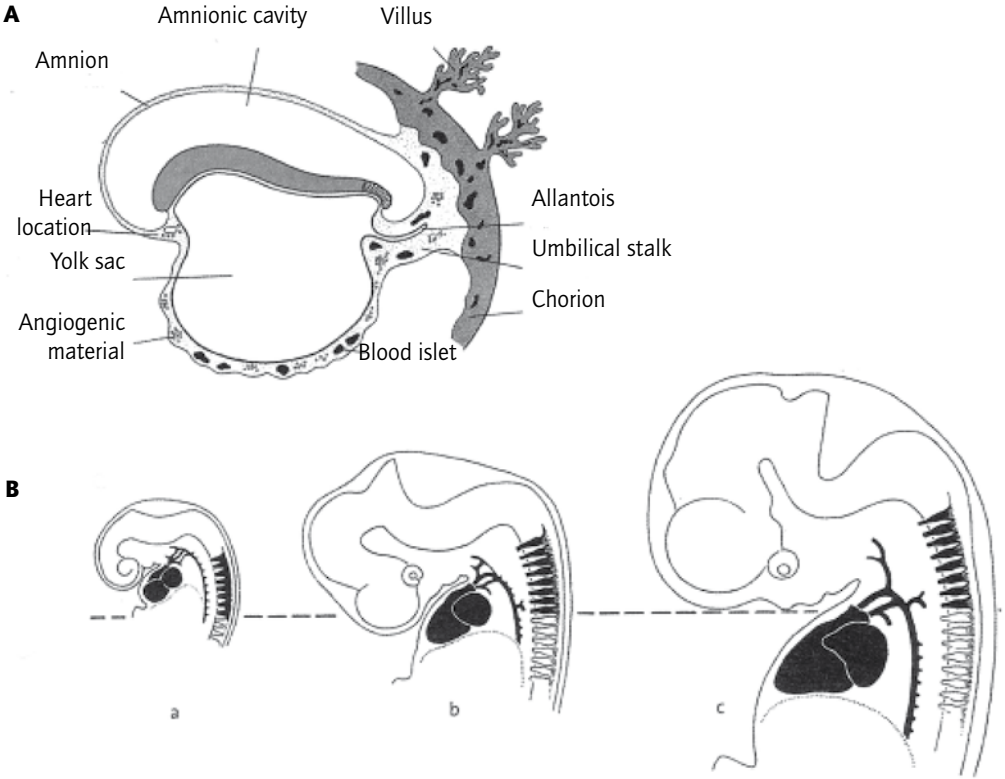


Fig. 5.6. The descent of the heart. A: Heart location in the embryo on day 19 (after Langman, 1995). B. Descent of the heart on day 29, 42, and 48 (Hinrichsen1990)

chest when the embryo folds laterally and the lateral sides fuse together anteriorly immediately after (see figure 5.6.). Initially the heart and vessels develop as a *paired, symmetric system* (see also section 4.2.1.); on day 21 the heart vessels and parts of the circulatory vessels have become fused.

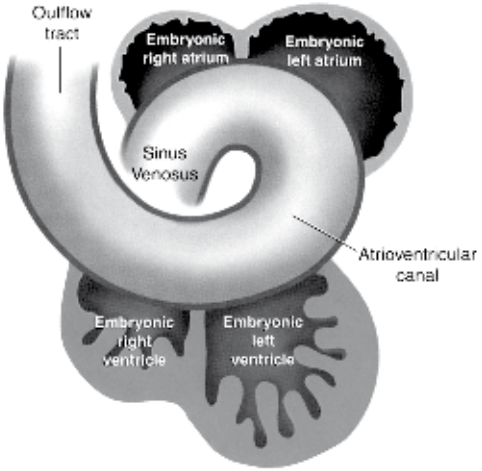


Fig. 5.7. The human embryonic heart at 4 weeks of development showing the primary heart tube with ballooning atria and ventricles (Moorman 1999)

The Cardiogenic Area

The morphological development of the heart is an autonomous process, independent of the environment. The cardiogenic area in the crescent part of the horseshoe expands and forms the cardiac loop, the forerunner of the primary heart tube, from which the future atria, ventricles, and outflow tracts develop. The cardiac loop bulges more and more into the pericardial cavity. Ballooning expansions from the primary heart tube will form the future atria and ventricles (fig. 5.7.). Research into the origin of the ballooning and the formation of septa in the primary heart tube seems to indicate that the placement of the ballooning expansions may be determined by the flow of blood through the primary heart tube (Moorman 1999 and 2000). Where the blood runs into the walls these start to balloon; outside the tract of the flow of blood, the septa develop (fig. 5.8.).

Embryologically, the *coronary arteries* originate epicardially, in the tissue surrounding the left ventricle. During heart development, they grow toward their final point of origin in the area behind the cusps of the aortic valve.

The heart is the first organ to form and function in the developing embryo. Other examples of how the flow of blood in heart and vessels initiates changes in shape are apparent at birth (see 5.4.1. The heart). Then the closure of the umbilical vessels is followed by an

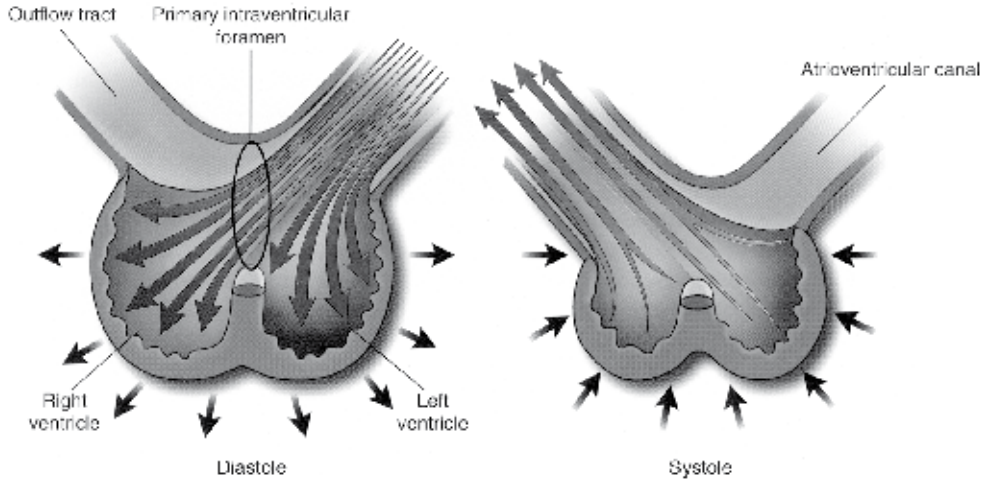


Fig. 5.8. Blood flow through the embryonic heart in diastole and systole. In diastole, blood to the right ventricle flows through the interventricular foramen, in systole blood from the left ventricle flows through the interventricular foramen (from Moorman 1999)

abrupt functional closure of the foramen ovale between the atria, as well as the closure of the ductus venosus, which had until then diverted the portal blood from flowing through the liver. Closure of the umbilical vessels and cessation of the large placenta circulation results in an acute increase in systemic vascular resistance. However, the foramen ovale also closes when the umbilical circulation is not abruptly halted. The aeration of the lungs decreases vascular resistance in the pulmonary circulation. The consequent change in flow between the atria and in the ductus venosus results in their direct functional closure, which eventually becomes anatomical. The ductus arteriosus also experiences a reversal of flow, yet its closure after birth seems to be related to increased oxygenation of the blood in the ductus.

The blood and vessels develop from the same angiogenic tissue, which is originally located at the periphery of the embryo. At first, capillaries develop and form a horseshoe shaped plexus. The heart forms in the crescent of the horseshoe as a symmetric, paired organ, and

becomes the most developed part of the vessels. The developing heart descends to its final location through growth of the central nervous system. Blood flow may have an effect on the final shape of the heart.

5.3. Blood Supply for Heart and Circulation

The heart has its own, separate blood supply, the coronary system (fig. 5.9.). The coronary circulation, in which 4-5% of the cardiac output flows, supplies the heart with blood. The right and left coronary arteries originate in the recession behind the cusps of the aortic valve. Blood flows in them during the relaxation phase (diastole) of the heart, in contrast to the systemic circulation, where blood flow is strongest during the contraction phase (systole) of the heart. During contraction of the heart, blood flow in the coronary arteries comes to a standstill and may even reverse at the end of systole.

The major determinant of coronary flow is the metabolic activity of the myocardium. Increased metabolic activity decreases coronary resistance and thus increases flow and vice versa. Only $^{1}/_{10}$th of a millimeter of the endocardial surface thickness receives its nutrients directly from the blood in the heart chambers.

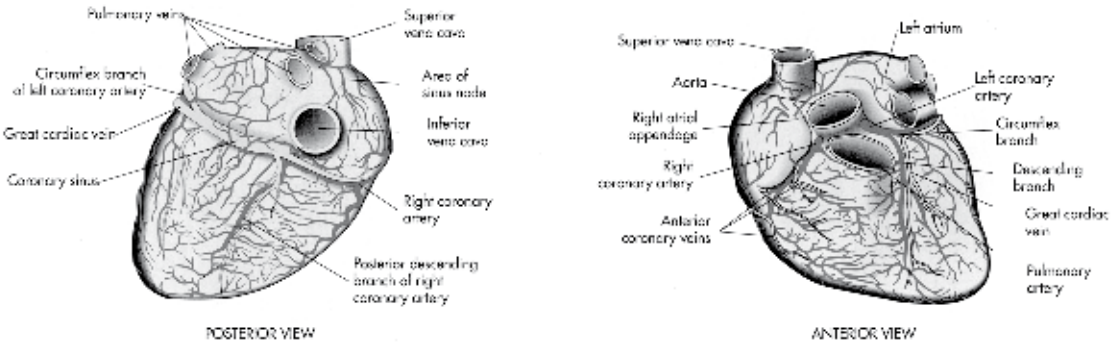


Fig. 5.9. The coronary vessels (from Berne 1998)

The right coronary veins empty into the right atrium directly, the left coronary veins empty into the coronary sinus first. A small amount of the blood can enter the heart chambers directly through the thebesian veins (see also section 5.2.2.) and the arteriosinusoidal and arterioluminal vessels.

The coronary vessels of cold-blooded animals have a thin inner layer of endothelial tissue. In warm-blooded animals, the endothelium becomes thicker. In humans, the endothelium thickness reaches 33% of the total vessel wall thickness, which makes it equal to the thickness of the two other vessel wall layers, the muscular layer and the layer with blood vessels and nerves around the vessels. Each of these three layers comprises 33% of the total wall thickness in humans. Plaque formation and myocardial infarction occurs in the endothelial layer and is specific for humans.

The larger arteries also have their own blood supply. The small vessels can receive their nutrients directly from the blood that flows through them.

The heart has its own special circulation, in which the blood flows when the heart is in its rest phase and blood flow slows down in the pulmonary and systemic circulation; and in which the blood comes to a standstill when the pulmonary and systemic circulation have the greatest flow. This reversal is a phenomenon that is essential for the existence of rhythm. In rhythm the direction of the flow needs to be reversed constantly in order to elicit the back and forth of rhythmicity. It shows that the heart is the archetype of rhythm.

5.4. Physiology of Heart and Circulation

5.4.1. Blood Flow in Heart and Circulation

The Capillaries and Arterioles

Blood flow in the capillaries occurs *rhythmically*, even before the heart is functional. The rhythm is relatively slow, turning on and off every few seconds or minutes. The rhythmical oscillatory movement in the capillaries is accompanied by rhythmic contraction and

relaxation of the musculature of the precapillary vessels. This phenomenon is called *vasomotion*.

Vasomotion is a mostly autonomous movement and is autoregulated. Smooth muscle fibers in the whole circulation are excitable and discharge electrical impulses. In the precapillary vessels, the rhythmical electrical discharge is accompanied by contraction of the smooth muscle fibers (section 5.4.2. Smooth muscle cells). The flow of blood in the capillaries can be enhanced by local metabolic requirements. Changes in the local metabolic needs causing a decreased oxygen concentration will result in an increase in the duration and frequency of flow through the capillaries. Another factor that may influence the flow through the capillaries is the activity of the erythrocyte membrane. The erythrocyte cell membrane has very special characteristics and can roll along the hemoglobin in the cell. Special proteins serve as connecting compounds both on the inside and on the outside of the erythrocyte cell membrane to allow greater plasticity of the membrane form. This gives the erythrocyte cell membrane both more form stability as well as making it more flexible in form. The erythrocyte shape adapts itself to fit in the capillaries; the rolling membrane allows the erythrocyte to move like a caterpillar through the capillaries (Busse 1982).

Diffusion in the capillary bed
In the capillaries, many of the constituents of the blood such as nutrients, electrolytes, and blood gases diffuse *passively* from the plasma to the tissues and back. The thermal motion of water molecules and dissolved substances in the blood drives the diffusion. Water-soluble substances move 80x faster through pores in the capillary membrane to the tissue interstitial space than the plasma moves through the capillary. Lipid-soluble substances such as O_2 and CO_2 can diffuse directly through the lipid membrane. The rate of diffusion is proportional to the concentration difference of the substance between the interstitial space and the capillary lumen.

Vasomotion is an observed autonomic movement of blood accompanied by contraction of precapillary vessels. Local metabolic needs and the rolling capacity of the erythrocytes through the capillaries influence capillary blood flow. Exchange of substances between

capillary lumen and tissue happens by diffusion driven by the thermal motion of water molecules.

The Heart

The heart muscle also contracts and relaxes *rhythmically*, at a rate of approximately 72 times per minute in rest. The rhythmic self-excitatory activity of the arterioles becomes further developed in the heart, where two specific areas rhythmically discharge electrical impulses faster than the other cells of the functional syncytium. The sinus node (or sinoatrial node) in the right atrium discharges at the fastest rate and therefore normally overrules the discharges in the atrioventricular node (a-v node), which is situated at the transition of the right atrium to the right ventricle. The impulses of the sinus node set the rhythm for the contractions of the heart muscle fibers at 72 beats/minute. The contractile strength (contractility) and the rate of the heart are determined largely by the venous return of blood from the circulatory periphery (see section 5.5.). The heart uses ketone bodies from the metabolism of lipids for its energy supply.

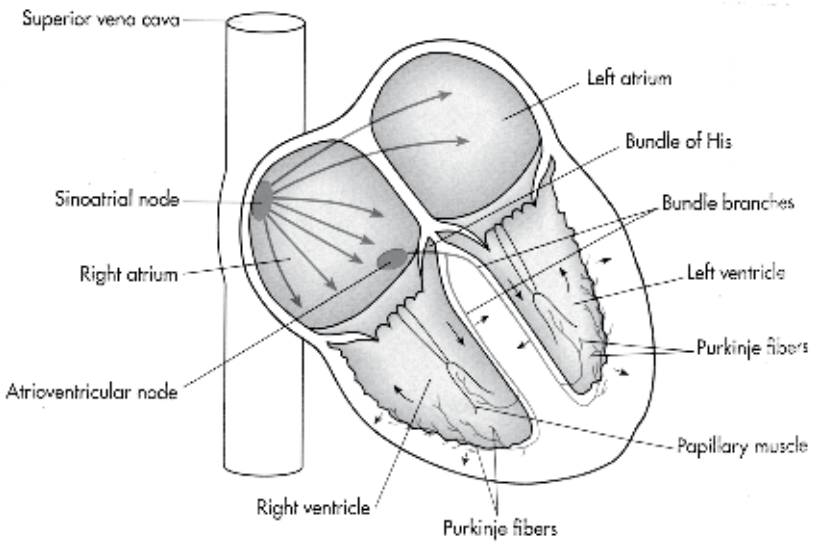


Fig. 5.10. The conduction of the nodal impulse throughout the myocardium (from Berne 1998)

Between the nodes and from the sinus node into the left atrium and from the a-v node into both ventricles, specialized myocardial cells conduct the electrical impulse to reach all heart muscle fibers at approximately the same time (fig. 5.10.). The functional syncytium of heart muscle fibers is directly connected to the cells of the sinus node and a-v-node, and to the specialized fibers that conduct the electrical excitatory impulse throughout the heart. The electrical impulse moves to the epicardial surface of the myocardium along the direction of the spiraling layers (Guyton 2000).

Contraction of the ventricles starts at the apex. However, at the base of the heart, where the outflow tracts start, the muscle layers are thickest and contraction is strongest. If the spiral arrangement of the heart muscle layers would result in a spiral contraction pattern and this would give a spiral shape to the blood stream out of the ventricle, then the thickness of the muscle layers at the base of the heart and the thin apex would be physiologically logical (see Kilner 1993, 2000, 2002).

The *four valves* of the heart aid in maintaining the direction of the flow. Yet the direction of flow is largely maintained even in the face of mitral insufficiency, when the mitral valve between left atrium and left ventricle does not close properly. A much greater than expected volume of blood takes its normal course out of the left ventricle into the aorta in such situations, rather than flowing back into the left atrium. All valves open and close *passively*. Of the blood in the heart about 50% is oxygenated and 50% non-oxygenated.

The centrally located heart is a completely active, rhythmical organ. The quality of rhythmic, self-excitatory activity of the arterioles is especially developed in the heart. The smooth muscle cell functions of rhythmic excitability, conduction, and contraction are taken up and perfected by three differentiated cell groups in the heart, the sinus and a-v nodes, the conducting fibers (including the Purkinje fibers in the ventricles), and the myocardial cells, respectively. The heart valves aid the direction of the blood flow.

The Large Arteries

Contraction of the heart ejects the blood out of the heart into the large arteries. These have muscular walls which can dilate and contract to control the flow of blood. During the

contraction phase of the heart, the aorta dilates to accommodate the rushing in of ejected blood. During diastole, the aortic wall will contract as a result of elastic recoil, and the blood will be aided on its way to the periphery as the arterial walls convert the potential energy of stretch into blood flow. The pressure in the aorta is higher than in the left ventricle after the rapid ejection phase of the heart. Yet this reversal of the pressure gradient does not result in the return of blood to the ventricle during the last part of the ejection of blood from the ventricle because of the momentum of the blood itself.

After the blood has passed through the arterioles, the fluctuations in flow from cardiac contractions ceases, and blood flow becomes dependent on autonomous mechanisms.

The flow of blood in the large arteries is partially dependent on the momentum of the blood itself, which it is given in the heart and which is enhanced by the elastic recoil of the smooth muscle layers of the arteries. In the arterioles the cardiac impulse is more evened out, and the blood moves with a slow, rhythmic flow through the capillaries.

The Veins

Blood flow in the veins is dependent on the flow of blood through the organs, which is determined by the metabolic requirements of tissues. It is enhanced by the contraction of muscles around the veins and by the valves in the veins. The sum of venous blood flowing back from the tissues to the heart is the *venous return*. It is the main determinant of heart rate and contractility (see section 5.5).

Venous return is determined by the metabolic requirements of the peripheral organs and tissues and in turn determines heart activity.

➔ *Blood flow in the heart and circulation gets its determining impulse from the metabolic needs of the tissues.*

5.4.2. Electrophysiology of the Smooth Muscles and the Myocardium

The muscle cells in vascular walls are smooth muscle cells. All muscle cells - skeletal muscle, heart muscle, and smooth muscle cells - contain thin actin and thick myosin filaments. Shortening of the fibers by sliding of the actin and myosin filaments alongside each other is associated with the contraction of muscular tissue (fig. 5.11.).

Smooth Muscle Cells

The amount of actin is 5-10 times greater than the amount of myosin in smooth muscle cells. Due to the special arrangement of actin and myosin, smooth muscle fibers can contract to 20% of their length, whereas skeletal fibers can contract up to just 70% of their length. On the other hand, smooth muscle cell contraction is slow, yet it may be prolonged and develop high forces with low ATP usage, due to the slow metabolic cycling of the myosin cross bridges with actin. Thus, the force of contraction is great in smooth muscle, but the rapidity of contraction is slow compared to skeletal muscle. Skeletal muscle contraction, however, can be consciously controlled, in contradistinction to smooth muscle or heart muscle contractions. The influx and transport of Ca^{2+}, which is much slower than sodium transport and therefore can contribute to the slow but sustained contraction, generates the action potential in the smooth muscle cells of vascular tissue. The action potential allows the calcium influx to increase and spreads the impulse over a larger region. Graded changes in the membrane potential of the sarcolemma may accompany changes in force of contraction. Sodium participates only little in generating the action potential in smooth muscle.

In the smaller arterioles the smooth muscle fibers exhibit automaticity, because they are self-excitatory. These smooth muscle fibers have the property of generating basic slow wave rhythms in the cell membrane potential that act as pacemaker waves (section 5.4.1. The capillaries and arterioles).

The Myocardium

The *muscle cells* of the heart appear striated, like skeletal muscle, due to the arrangement of actin and myosin filaments. The ratio between actin and myosin is 2:1. The duration of

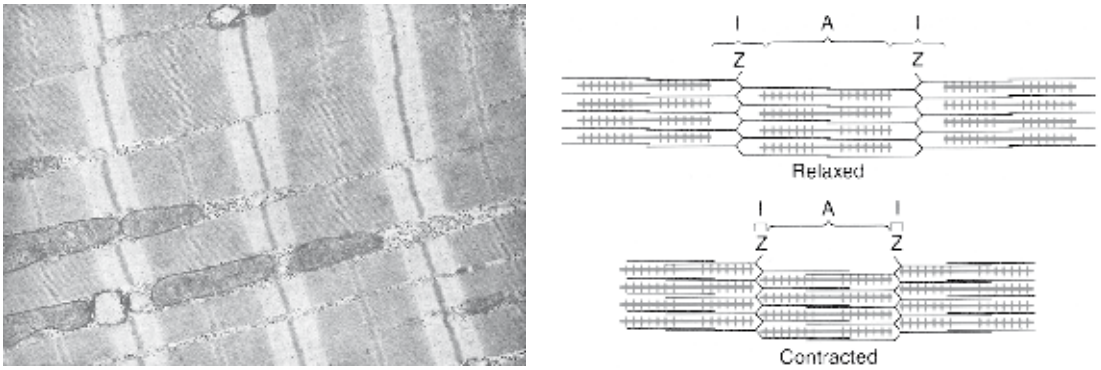


Fig. 5.11. Electron micrograph of myofibrils and schematic representation of the placement of actin filaments (light lines) and myosin filaments (dark lines) in contraction and relaxation in striated muscle (from Guyton 2000)

contraction in cardiac muscle is also longer than in skeletal muscle. The specialized excitatory muscle cells in the sinus and a-v nodes hardly contract but have rhythmicity and generate the action potentials that induce the rhythmical beating of the heart. The action potential in cardiac *muscle* is due to opening of fast sodium channels as well as slow calcium channels. By comparison, skeletal muscle cells operate solely under the influence of fast sodium channels. The fast sodium channels cause a phase of rapid depolarization (a few 10,000ths of a second); the slow calcium channels sustain and prolong polarization (several 10ths of a second). There is excitation/contraction coupling in the myocardium, like in skeletal muscle, and unlike in smooth muscle. The self-excitatory effect of the *nodal cells* is related to the constant slow leaking of sodium during relaxation, which lays the basis for the next action potential. The fast sodium channels are not operative in these cells. The actual quantity of sodium that enters the cell is so small that it does not affect the intracellular sodium concentration. The action potential in skeletal muscle is also based on sodium influx and transport, like the action potential in the nerves that innervate skeletal muscles.

➔ *Smooth muscle cells are the most primitive muscle cells. Their electrical activity is*

mainly based on calcium metabolism. Cardiac muscle cells differentiate and specialize to take on the different functions of self-excitation, conduction, and contraction. Their electrical activity is chiefly based on calcium transport in muscular tissue and sodium transport in nodal tissue. Skeletal muscles have the most specialized and most developed muscle cells. They can be moved consciously, with the help of the nervous system, in contradistinction to smooth muscle and heart muscle. Their electrical activity is mainly based on sodium transport. Cardiac muscle takes in a middle position between smooth muscle and skeletal muscle.

5.5. Regulation in Heart and Vessels

5.5.1. The Heart

The Frank-Starling Mechanism and Regulation of Heart Rate

Regulation of the flow of blood through the heart is normally almost entirely done by an intrinsic mechanism, the Frank-Starling mechanism (fig. 5.12.). This mechanism implies that venous return to the heart controls the force of contraction of the ventricles. Venous return also regulates the rate of firing of the sinus node through stretching of the atrial wall. The stretching of the ventricles and atria, through increased filling as venous return increases, results in an increase in the amount of blood that is ejected by the heart through increased contractile strength and increased heart rate.

Venous return to the heart is dependent on the return of blood from the tissues. Each peripheral tissue controls its own blood flow and venous return to the heart is the total of all local blood flow to the right atrium.

Autonomic Influence

Heart rate and contractility can also be modified by the autonomic nervous system. Sympathetic stimulation increases cardiac output by increasing both heart rate and force of contraction. Parasympathetic stimulation mainly decreases the heart rate. When the

heart is denervated, as is the case in heart transplant patients, cardiac reaction to stress is still quite adequate. This demonstrates the autonomous nature of the heart and the effectiveness of the Frank-Starling mechanism. *Intrinsic regulation of cardiac output through venous return is the main determinant of heart activity.*

Temperature

Contractility and heart rate are also regulated by temperature. In fever the contractility is greater and the heart rate may be doubled.

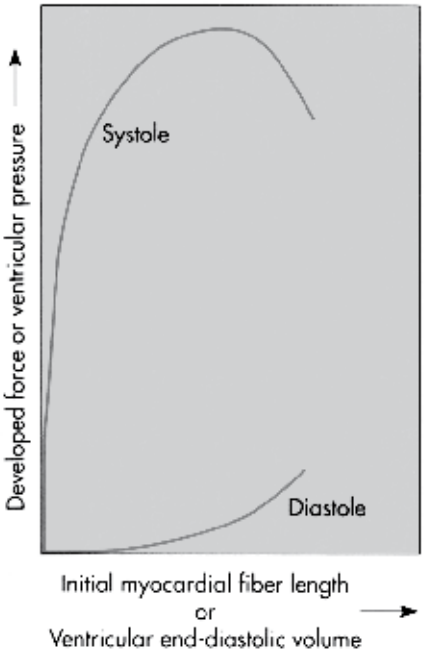


Fig. 5.12. The Frank-Starling mechanism: increased end-diastolic volume (i.e. increased myocardial fiber length) results in increased contractile force in systole (from Berne 1998)

5.5.2. The Vessels

Blood flow in the larger arteries is regulated by the cardiac output and the contractility and elasticity of the vessels. Blood flow in the smaller vessels is determined by the metabolic activity of the organ or tissue in question. In humans, the perfusion of the subcutaneous capillary network is influenced by soul states, such as shame (blushing). Subcutaneous capillary perfusion changes can also be used to regulate heat loss through the skin. The human subcutaneous capillary network is unique in this respect and both of these processes are only possible in the human organism.

Regulation of the flow in the heart and vessels is mainly intrinsic and autonomic.

➔ *The central organ of the heart is totally dependent on the periphery to regulate its activity. The movement of heart and vessels is determined by the flow of the blood as much as the heart and vessels' movement determines the flow of the blood.*

5.6. The Function of the Heart and Circulation for the Organism

The heart and circulation bring rhythmic movement to the fluids of the body. They impart their own intrinsic movement to the blood they carry, which imparts this movement to the whole organism. The heart and circulation carry warmth throughout the organism by means of the blood and effect a differentiated warmth organism by individualizing the blood supply to different tissues. The heart and circulation are intimately related to the blood.

The heartbeat has two components: the first and the second heart sound. Each human being's heartbeat is unique. The tone and the rhythmic relation of the first and second heart sounds are different for everyone. The blood carries the heartbeat and rhythm into the organism. The heart and circulation, together with the blood, ensure that the organism can function as a *rhythmic whole*. In contrast, the hormonal substances, which are secreted and carried in the blood, ensure the *metabolic* unity of the organism; and the nervous system, the fibers of which often run next to the vessels, ensures that the organism functions as a whole in regard to *sensory* impulses. Embryologically, the heart and circulation are functional before the hormonal and nervous systems, and heart and circulation therefore carry the first responsibility to maintain unity in the growing organism of the embryo. (For a more detailed description of the three areas mentioned here and their characteristics and functions see the *Anatomy Module* of **BOLK**'S COMPANIONS FOR THE STUDY OF MEDICINE.)

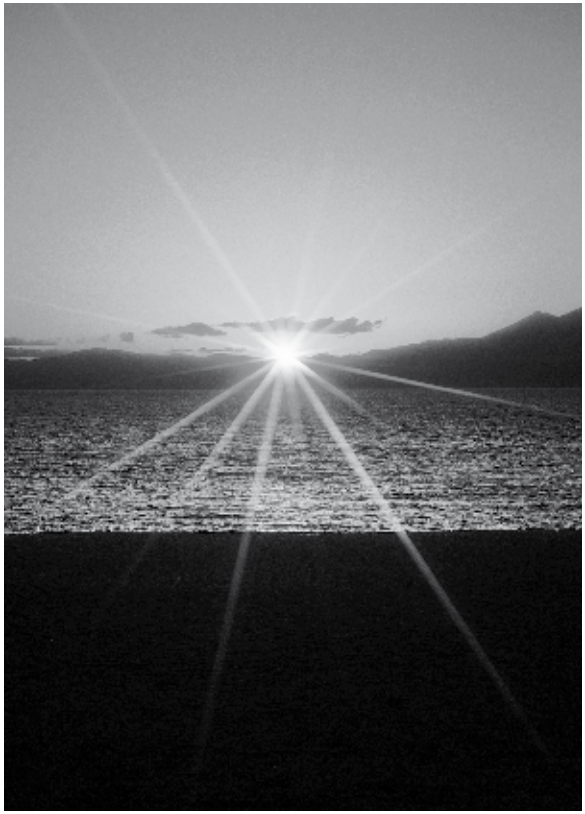
➔ *The function of the heart, blood, and vessels is to bring unity to the organism. The blood warms the organism, enabling it to function as a rhythmic whole.*

5.7. Conclusion

- Morphology:
  Heart and circulation have their *own strong form*. The systemic and pulmonary circulations together form a *lemniscate*. The heart muscle fibers form a double spiral.
- Embryology*:*
  The *heart and circulation as well as the blood* originate from the same angioblast cells at the beginning of the third week of embryological development. The relation between the two becomes functional as they act together to deliver and collect substances, rhythm, and warmth to and from the tissues.
- Blood supply:
  The heart has its *own special coronary circulation* that functions in opposite phase to the pulmonary and systemic circulations. This reversal reveals the *archetypal rhythmic* quality of the heart.
- Physiology:
  The heart is an *active, autonomous* organ that generates its own rhythmicity. Blood flow is mainly determined by the metabolic needs of the tissues. The flow of blood is individualized in peripheral tissues according to their metabolic needs. *Passive* diffusion enhanced by *thermal* motion of molecules is the main mechanism for the exchange between the plasma and the tissues in the periphery.
- Regulation*:*
  The output of the heart is mainly determined by the *venous return* from all the tissues of the body. The blood that flows from the heart supplies the tissues. In this way the heart is in living, active interrelation with the peripheral tissues. This relation could be represented by a *lemniscate*. The heart is largely *autonomous*.
- Function:
  The heart exhibits its own *activity* in the beating of the heart and *imparts this activity to the whole organism* through the rhythm of the flowing blood and makes the organism into a unity.

	Lung + Respiratory Tract	Liver + Intestinal Tract	Kidneys + Urogenital Tract	Heart + Circulation
Morphology	Shape from without, tubular organ, **membranous structure**	Mostly shaped from without, uniform parenchyme, tubular organs	Own active form, differentiated parenchyme with cortex and medulla, tubular parts specialized	Own active form, **newly formed tubular lumen**
Blood supply	50% of *weight* is blood, largely O_2 unsaturated, capillary blood in thin film	Largest *flow*, special *venous portal system*, ¼ is O_2 saturated, ¾ has low O_2 saturation, capillary blood in thin layer	Second largest flow, *unique arterial system*, high O_2 saturation, capillaries in tufts	**Own circulation in reverse phase,** ½ O_2 saturated, ½ O_2 unsaturated
Physiology	Passive diffusion	**Great activity in metabolic cycles**	Both active and passive processes	**Imparts rhythmic activity and warmth to the whole organism**
Regulation	Mainly from without, via the central nervous system	Both through local hormones and local autonomic plexuses, some via central nervous system	Both local and external hormones and buffering processes, kidneys secrete regulatory hormones for functions in organism	**Mainly determined by the periphery,** autonomous
Function	Passively supplying	Passively supplying, maintaining, and storing	**Actively regulating the internal milieu of the organism**	**Makes the organism into a unity**
Characteristic	Membrane-like tubular structure, *diffusion of gases* (O_2 and CO_2) and water	Physiologically active in metabolic cycles, diffusion and *absorption of fluid nutrients* in tubular part	Active regulatory function in the organism, diffusion and *resorption of blood constituents* in tubular parts	Middle position in organism, *makes the organism a unity*

➔ *The characteristic feature of heart and circulation is that they are not only constantly active, autonomous organs, but that they also permeate the whole organism with their rhythmic activity and warmth. The "tubular shape" of the vessels arises anew in the angiogenic tissue during embryological development. The "parenchyme" of the heart is actively moving muscular tissue. The heart has its own special circulation that reveals its rhythmic nature. The heart takes in a middle position in the organism morphologically and functionally. Heart and circulation contribute to the integrated functioning of the organism as a unity.*



6. Review and Conclusion

6.1. Characteristic Features of the Organs

The four organ systems we have discussed so far each have their own characteristic features. Characteristic features of each organ system are an expression of the forces or formative principles working in them. The formative principles that express themselves morphologically and physiologically in these four organ systems can be recognized to also work in nature as a whole.

6.1.1. The Lung and Respiratory Tract

The lung and respiratory tract are an overall *passive organ* system. They have a characteristic *membrane-like structure*. They fulfill their task by making diffusion of gases possible. To this end, the surface area of the respiratory tract becomes many times enlarged in the alveoli. The respiratory tract is a tubular organ and has little or no parenchyme. The respiratory tract membranous structure is supported by bone and cartilage to hold its form.

The following diagram could represent the lung and respiratory tract with its membrane-like structure and its capacity of diffusion (fig. 6.1.).

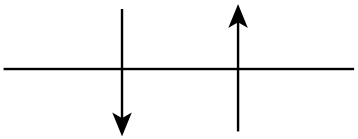


Fig. 6.1.

The physiology of the lung and respiratory tract is based on principles that have a **physical** character: the warming and humidifying of air; the elasticity of the tissue; the dependence of the flow of air on a positive or negative pressure in the lungs; the large surface area that is created; the diffusion of gases; the activity of surfactant as a surface tension active compound. The respiratory tract in the organism gets its form and is suspended from mineralized substance (cartilage and bone).

The Working of the Lungs' Formative Principle in Nature as a Whole

The characteristic formative principle working in the lung and respiratory tract can be found in nature where physical forces are mainly active. This is in *stones and minerals* that are not alive. Minerals passively allow the *physical* forces in the environment to shape them and work on them.

*The formative principle active in the lung and respiratory tract has **physical** characteristics. In nature its field of activity is in mineral substance.*

6.1.2. The Liver and Digestive Tract

The digestive tract is tubular in shape like the respiratory tract. In addition to the tubular intestines, a parenchymatous organ develops in the digestive tract. The liver is a homogenous parenchymatous organ, with the hepatocyte as the main cell type. Physiologically, the liver and digestive tract display *great activity*. The cyclic activity of liver physiology is expressed in its ability to convert substrates to active metabolites or to storage forms, and vice versa. The metabolic cycles concern anabolic (growth) and catabolic (breakdown and decay) processes in the liver itself as well as the cycles in the organism between liver and muscles, and liver and fat cells. The liver plays a major role in carbohydrate metabolism, which is the main source of direct metabolic energy for the organism. Liver activity adapts itself to the needs of the organism. In the digestive tract, passive diffusion is joined by active absorption. In other aspects (morphology, function and regulation) liver and digestive tract are mainly passive like the lung. In spite of their differences in consistency and activity, the lower respiratory tract, the digestive tract, and the liver all arise from the same embryological organ, the primitive foregut, which arises from the yolk sac. *The forces that model the digestive tract and the liver have an added quality compared to those of the respiratory tract.*

The following diagram (fig. 6.2.) may represent the physiological activity of liver and digestive tract.

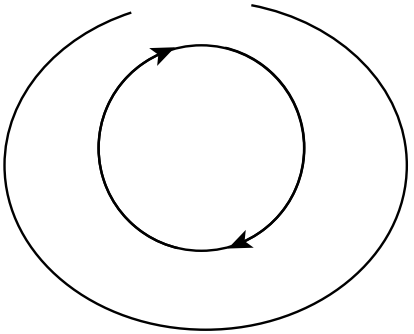


Fig. 6.2.

The physiology of the liver and digestive tract is based on principles that have a **vegetative** character: it concerns itself with growth and decay; it is involved in metabolic energy storage and production; it is cyclic in nature, and the activity of physiological processes adapts itself to the environment.

The Working of the Liver's Formative Principle in Nature as a Whole

The characteristic formative principle working in the liver and digestive tract can be found in nature where vegetative forces are mainly active. This is in living *plants*. Plants go through cycles of growth and decay in the yearly rhythm of growth in the spring and summer, and decay in the fall and winter. They are an important source of metabolic energy for animals and humans. They have a more passive relation to their environment, adapting to high altitudes and hot summers morphologically and physiologically.

*The formative principle active in the digestive tract and liver is characterized by additional **vegetative**, cycle creating forces. Its field of activity in nature is where growth (anabolic metabolism) and decay (catabolic metabolism) take place. These cyclic forces of growth and decay are characteristically active in plants.*

6.1.3. The Kidneys and Urinary Tract

The kidneys and urinary tract are morphologically "foreign" to the abdomen, as are the related adrenals and genitals. Embryologically, the kidneys and urinary tract develop from mesoderm (mesenchyme) rather than endoderm like the lungs and intestinal organs. They first arise in the cervical region close to the developing nervous system and go through an embryological "descent" into the lumbosacral region, and later through a partial "ascent" to arrive in the dorsal upper abdomen. The kidneys are *active organs* on many levels, morphologically, physiologically, and also in their function for the organism. The kidneys are parenchymatous organs that are not homogenous like the liver. They have, morphologically and functionally, two different and physiologically opposite areas, *cortex and medulla*, each of which consists of various different cell types. The kidneys actively *regulate* the volume and pH of extracellular fluids. For that purpose they have developed, in addition to the diffusion such as takes place in the respiratory tract and the absorption in the digestive tract, an ingenious system of filtration and *active reabsorption*. Protein metabolism plays an important

role in this process. The juxtaglomerular apparatus in the kidneys has a perceptive and regulating task. These are not cyclic processes but they lead from one (old) situation to another (new) situation. *The forces that model the kidneys and urinary tract have an added formative quality compared to those of the digestive and respiratory tract.*

The following diagram (fig. 6.3.) may represent the regulatory activity of the kidneys in the organism. It represents going from an old situation to a new situation.

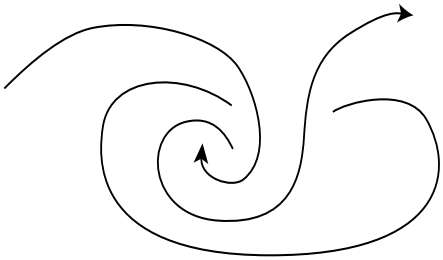


Fig. 6.3.

The characteristic physiology and morphology of the kidneys reminds us of their embryological, morphological, and physiological relation to the **interactive** forces of the central nervous system that perceive and react, regulating processes in the whole organism. The kidneys perceive and react, and have a regulating function for the organism; they specialize and differentiate; they are hormonally related to many other organs in the body, specifically also the central nervous system.

The Working of the Kidney's Formative Principle in Nature as a Whole

The formative principle that is characteristically active in the kidneys and urinary tract can be found in nature where the nervous system starts to play a role in interactive processes of perception and reaction. This is in *animals*. Animals, in their specialized ways, actively interact with their environment. They eat it, walk around, fertilize it (the insects through their contact with the plants, the mammals through their excretions), transform it (for instance nectar into honey). In doing so they have a regulating function in their environment. Perception plays an important role in their active relation to the environment.

*The formative principle that is active in the kidneys and urinary tract is characterized by additional **interactive** forces, such as are also active in the nervous system. These forces create the polarity of cortex and medulla. Their field of action in nature is where the nervous system starts to function as a regulatory organ. This is in animals.*

6.1.4. The Heart and Circulation

The heart and circulation are *active on all fronts*, like the kidneys. But they also *impart their activity to the organism,* through the blood. The blood is intimately related to heart and circulation, since it originates from the same embryological angioblast cells. Heart, vessels, and blood move in rhythmic pulsation, and the fluids of the whole organism move along with them. They also impart their warmth to the whole organism. Yet the activity of heart and vessels is directly dependent on the peripheral tissues, insofar as blood flow in the capillaries is dependent on local metabolic activity and cardiac output is determined by venous return from the periphery. Lipid metabolites, in the form of ketone bodies, provide for the energy supply of the heart.

The heart and circulation are tubular, with an expansion and differentiation in heart tissue. But the tubular structures arise *de novo*, unlike in the respiratory tract, the digestive tract, and the urinary tract. Unlike the liver and the kidneys, the heart and vessels are not parenchymatous organs. They consist of *rhythmically moving muscular* tissue. The heart and circulation are morphologically more like the digestive tract and physiologically simpler than the kidney tubular system. Yet, heart and circulation function on a higher level than the three other systems since they impart their rhythm and warmth to the whole body. Heart and circulation function *autonomously*, yet they *serve* the organism's needs.

The following diagram (fig. 6.4.) may represent this. The figure eight or lemniscate represents the mutual dependence of heart and periphery, and of capillary flow and local metabolism. The lemniscate shape is also a morphological feature of the circulation with the heart at its center. When we represent the activity in the periphery as arrows directing outwards in the lower loop of the lemniscate, then, if we continue the arrows going upwards along the lemniscate, the arrows will point inward in the upper part of the lemniscate, representing the activity of the heart.

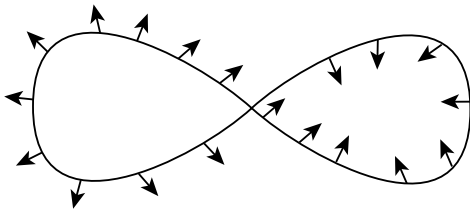


Fig. 6.4.

Embryologically, the circulation is first developed in the lateral periphery of the

embryo and "outside" the embryonic disc in the yolk sac. (Of course, the yolk sac also develops from the zygote.) The heart arises in the area above the central nervous system, and only arrives at its final location in the chest after the growth of the central nervous system has overtaken it. The heart "descends" into the embryological organism like the kidneys, but its origins are higher up than those of the kidneys, are even at the borders of the developing embryonic disc. *The heart and circulation have an additional quality of forces shaping them and working in them.*

The physiology of heart and circulation tract is based on principles that have an **integrating** character: heart and circulation penetrate everything with rhythm and warmth; they attend to the perfusion of tissues through the blood and make the organism an autonomous unity; their activity is dependent on the activity of the organs and organ activity is dependent on the heart and circulation.

The Working of the Heart and Circulation's Formative Principle in Nature as a Whole

The formative principle that is characteristically active in heart and circulation brings integrating forces into the organism. Its field of action is throughout nature where active integration plays a role. This is where *humans* may become active by cultivating nature such that they attend to and enhance the self-regulating forces of natural ecosystems, acting autonomously, but serving nature's needs.

The physical principle works in lifeless nature (minerals and stones), naturally. In plants, the vegetative principle works additionally, naturally. The principle of regulatory interaction, characteristic for the nervous system, works in animals in addition to that, also as a matter of fact. For us humans, ***bringing an integrating principle to nature is a task, not an accomplished fact****. Our interaction with nature often remains at the level of the forces that regulate and specialize, much like the nervous system does, without establishing the mutual, heartfelt connection serving nature that can be represented by the lemniscate.*

➔ *The four organ systems that were discussed have four different archetypal principles that work in them. These four formative principles can also be recognized in nature as a whole. The lung and respiratory tract are the characteristic expression of physical "mineral" forces in the organism, the liver and digestive tract of vegetative "plant" forces, the kidneys and urogenital tract of regulatory interactive "animal" forces, and in the heart and circulation the forces come to expression that we humans have to develop as heart forces.*

Literature

Berne R and Levy M. Physiology. Fourth edition. Mosby, 1998.

Bie G vd. Wholeness in Science. Louis Bolk Institute Driebergen, 2012.

Busse R. Kreislauf Physiologie, Thieme Verlag, 1982.

Benninghoff-Goerttler. Lehrbuch der Anatomie des Menschen, zweiter Band. Urban & Schwarzenberg, 1967.

Bortoft H. Goethe's scientific consciousness. Institute for Cultural Research, 1986.

Fishman A. Pulmonary diseases and disorders. Second Edition. McGraw-Hill Book Company, 1988.

Goldberger AL et al. Bronchial asymmetry and Fibonacci scaling. Experientia 41/1985, pp. 1537-1538.

Guyton A and Hall J. Textbook of Medical Physiology. Tenth edition. W. B. Saunders Company, 2000.

Hinrichsen KV et al. Humanembryologie (Human Embryology). Springer Berlin, 1990.

Kilner PhJ et al. Morphodynamics of Flow through Sinuous Curvatures of the Heart. Biorheology 2002; 39; 409-417

Kilner PhJ et al. Asymmetric Redirection of Flow through the Heart. Nature 13 April 2000. 404: 759-761

Kilner PhJ et al. Helical and Retrograde Secondary Flow Patterns in the Aortic Arch studied by Three-Directional Magnetic Resonance Velocity Mapping. Circulation 1993;88 [part 1]:2235-2247

Langman J. Medical Embryology. Williams&Wilkins Baltimore, 1995.

Linder M. Nutritional Biochemistry and Metabolism. Second edition. Appleton & Lange, 1997.

Moorman A and Lamers W. Development of the Conduction System of the Vertebrate Heart. From Heart Development, by Harvey, R. P., and Rosenthal, p.195-207, Academic Press, 1999.

Moorman A et al. Presence of Functional Sarcoplasmic Reticulum in the Developing Heart and its Confinement to Chamber Myocardium. Developmental Biology 223, p. 279-290, 2000.

Rose S. Lifelines. Life beyond the Gene. Oxford. Oxford University Press, 1998.

Sadler, T, Langman's Medical Embryology. Seventh edition. Williams & Wilkins, 1995.

Tellingen C v. Biochemistry. From a phenomenological Point of View. Louis Bolk Institute Driebergen, 2002.

Verhulst J. Der Erstgeborene. Verlag Freies Geistesleben, 1999, pp. 246-262, ISBN 3-7725-1557-6.

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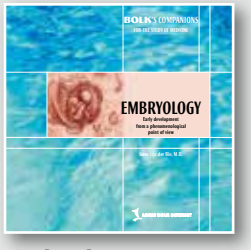

Embryology
Early Development from a Phenomenological Point of View

Guus van der Bie, M.D.
Publicationnumber GVO 01

Can we give a scientific basis to our feeling that humans have unique human features? Are the human mind and the human organism 'nothing but' another variation of animal life? Can we find answers for the questions that satisfy both head and hart?
How these quetions are answered depends on the scientific method we use: the current scientific method to learn about biological facts and the phenomenological method to understand more about the meaning of these facts.
Early embryological development can teach us about the unique and characteristic qualities of the human being.
The result is, for example, a possibility to understand the relation between consciousness, psychology, and behavior and the shape of the body.

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Metabolism from a Phenomenological Point of View

Christina van Tellingen, M.D.
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Biochemistry offers insight into the continuous changes within the human organism. But can we maintain awareness of the coherence of the (changing) organism as we study the details? How can the many processes be understood as prototypical aspects of a unique organism?
The scope of the answers to these questions can be enhanced by using a combination of the current scientific method and a phenomenological method developed specifically to research the coherence of processes within living organisms. The current scientific method is used to discover biological facts. The phenomenological approach helps us in finding the meaning of the facts.
What emerges is a new grasp of the interrelations between biological processes, consciousness, psychology, and behavior.

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How these questions are answered depends on the scientific method we use. In this publication two methods are used: the current scientific method to learn about anatomical facts and the phenomenological method to understand the meaning of these facts.
Human morphology can then be understood as an expression of the unique and characteristic qualities of the human being.
This results in new possibilities for understanding the relation between consciousness, psychology, behavior, and morphological aspects of the body.

Immunology
Self and Non-self from a Phenomenological Point of View

Guus van der Bie MD
Publicationnumber GVO 05

Why write this new booklet on immunology when there are already so many excellent texts on the subject? This Companion is about questions such as: why is it that the immune system functions as one organ? What coordinates the immunological functions?
Here, an attempt is made to develop a viewpoint to answer these questions. By using a phenomenological approach, the factual knowledge obtained through reductionism is placed in a larger perspective.
The concept that is presented in this Companion is derived from the functioning of organisms, observed in the way that was introduced by Goethe in his phenomenological method. This also includes the acquisition of insight into the holistic concept behind the immune system. Moreover, the organism as a whole can then be seen as an expression of the same concept.

Pharmacology
Selected Topics from a Phenomenological Point of View

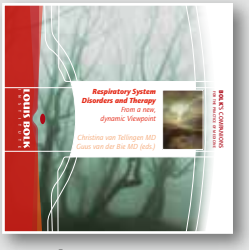
Christina van Tellingen MD
Publicationnumber GVO 06

Pharmacology gives us insight into the way organic processes change when foreign compounds are introduced into the organism. Pharmacology is a changeable subject, depending on the needs and knowledge of the time. Can we find an inner coherence in the manifold ways compounds influence organisms? What should such a framework be based on? How can we understand the effect on human consciousness that most compounds have?
We can enhance the scope of the answers to these questions by using a combination of the current scientific method and a phenomenological method. It illuminates the known facts about the activity of compounds in organisms, and provides the means to find their significance.

The Healing Process
Organ of Repair

Guus van der Bie MD
Tom Scheffers MD
Christina van Tellingen MD
Publicationnumber GVO 07

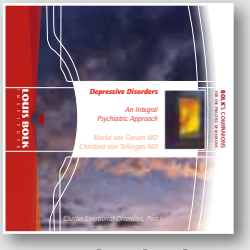
After finalizing the series BOLK'S Companions for the Study of Medicine for the moment, this module on The Healing Process introduces a new series of BOLK'S Companions that studies the Practice of Medicine. In it, we research the healing process itself. There proved to be an enormous volume of scientific literature on the subject. It is easy to loose oneself in the countless details included in the descriptions of this process.
The phenomenological method of systems biology makes it possible to examine physiological and pathological processes in terms of the processes themselves. This results in a characterization of the various phases of the wound healing process. Out of this, new insights into the origin of health and disease emerged that also offer possible leads for medical practice.



Respiratory System Disorders and Therapy
From a New, Dynamic Viewpoint

Christina van Tellingen MD
Guus van der Bie MD (eds.)
Publicationnumber GVO 08

In this Companion, the experience of three of our own patients with asthma and pneumonia is used as backdrop for our study of airway disorders. Nearly all of us have had some experience with respiratory disease, given that colds, flus, sinusitis, and bronchitis are so common. Most physicians and therapists know people with asthma and pneumonia from own experience and will readily recognize the descriptions we provide.
The experience with these patients leads us through a study of airway disease which eventually opens up to a wider view with new insights and innovative avenues of treatment for respiratory disorders in general.
Our research has alerted us to the part rhythm plays in the healthy respiratory tract and in the treatment of its disease. Rhythm, consequently, is the subject of the final paragraphs of this Companion.



Depressive Disorders
An Integral Psychiatric Approach

Marko van Gerven MD
Christina van Tellingen MD
Publicationnumber GVO 09

The treatment of depressive disorders is increasingly under scrutiny. We classified the risk factors of depressive disorders according to the scientific method applied in systems biology and phenomenology. The ordering in four biological levels that resulted from this, helps clarify the causes of the disorder. Together with the developmental history, it can lead to an individualized treatment of the patient, tailored to his or her specific situation. The treatment aims at restoring the deficient forces of self-healing.
This Companion presents a working model based on this methodological approach, as well as a variety of case histories to illustrate how applying this model can aid diagnosis and treatment in practice. Tables are added ordering well-researched regular and integral treatment methods according to the four biological levels.

Wholeness in Science
A Methodology
for Pattern Recognition and Clinical Intuition

Guus van der Bie MD

How do you develop clinical intuition? How do physicians gain practical knowledge about disease?

The above questions are vital for medicine. Diseases do not merely concern a partial defect, they recreate the life of the patient. At the hand of Pfeiffer's disease, the author shows that experienced physicians conceive of diseases as integrated concepts, which they can apply to the individual situation of the patient. Their clinical intuition is a form of pattern recognition and pattern recognition supports the ability to recognize an integrated 'whole.'

The practical exercises of this Companion allow readers to train and expand their ability of pattern recognition through Goethe's methodology. Clinical intuition, as experiential knowledge, appears to be a skill that can be actively developed.

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Physiology

Organphysiology from a Phenomenological Point of View

Can physiology give more insight into the living human organism than the mere facts reveal at first? Is the level of activity the same for all organs? Are the vital qualities at work in organs unique for organisms and limited to biological activity? Can we find a scientific basis to research the coherence between organ systems?

By enhancing the current scientific method with phenomenological points of view we can find meaning in the facts and understand them as an expression of life itself. The phenomenological method makes the relation between organs visible and comprehensible. It approaches scientific facts from the point of view of their coherence and can give totally new insights this way.

What emerges is a grasp of the interrelations between biological processes, consciousness, and nature.