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Preface

Pathophysiology describes the mechanisms which lead from the primary cause via individual malfunctions to a clinical picture and its possible complications. Knowledge of these mechanisms serves patients when the task is to develop a suitable therapy, alleviate symptoms, and avert imminent resultant damage caused by the disease.

Our aim in writing this Atlas of Pathophysiology was to address students of medicine, both prior to and during their clinical training, and also qualified doctors as well as their co-workers in the caring and therapeutic professions and to provide them with a clear overview in words and pictures of the core knowledge of modern pathophysiology and aspects of pathobiochemistry. Readers must themselves be the judge of the extent to which we have achieved this; we would be happy to receive any critical comments and ideas.

The book begins with the fundamentals of the cell mechanism and abnormalities thereof as well as cell division, cell death, tumor growth, and aging. It then covers a wide range of topics, from abnormalities of the heat and energy balance, via the pathomechanisms of diseases of the blood, lungs, kidneys, gastrointestinal tract, heart and circulation, and of the metabolism, including endocrin abnormalities, diseases of the musculature, the senses, and the peripheral and central nervous system. Following a short review of the fundamentals of physiology, the causes, course, symptoms, and arising complications of disease processes are described along with, if necessary, the possibilities of therapeutic intervention. The selective further reading list will assist the interested reader wishing to gain more indepth knowledge, and a detailed subject index, which is also a list of abbreviations, aims to assist rapid findings of topics and terminology.

This Atlas would have been inconceivable without the great commitment and outstanding expertise and professionalism of the graphic designers, Ms. Astried Rothenburger and Mr. Rüdiger Gay. We would like to extend our warmest gratitude to them for their re-
newed productive co-operation. Our thanks also go to our publishers, in particular Dr. Liane Platt-Rohloff, Dr. Clifford Bergman, and Mr. Gert Krüger for their friendly guidance, and Ms. Marianne Mauch for her exceptional skill and enthusiasm in editing the German edition of the Atlas. Ms. Annette Ziegler did a wonderful job with the setting, Ms. Koppenhöfer and Ms. Loch sorted and compiled the subject index with great care. Throughout all the years it took for this book to come into being, Dr. Heidi Silbernagl constantly stood by us and offered us her loyal and critical opinion of our pictures and manuscripts.

Several colleagues were likewise very helpful. First and foremost we would like to thank Prof. Niels Birbaumer for his valuable advice concerning the chapter ‘Nervous System, Musculature’, but we also thank Prof. Michael Gekle, Dr. Erich Gulbins, Dr. Albrecht Lepple-Wienhues, Dr. Carsten Wagner, and Dr. Siegfried Waldegger. Finally, we are grateful to Prof. Eva-Bettina Bröcker, Prof. Andreas Warnke, and Prof. Klaus Wilms for being so kind as to allow us to reproduce their photographs here.

We hope that readers will find in this Atlas what they are looking for, that what we have attempted to say in words and pictures is understandable, and that they enjoy using this book throughout their studies and their working life.

Würzburg and Tübingen, Germany
January 2000

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Undine, Karl, Philipp, Lisa
Florian Lang
Cell Growth and Cell Adaptation

It is more than a hundred years ago that Rudolf Virchow first conceived of his idea of cellular pathology, i.e., that disease is a disorder of the physiological life of the cell. The cell is the smallest unit of the living organism (Wilhelm Roux), i.e., the cell (and not any smaller entity) is in a position to fulfill the basic functions of the organism, namely metabolism, movement, reproduction and inheritance. The three latter processes are made possible only through cell division, although cells that can no longer divide can be metabolically active and are in part mobile.

With the exception of the germ cells, whose chromosome set is halved during meiotic division (meiosis), most cells divide after the chromosome set has first been replicated, i.e., after mitosis (so-called indirect division of the nucleus) followed by division of the cell (cytokinesis). In this process every cell capable of mitosis undergoes a cell or generation cycle (→A) in which one mitosis (lasting ca. 0.5–2 h) is always separated from the next one by an interphase (lasting 6–36 h, depending on the frequency of division). Most importantly, the cell cycle is governed by certain cycle phase-specific proteins, the cyclines. They form a complex with a protein kinase, called cdc2 or p34<sup>cdc2</sup>, which is expressed during all phases. When cytokinesis is completed (=end of telophase; →A), cells that continually divide (so-called labile cells; see below) enter the G<sub>1</sub> phase (gap phase 1), during which they grow to full size, redifferentiate and fulfill their tissue-specific tasks (high ribonucleic acid [RNA] synthesis, then high protein synthesis). This is followed by the S phase, which lasts about eight hours. During this phase the chromosome set is doubled (high DNA synthesis). After the subsequent G<sub>2</sub> phase, which lasts about one to two hours (high protein and RNA synthesis; energy storage for subsequent mitosis; centriole division with formation of the spindle), the next mitosis begins. The prophase (dedifferentiation of the cell, e.g., loss of microvilli and Golgi apparatus; chromosomal spiraling) is followed by the metaphase (nuclear envelope disappears, chromosomes are in the equatorial plane). Then comes the anaphase (some division and migration to the poles) followed by the telophase (formation of nuclear envelope). Cytokinesis begins in the late stage of the anaphase with development of the cleavage furrow in the cell membrane. After this a new G<sub>1</sub> phase begins.

Cells with a short life-span, so-called labile cells, continually go through this cell cycle, thus replacing destroyed cells and keeping the total number of cells constant. Tissues with labile cells include surface epithelia such as those of the skin, oral mucosa, vagina and cervix, epithelium of the salivary glands, gastrointestinal tract, biliary tract, uterus and lower urinary tract as well as the cells in bone marrow. The new cells in most of these tissues originate from division of poorly differentiated stem cells (→ p. 28 ff.). One daughter cell (stem cell) usually remains undifferentiated, while the other becomes differentiated into a cell which is no longer capable of dividing, for example, an erythrocyte or granulocyte (→A). Spermatogenesis, for example, is also characterized by such differentiated cell division.

The cells of some organs and tissues do not normally proliferate (see below). Such stable or resting cells enter a resting phase, the G<sub>0</sub> phase, after mitosis. Examples of such cells are the parenchymal cells of the liver, kidneys, and pancreas as well as connective tissue and mesenchymal cells (fibroblasts, endothelial cells, chondrocytes and osteocytes, and smooth muscle cells). Special stimuli, triggered by functional demand or the loss of tissue (e.g., unilateral nephrectomy or tubular necrosis; removal or death of portions of the liver) or tissue trauma (e.g., injury to the skin), must occur before these cells re-enter the G<sub>1</sub> phase (→A, B). Normally less than 1% of liver cells divide; the number rises to more than 10% after partial hepatectomy.

The conversion from the G<sub>0</sub> phase to the G<sub>1</sub> phase and, more generally, the trigger for cell proliferation requires the binding of growth factors (GFs) and growth-promoting hormones (e.g. insulin) to specific receptors that are usually located at the cell surface. However, in the case of steroid receptors these are in the cytoplasm or in the cell nucleus (→C).
### A. Cell Cycle

- **Interphase:** 6 – 36 h
  - **S-phase:** DNA replication 8 h
  - **G2:**
    - **Gap phase 2:** Protein and RNA synthesis, centriole division 1 – 2 h
  - **Mitosis:** Cytokinesis 0,5 – 2 h
  - **Gap phase 1:** Growth, differentiation 1 – 2 h
  - **Gap phase 0:** Liver, kidney, etc.
- **S:**
  - **G0:**
  - **G1:** Liver, kidney, etc.

### B. Compensatory Hyperplasia

- Metabolic overload, stress, cytokines, etc.
- Expression of protooncogenes (c-fos, c-myk)
- Hormones (norepinephrine, insulin, glucagon)
- Growth factors (TGFα, HGF, etc.)

Renewed cell division
The GF receptors are activated (usually tyrosine kinase activity; → p. 7ff., A 10), which results in phosphorylation of a number of proteins. Lastly, the signaling cascade reaches the nucleus, DNA synthesis is stimulated and the cell divides (→ p. 14).

In addition to tissue-specific growth factors (e.g., hepatic growth factor [HGF] in the liver), there are those with a wider spectrum of action, namely epidermal growth factor (EGF), transforming growth factor (TGF-α), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) as well as certain cytokines such as interleukin 1 and tumor necrosis factor (TNF). Growth inhibition (→ p. 14) occurs, for example, in an epithelium in which a gap has been closed by cell division, when neighboring cells come into contact with one another (contact inhibition). Even compensatory growth in the liver stops (→ B) when the original organ mass has been regained. TGF-β and interferon-β are among the signals responsible for this growth regulation.

The regeneration of labile and stable cells does not necessarily mean that the original tissue structure is reconstituted. For this to happen the extracellular matrix must be intact, as it serves as the guiding system for the shape, growth, migration, and differentiation of the cell (→ C). The extracellular matrix consists of fibrous structural proteins (collagen I, II–V; elastin) and an intercellular matrix of glycoproteins (e.g., fibronectin and laminin) that are embedded in a gel of proteoglycans and glucosaminoglycans. The extracellular matrix borders on epithelial, endothelial, and smooth muscle cells in the form of basal lamina (→ E). Integrins are proteins of the cell membrane that connect the extracellular matrix with the intracellular cytoskeleton and transmit signals for the growth, migration, and differentiation of the cell to the cell interior (→ C). If, as happens in severe tissue damage, the matrix is extensively destroyed (e.g., in a deep gastric ulcer [→ p. 144 ff.] or large skin wound), the original tissue is replaced by scar tissue. In this case otherwise resting cells of the connective tissue and mesenchyme also proliferate (see above).

When so-called permanent cells have died they cannot be replaced, because they are unable to divide. Such cells include, among others, nerve cells in adults. The capability of regeneration of an adult’s cardiac and skeletal muscle cells is also very limited (→ e.g., myocardial infarction; p. 220).

Adaptation to changed physiological or unphysiological demands can be achieved through an increase or decrease in the number of cells (hyperplasia or aplasia; → D, E). This can be triggered by hormones (e.g., development of secondary sex characteristics and growth of mammary epithelium during pregnancy) or can serve the process of compensation, as in wound healing or after reduction of liver parenchyma (→ B). Cell size may either increase (hypertrophy), or decrease (atrophy) (→ E). This adaptation, too, can be triggered hormonally, or by an increase or decrease in demand. While the uterus grows during pregnancy by both hyperplasia and hypertrophy, skeletal and cardiac muscles can increase their strength only by hypertrophy. Thus, skeletal muscles hypertrophy through training (bodybuilding) or atrophy from disuse (e.g., leg muscle in a plaster cast after fracture or due to loss of innervation). Cardiac hypertrophy develops normally in athletes requiring a high cardiac output (cycling, cross-country skiing), or abnormally, for example, in hypertensives (→ p. 208 ff.). Atrophied cells are not dead; they can be reactivated—with the exception of permanent cells (brain atrophy). However, similar signal pathways lead to atrophy and to “programmed cell death” or apoptosis (→ p. 12), so that an increased number of cells may die in an atrophic tissue (→ D).

Metaplasia is a reversible transformation of one mature cell type into another (→ E). This, too, is usually an adaptive course of events. The transitional epithelium of the urinary bladder, for example, undergoes metaplasia to squamous epithelium on being traumatized by kidney stones, and so does esophageal epithelium in reflux esophagitis (→ p. 136 ff.), or ciliated epithelium of the respiratory tract in heavy smokers. The replacement epithelium may better withstand unphysiological demands, but the stimuli that sustain lasting metaplasia can also promote the development of tumor cells (→ p. 14).
C. Regulation of Cell Proliferation, Motility and Differentiation

- Growth-promoting hormones
- Steroid hormones
- Growth factors
- Extracellular matrix
- Integrins
- Cytoskeleton

D. Changes in Cell Population

- Stimulated Proliferation Inhibited
- Inhibited Apoptosis Stimulated
- Larger Cell population Smaller
  - Stem cell population larger
  - Stem cell population smaller
  - Differentiation

E. Cell Adaptation

- Pregnancy (uterus)
- Hypertension (heart)
- Plaster cast (skeletal muscles)
- Chronic gastritis (gastric epithelium)
- Smoking (respiratory epithelium)
- Reflux esophagitis (esophageal epithelium)

- Normal
- Epithelial cells
- Basal lamina

- Hypertrophy
- Atrophy
- Hyperplasia
- Metaplasia
Abnormalities of Intracellular Signal Transmission

As a rule, hormones do not influence cell functions directly, but via secondary intracellular signals. This signal transmission is disrupted in some diseases and can be influenced by certain drugs and toxins.

Some hormones bind to receptors of the cell membrane (→ A1 – 3). Usually through mediation of guanine nucleotide-binding proteins (G proteins), the hormone–receptor interaction causes the release of an intracellular second messenger which transmits the hormonal signal within the cell. A given hormone can cause different intracellular second messengers to be formed, depending on the target cell and receptor. Abnormalities can occur if, for example, the number of receptors is reduced (e.g., down-regulation in persistently high hormone concentrations), the receptor’s affinity for the hormone is reduced, or coupling to the intracellular signaling cascade is impaired (→ A; receptor defects).

The so-called large, heterotrimeric G proteins consist of three subunits, namely α, β, and γ. When the hormone binds to the receptor, guanosine 5’-triphosphate (GTP) is bound to the α subunit in exchange for guanosine 5’-diphosphate (GDP), and the α subunit is then released from the β subunit. The α subunit that has been activated in this way is then inactivated by dephosphorylation of GTP to GDP (intrinsic GTPase) and can thus be re-associated with the β-γ subunits.

Numerous peptide hormones use cyclic adenosine monophosphate (cAMP) as second messenger in such a way that, mediated by a stimulating G protein (Gs), adenyl cyclase (AC) is activated and thus more cAMP is formed (→ A1). cAMP activates protein kinase A (PKA), which phosphorylates, among others, enzymes and transport molecules. cAMP can also be involved in gene expression via PKA and phosphorylation of a cAMP-responsive element-binding protein (CREB). cAMP is converted to noncyclic AMP by intracellular phosphodiesterases and the signal thus turned off. The following hormones act via an increase in intracellular cAMP concentration: corticotropin (ACTH), lutotropin (luteinizing hormone [LH]), thyrotropin (TSH), prolactin, somatotropin, some of the liberines (releasing hormones [RH]) and statins (release-inhibiting hormones [RIH]), glucagon, parathyroid hormone (PTH), calcitonin, adiuretin ([ADH] V2 receptors), gastrin, secretin, vasoactive intestinal peptide (VIP), oxytocin, adenosine (A2 receptor), serotonin (S2 receptor), dopamine (D1 receptor), histamine (H2 receptor), and to some extent the prostaglandins.

Some peptide hormones and neurotransmitters, for example, somatostatin, adenosine (A1 receptor), dopamine (D2 receptor), serotonin (S3), angiotensin II, and acetylcholine (M2 receptor), act by inhibiting AC and thus reducing the intracellular cAMP concentration, via an inhibiting G protein (Gi) (→ A2). Some hormones can, by binding to different receptors, either increase the cAMP concentration (epinephrine: β-receptor; dopamine: D1 receptor), or reduce it (epinephrine: α2-receptor; dopamine: D2 receptor).

The cAMP signaling cascade can be influenced by toxins and drugs, namely cholera toxin from Vibrio cholerae, the causative organism of cholera, and other toxins prevent the deactivation of the αs subunit. The result is the uncontrolled activation of AC and subsequently of cAMP-dependent Cl– channels, so that unrestrained secretion of sodium chloride into the gut lumen causes massive diarrhea (→ p.150). Pertussis toxin from Hemophilus pertussis, the bacillus that causes whooping-cough (pertussis), blocks the Gi protein and thus raises, among others, the cAMP concentration (disinhibition of AC). Forskolin directly stimulates AC, while xanthine derivatives, for example, theophylline, inhibit phosphodiesterase and thus the breakdown of cAMP, which also leads to an increase in cAMP concentration (→ A4). The xanthine derivatives are used therapeutically, among other drugs, to cause the bronchial musculature to dilate in asthma by raising the cAMP concentration.

In addition to cAMP, cyclic guanosine monophosphate (cGMP) serves as an intracellular messenger (→ A5). cGMP is formed by guanylyl cyclase. cGMP achieves its effect primarily via activation of a protein kinase G (PKG). Atrial natriuretic factor (ANF) and nitric oxide (NO), among others, also act via cGMP.

Other intracellular transmitters are 1,4,5-
inositol trisphosphate (IP₃), 1,3,4,5-inositol tetraakisphosphate (IP₄), and diacylglycerol (DAG). A membrane-bound phospholipase C (PLC) splits phosphatidylinositol diphosphate (PIP₂) into IP₃ and DAG after being activated by a so-called G₀ protein. This reaction is triggered by, among others, epinephrine (α₁ receptor), histamine (H₁ receptor), ADH (V₁ receptor), pancreozymin (CCK), angiotensin II, thyrotropin-releasing hormone (TRH), substance P, and serotonin (S₁ receptor). IP₃ releases Ca²⁺ from intracellular stores. Emptying of the stores opens Ca²⁺ channels of the cell membrane (→ A6). Ca²⁺ can also enter the cell through ligand-gated Ca²⁺ channels. Ca²⁺, in part bound to calmodulin and through subsequent activation of a calmodulin-dependent kinase (CaM kinase), influences numerous cellular functions, such as epithelial transport, release of hormones, and cell proliferation. DAG stimulates protein kinase C (PKC), which is also activated by Ca²⁺. PKC in turn regulates other kinases, transcription factors (see below) and the cytoskeleton. PKC also activates the Na⁺/H⁺ exchanger leading to cytosolic alkalinization and an increase in cell volume. Numerous cell functions are influenced in this way, among them metabolism, K⁺ channel activities, and cell division.

The formation of inositol from inositol monophosphate is inhibited by the antideprenant lithium (Li) (→ A7). PKC is activated by phorbol esters (→ A8).

Arachidonic acid, a polyunsaturated fatty acid, can be split from membrane lipids, including DAG, by phospholipase A (→ A9). Arachidonic acid itself has some cellular effects (e.g., on ion channels), but through the action of cyclo-oxygenase can also be converted to prostaglandins and thromboxan, which exert their effect partly by activating adenyl cyclase and guanylyl cyclase. Arachidonic acid can also be converted to leukotrienes by lipoygenase. Prostaglandins and leukotrienes are especially important during inflammation (→ p. 48 ff.) and not only serve as intracellular messengers, but also as extracellular mediators (→ p. 296). Lipoygenase inhibitors and cyclo-oxygenase inhibitors, frequently used therapeutically (e.g., as inhibitors of inflammation and platelet aggregation), inhibit the formation of leukotrienes and prostaglandins.

Insulin and numerous growth factors activate tyrosine kinases (→ A10), which transmit cellular effects via other kinases, enzymes, and transport proteins. The tyrosine kinases can themselves be part of the receptor, or can attach themselves to the receptor on activation. Kinases frequently act by phosphorylating other kinases and thereby trigger a kinase cascade. Thus, the mitogen-activated protein kinase (MAP kinase) is activated by another kinase (MAP kinase cascade). This “snowball effect” results in an avalanche-like increase of the cellular signal. The p-38 kinase and the Jun kinase that regulate gene expression via transcription factors are also activated via such cascades.

Other signaling molecules, such as the small G proteins (p₂₁Ras) or transcription factors (e.g., c-Jun, c-Fos, c-Myc, NF-B, AP-1), are important for signal transduction of growth factors (→ p. 14) and in apoptosis (→ p. 12).

Mutations of the (proto-onco)genes of receptors for growth factors, of tyrosine kinases, of Ras, Jun, or Myc to oncogenes can promote autonomous cell proliferation, i.e., the development of tumor cells (→ p. 14).

Some mediators (e.g., the tumor necrosis factor [TNF] and CD95 [Fas/Apo1] ligand) activate acid sphingomyelinase, which forms ceramide from sphingomyelin (→ A11). Ceramide triggers a series of cellular effects, such as activation of small G proteins (e.g., Ras), of kinases, phosphatases, and caspsases, i.e. proteases which cleave proteins at cystein-aspartate sites. The effects of ceramide are especially important in signal transduction of apoptotic cell death (→ p. 12).

Steroid hormones (e.g., aldosterone) do not usually act via receptors on the cell membrane, but rather pass easily through the cell membrane due to their solubility in lipids, and then bind to intracellular (cytosolic or nuclear) receptor proteins (→ A12). The hormone–receptor complex attaches itself to the DNA of the cell nucleus and in this way regulates protein synthesis.
A. Intracellular Signal Transmission and Possible Disorders

Stimulating hormones
1
R_s
GTP
Activated G_s protein

Receptor defects
2
R_i
Activated G_i protein

Inhibitory hormones

Mutations: Oncogenes

Growth factors, insulin, etc.

Steroid hormones

Tyrosine kinase

Activated G, protein

Forskolin

Adenylyl cyclase

GTP

Cholera toxin

Pertussis toxin

GDP

Phosphodiesterase

Xanthine derivatives

ATP

cAMP

Kinase cascade

Protein kinase A

Cell nucleus

DNA

CREB

mRNA

Induced protein

Activation or inactivation of:

Fundamentals

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Necrotic Cell Death

The survival of the cell is dependent on the maintenance of cell volume and the intracellular milieu (→ A). As the cell membrane is highly permeable to water and water follows the osmotic gradient (→ A1), the cell depends on osmotic equilibrium to maintain its volume. In order to counterbalance the high intracellular concentration of proteins, amino acids, and other organic substrates, the cell lowers the cytosolic ionic concentration. This is done by Na⁺/K⁺-ATPase, which pumps Na⁺ out of the cell in exchange for K⁺ (→ A2). Normally the cell membrane is only slightly permeable for Na⁺ (→ A3), but highly permeable for K⁺, so that K⁺ diffuses out again (→ A4). This K⁺-eflux creates an inside negative potential (→ A5) which drives Cl⁻ out of the cell (→ A6). In this ionic shift, which uses up adenosine 5'-triphosphate (ATP), reduction of the cytosolic concentration of Na⁺ and Cl⁻ (adding up to ca. 230 mosm/L) is much greater than the rise in cytosolic K⁺ concentration (ca. 140 mosm/L).

Reduction in intracellular Na⁺ concentration by Na⁺/K⁺-ATPase is necessary not only to avoid cell swelling, but also because the steep electrochemical gradient for Na⁺ is utilized for a series of transport processes. The Na⁺/H⁺ exchanger (→ A9) eliminates one H⁺ for one Na⁺, while the 3 Na⁺/Ca²⁺ exchanger (→ A8) eliminates one Ca²⁺ for 3 Na⁺. Na⁺-bound transport processes also allow (secondarily) active uptake of amino acids, glucose, etc. into the cell (→ A7). Lastly, depolarization achieved by opening the Na⁺ channels (→ A10) serves to regulate the function of excitable cells, e.g. the signal processing and transmission in the nervous system and the triggering of muscle contractions.

As the activity of Na⁺-transporting carriers and channels continuously brings Na⁺ into the cell, survival of the cell requires the continuous activity of Na⁺/K⁺-ATPase. This intracellular Na⁺ homeostasis may be disrupted if the activity of Na⁺/K⁺-ATPase is impaired by ATP deficiency (ischemia, hypoxia, hypoglycemia). The intracellular K⁺ decreases as a result, extracellular K⁺ rises, and the cell membrane is depolarized. As a consequence, Cl⁻ enters the cell and the cell swells up (→ B). These events also occur when the energy supply is compromised, or when Na⁺ entry exceeds the maximal transport capacity of the Na⁺/K⁺-ATPase. Numerous endogenous substances (e.g., the neurotransmitter glutamate) and exogenous poisons (e.g., oxidants) increase the entry of Na⁺ and/or Ca²⁺ via the activation of the respective channels (→ B).

The increase in intracellular Na⁺ concentration not only leads to cell swelling, but also, via impairment of the 3Na⁺/Ca²⁺ exchanger, to an increase in cytosolic Ca²⁺ concentration. Ca²⁺ produces a series of cellular effects (→ p. 6 ff.); among others it penetrates into the mitochondria and, via inhibition of mitochondrial respiration, leads to ATP deficiency (→ B).

If there is a lack of O₂, energy metabolism switches to anaerobic glycolysis. The formation of lactic acid, which dissociates into lactate and H⁺, causes cytosolic acidosis that interferes with the functions of the intracellular enzymes, thus resulting in the inhibition of the glycolysis so that this last source of ATP dries up (→ B).

If an energy deficiency arises, the cell is more likely to be exposed to oxidative damage, because the cellular protective mechanisms against oxidants (O₂ radicals) are ATP-dependent (→ B). There is then a risk of the cell membrane being destroyed (lipid peroxidation) and intracellular macromolecules being released in the intracellular space. As the immune system is not normally exposed to intracellular macromolecules, there is no immune tolerance to them. The immune system is activated and inflammation occurs, resulting in further cell damage.

The time-span before necrotic cell death occurs due to interruption of energy supply depends on the extent of Na⁺ entry, thus, for example, on the activity of excitable cells or the transport rate of epithelial cells. As the voltage-gated Na⁺ channels of excitable cells are activated by depolarization of the cell membrane, depolarization can accelerate cell death.
### A. Homeostasis of Volume and Electrolytes in the Cell

- **Na**\(^+\)/**K**\(^+\)-ATPase
- **H**\(_2\)O
- Metabolism

#### Metabolism

1. **H**\(_2\)O
2. **Na**\(^+\)
3. **H**\(_2\)O
4. **K**\(^+\)
5. **Cl**\(^-\)
6. **H**\(_2\)O

#### ATP

- Amino acids, glucose, etc.

#### Na\(^+\), K\(^+\), Ca\(^2+\), Cl\(^-\), H\(_2\)O

1. **Na**\(^+\)
2. **Ca**\(^2+\)
3. **Na**\(^+\)
4. **Na**\(^+\)
5. **Na**\(^+\)
6. **Na**\(^+\)
7. **Na**\(^+\)
8. **Na**\(^+\)
9. **Na**\(^+\)
10. **K**\(^+\)

#### In nerve and muscle cells: Na\(^+\) channels

### B. Necrosis

- **Hypoglycemia**
- **Hypoxia, ischemia**
- **Glucose deficiency**
- **O\(_2\) deficiency**
- **Anaerobic glycolysis**
- **Mitochondrial respiration**
- **Phospholipase A\(_2\)**
- **Ca\(^{2+}\)**
- **ATP**
- **Na**\(^+\)
- **K**\(^+\)
- **H**\(_2\)O
- **Cl**\(^-\)

#### Poisoning (e.g., oxidants)

#### Endogenous substances (e.g., glutamate)

#### Cell activity (excitation, transport)

#### Oxidants

#### Macromolecules

#### Membrane destruction

#### Inflammation

#### Cell swelling

#### Cell death
Apoptotic Cell Death

Every day hundreds of billions of cells in our body are eliminated and replaced by division of existing cells (→ p. 2 ff.). Apoptosis, as opposed to necrosis (→ p. 10), is a programmed cell death and, like cell division (→ p. 2 ff., 14), is a finely regulated physiological mechanism. It serves to adapt the tissue to changing demands, to eliminate superfluous cells during embryonic development and to remove harmful cells such as tumor cells, virus-infected cells, or immune-competent cells that react against the body's own antigens.

Apoptosis is mediated by a signaling cascade (→ A): protein-cleaving caspases activate sphingomyelinase that releases ceramide from sphingomyelin. One of the consequences is activation of the small G proteins Ras and Rac, superoxide formation and destruction of the mitochondria together with liberation of cytochrome c. By activating tyrosine kinases, ceramide inhibits K⁺ channels, activates Cl⁻ channels, and acidifies the cells. MAP kinase cascades and the cytosolic concentration of Ca²⁺ are also important in apoptosis.

Apoptosis can be encouraged by certain genes (e.g., bax) or inhibited by others (e.g., bcl2). Ultimately, activation of an endonuclease leads to DNA fragmentation, the cell loses electrolytes and organic osmolytes, proteins are broken down and the cell finally shrinks and disintegrates into small particles that are easily taken up by macrophages. In this way the cell disappears without intracellular macromolecules being released and, therefore, without causing inflammation.

Apoptosis is triggered (→ A), for example, by TNF-α, glucocorticoids, activation of the CD95(Fas/Apo1) receptor or the withdrawal of growth factors (GFs). DNA damage encourages apoptosis via a p53-protein. In ischemia, for example, the affected cells sometimes express the CD95 receptor and thus become exposed to apoptosis. In this way they “anticipate necrotic cell death” and so at least prevent the release of intracellular macromolecules that would cause inflammation (→ p. 10).

Pathologically increased apoptosis (→ B) can occur through the local formation of apoptotically effective mediators, the (inappropriate) expression of their receptors, or the receptor-independent stimulation of signaling cascades. These events can be caused by ischemia, toxins, massive osmotic cell shrinkage, radiation, or inflammation (infections, autoimmune disease). This results in the inadequate death of functionally essential cells, leading to organ insufficiency (→ B). In this way apoptosis will, for example, bring about transplant rejection, neuronal degeneration (e.g., Parkinson's or Alzheimer's disease, amyotrophic lateral sclerosis, quadriplegia, multiple sclerosis) as well as toxic, ischemic, and/or inflammatory death of liver cells (liver failure), of B cells of the pancreatic islets (type 1 diabetes mellitus), of erythropoietic cells (aplastic anemia), or of lymphocytes (immunodeficiency, e.g., in HIV infection).

Pathologically reduced apoptosis leads to an excess of affected cells (→ C). Among the causes are disorders of endocrine or paracrine regulation, genetic defects, or viral infections (e.g., with the Epstein–Barr virus). They prevent physiological apoptosis by means of an excess of antiapoptotically effective growth factors, via increased expression, for example, of Bcl2, or decreased expression of functioning p53 or CD95 ligand. Absent apoptosis of virus-infected cells can result in persistent infections. Cells that escape apoptosis can develop into tumor cells. Insufficient apoptosis of immunocompetent cells, directed against the body's own cells, is a cause of autoimmune disease. In addition, an excess of cells can cause functional abnormalities, for example, persistent progesterone formation in the absence of apoptosis of the corpus luteum cells. Lack of apoptosis can also result in abnormal embryonic development (e.g., syndactyly).
A. Triggering and Development of Apoptosis

- Ischemia etc.
- TNF-α
- Lack of growth factors
- Radiation
- Poisons

Apoptosis

- CD95 receptor
- Sphingomyelinase
- Ceramide
- Mitochondrial destruction
- Caspases
- Tyrosine kinase
- DNA repair
- DNA damage
- Bcl2
- Bax
- p53

B. Increased Apoptosis

Poisons, radiation, ischemia, genetic defects, infections, autoimmune diseases

- Apoptotic cell death
- Neuronal degeneration
- Parkinson’s, Alzheimer’s, amyotrophic lateral sclerosis, paraplegia, multiple sclerosis

- Liver failure
- Immune deficiency
- Aplastic anemia
- Transplant rejection
- Diabetes mellitus

C. Reduced Apoptosis

- e.g. viruses
- e.g. genetic defects
- e.g. endocrine disorders

- Bcl2
- p53
- CD95 ligand
- Growth factors

- Apoptotic cell death
- Persistent infections
- Tumors
- Autoimmune diseases
- Hyperfunction
- Development abnormalities

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Development of Tumor Cells

Cell division (mitosis) is normally precisely adapted, via local release of growth factors, to meet the specific requirement of cells (→ p. 4). The growth factors (GFs) stimulate receptors in the cell membranes, which either themselves show tyrosine kinase activity or stimulate it (→ A1). Through the mediation of adaptor proteins (GRβ2), the GDP/GTP exchange factor SOS binds to certain phosphotyrosine residues and then activates the small G protein Ras. The latter, via serine/threonine kinase Raf (→ A2), stimulates a cascade of kinases (mitogen-activated protein kinase cascade [MAPK cascade]), and thus leads to the activation of transcription factors which induce the expression of genes essential for cell division. Transcription factors which are important for cell division include Fos, Jun, Myc, Myb, Rel, E2F and DP1. Thyroid hormones bind to nuclear receptors (ErbA; → A3), the hormone–receptor complex then similarly promotes gene expression and cell division.

Mechanisms that promote proliferation are countered by growth-inhibiting factors that normally stop excess cell division. They become effective, for example, when the cell contains damaged DNA and cell division would lead to defective daughter cells being formed. An example of a growth-inhibiting factor is retinoblastoma protein (Rb), which binds to transcription factors E2F and DP1, and thus inactivates them (→ A4). For its part Rb is kept inactivated by the complex consisting of cyclin E and the kinase CDK2 (= E-CDK2) as well as the complex of cyclin D and the kinase CDK4 (= D-CDK4). In this way E-CDK2 and D-CDK4 promote cell division, but their effect is canceled by the p21-protein that is expressed under the influence of transcription factor p53. The latter therefore inhibits cell division (→ A4).

Oncogenes can arise through mutations of proliferation-relevant genes. Oncoproteins, the products of oncogenes, are active even without physiological stimulators and can thus trigger mitosis independent of physiological growth factors. Examples of oncoproteins (→ A; violet boxes) are:

- growth factors that are formed by tumor cells and autocrinely stimulate their own cell division (e.g., Sis, a fragment of the PDGF)
- receptors for thyroid hormones (ErbA)
- receptors for growth factors (e.g., ErbB for EGF and Fms for monocyte-colony–stimulating factor)
- tyrosine kinases (e.g., Abl, Src, Fes)
- small G proteins (Ras)
- serine/threonine kinases (e.g., Raf, Mos)
- transcription factors (Fos, Jun, Myc, Myb, Rel)

As an example, inactivation of Ras is accelerated by a GTPase-activating protein (GAP) (→ B). Certain mutations of Ras cancel its sensitivity to GAP, and Ras remains active. However, mutations may also produce defective proliferation-inhibiting proteins. Thus, a loss of Rb or p53 promotes uncontrolled cell division (→ A5). Furthermore, a defect of p53 inhibits apoptosis (→ p. 13 A).

Mutations (→ A, left) can be triggered by chemical cancerogens or radiation, whereby disorders of DNA repair favor the occurrence of mutations. The cells are especially sensitive to mutations during mitosis, i.e., proliferating tissues are more frequently subject to mutation than fully differentiated tissue. This is particularly true for inflammations and tissue lesions, as they stimulate cell division. Tumor-favoring mutations can also be inherited. Lastly, viruses can bring oncogenes into the host cells (→ A6, B1), or can encourage malignant degeneration by inactivation (Rb, p53) or activation (e.g. Bcl2) of host-specific proteins.

A single mutation is not sufficient for the development of a tumor; several mutations must occur (→ C2) before the cell is transformed into a tumor cell. Tumor promoters (e.g., phorbol esters; → p. 6) promote the replication of mutated cells and thus the development of tumors, without themselves causing mutations (→ C3).
A. Mechanisms of Tumor Genesis

Thyroid hormones: T3, T4
Growth factors

1. Sis
2. GRB2, SOS, Raf
3. ErbA
4. ErbB

Tyrosine kinase
Serine/threonine kinase
MAPK cascade

Transcription factors:
E2F, DP1, Fos, Jun, Myc, Myb, Rel

B. Malfunction of Ras

Ras active
GTP
GTP

Ras inactive
P
GDP

Ras mutated
GTP

C. Development of Tumor Cells

1. Viruses
2. Mutations
3. Promoters

Viruses

Mutated cells

Normal cell
Apoptosis

Tumor cells

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Effects of Tumors

If uncontrolled cell division occurs (→ p.14), cells undergo increasing dedifferentiation. If this happens, the changed cells are often recognized and eliminated by the immune system. Tumor cells can escape this development by, for example, expressing the ligand for the CD95 receptor (→ A1) on their surface and thus driving the lymphocytes to apoptosis (→ p.12). A compromised immune response (e.g., HIV infection; → p.58) also helps tumor cells to survive.

If the tumor cell proliferates, a tumor develops that may have severe consequences through its local extension alone. Thus, a brain tumor can displace neighboring neurons and may thus cause, for example, epilepsy (→ A2 and p.338). As the bony nature of the cranium prevents any significant increase in brain volume, a brain tumor ultimately leads to a life-threatening increase in intracranial pressure (→ p.358). A bronchial carcinoma can interrupt the supply of air to the related alveoli and thus provoke their collapse (atelectasis; → p.72).

Markedly dedifferentiated tumors gain the capacity to migrate to other tissues (metastasis; → A3). For this to occur, the tumor cell must free itself from the bonds to its neighbour cells, intrude into blood vessels, leave the bloodstream on reaching another organ, and form new colonies there. Leaving the original site of the cell requires the ability to migrate, and the breakdown of tissue boundaries. The latter is achieved by releasing proteolytic enzymes, or by suppressing expression or action of proteinase inhibitors. Once the tumor cells have entered a blood vessel they get stuck in the next capillary. To leave the bloodstream they must dock onto specific adhesion molecules of the endothelium and break through the vessel wall.

The increase in size of the tumor or its metastases requires the appropriate capillarization, so that the tumor is supplied with O₂ and substrates. Angiogenesis is stimulated through the release of mediators and can be inhibited by angiogenesis inhibitors (e.g. angiostatin, endostatin). If the tumor is very large, the necessary additional blood flow through the tumor increases the circulatory load (cardiac output ↑; → B).

The energy requirement of the tumor cells is frequently met by anaerobic glycolysis, even if the O₂ supply is adequate, although the energy yield per mol glucose is only 5% of the oxidative glucose breakdown. The result is hypoglycemia and acidosis (→ B). The hypoglycemia stimulates the release of glucagon, epinephrine, and glucocorticoids that promote the breakdown of fat and protein. Ultimately, patients will lose weight (tumor cachexia; → B). Sometimes tumor cells can activate hemostasis and/or fibrinolysis so that blood clotting or blood loss may occur. Hemorrhage, the high iron requirement of tumor cells and tumor cachexia commonly lead to anemia (→ p.38).

Tumors often cause abnormalities by a marked increase of tissue-specific activities, or by taking on new, non-tissue-specific activities. Thus, plasma-cell tumors frequently form large amounts of abnormal antibodies that damage organs, for example, the kidneys (→ p.102). Through their dedifferentiation, tumor cells also express proteins, against which antibodies can be formed. Antibodies that have been formed by or against tumor cells can, among other effects, block ionic channels and receptors and thus for example cause myasthenia (→ p.304).

Even small tumors of endocrine tissues and dedifferentiated tumors of non-endocrine tissues (in particular small-cell bronchial carcinoma) frequently cause massive hormonal abnormalities (→ B). The increased release of hormones can result in numerous abnormalities (→ chap. 9), for example, raised blood pressure, hypotonic hyperhydration, catabolism, acromegaly, hypoglycemia, bone breakdown, hypercalcemia and renal stones, polycthemia, hyperthyroidism, virilization, galactorrhoea, diarrhea, and peptic ulcers. On the other hand, hormones are used as diagnostic tumor markers, e.g. calcitonin (medullary thyroid carcinoma), choriogonadotropin (testicular carcinoma among others) and ACTH (lung tumors).

Death of tumor cells, through the release of cellular K⁺, results in hyperkalemia, and the breakdown of nucleic acid leads to hyperuricemia (→ B and p.250).
A. Tumors: Failure of Lymphocytic Defense, Local Damage, and Metastases

1. Lymphocytic defense

- Lymphocyte
- Tumor cell
- CD95 ligand
- Apoptosis

2. Local damage, e.g. brain tumor

- Neuronal displacement
- Intracranial pressure
- Epilepsy
- Migration
- Penetration

3. Metastatic spread

- Blood stream
- Adhesion
- Penetration
- Proliferation

B. Effects of Tumors

- Tumors
- Death of tumor cells
  - Uric acid
  - Hyperuricemia
  - Hypokalemia
  - Hyperkalemia

- Energy requirement
- Glucose consumption
  - Abnormal blood clotting
  - Blood loss
  - Iron consumption
  - Lactate + H⁺

- Iron deficiency
- Angiogenesis
- Acidosis
  - Cardiac output

- Hypoglycemia
  - Glucagon
  - Cortisol
  - Catecholamines

- Adrenal gland dysfunction
  - Blood pressure
  - Aldosterone

- Hormonal disorders
  - Parathyroid hormone, DAF
  - Testosterone
  - VIP, serotonin
  - TSH
  - ADH

- Anemia
  - Parathyroid hormone, DAF
  - Testosterone
  - VIP, serotonin
  - TSH

- Hypothyroidism
- Hyperhydration
- Tumor cachexia
- Bone breakdown
- Galactorrhea
- Ulcers
- Acromegaly
- Renal damage
- Virilization
- Diarrhea
- Hyperthyroidism

- Kidney function impairment
- Cardiac function impairment
- Respiratory function impairment
- Digestive function impairment
- Endocrine function impairment

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Aging and Life Expectancy

Aging is a normal, inevitable process that ends with death. While the mean life expectancy of a newborn is estimated to have been a mere 10 years 50,000 years ago and ca. 25 years in ancient Rome (\(\rightarrow A1\)), it is nowadays between 38 (in Sierra Leone) and 80 years (Japan). It is mainly due to decreased infant mortality and the effective treatment of infections (especially in children) that life expectancy in the industrial nations has increased markedly in the past 100 years (e.g., in the USA from 42 to 72 years in men and to 79 in women). As a result, diseases of the elderly are the most common causes of death: ca. 50% are diseases of the cardiovascular system; 25% are tumors.

These are largely diseases that prevent a maximal life-span being reached, which, now as then, is about 100 years (\(\rightarrow A1\)). Thus, of those aged 98 years, only 10% will still be alive three years later and after 10 years only 0.005% (\(\rightarrow A2\)). The world record set by the French woman Jeanne Calment (122 years) is thus an extremely rare exception.

The causes of aging are unclear. Even individual cultured cells will “age”, i.e., after a certain number of cycles they stop dividing (fetal pulmonary fibroblasts after ca. 60 divisions; \(\rightarrow B\)). Only a few cells are “immortal” (unlimited proliferation, e.g., germinal, tumor, and hemopoietic stem cells). Life-span and age are in part genetically determined. Thus, mutation of the gene age-1 of the nematode can double its life-span, and the human gene that codes for DNA-helicase can cause premature aging (progeria of the adult = Werner’s syndrome).

Recently a gene (MORF4) was discovered whose exclusion by mutation makes cultured cells immortal: if the normal MORF4 gene is passed to (immortal) cancer cells, it stops their proliferation. In “old” cells, MORF4 is up-regulated; in proliferating cells it is down-regulated. The age-1 mutation produces, among other effects, an increased resistance against free radicals. That oxidative damage is important for aging, is also suggested by the fact that membrane lipids, DNA, and proteins damaged by \(O_2^+\) radicals accumulate with age, while at the same time the activity of enzymes that guard against oxidation is reduced. On the other hand, defects of the helicase gene result in the accumulation of harmful somatic DNA mutations and in a decreasing telomere length, which limits the ability of the cell to divide.

Many inherited diseases and (often polygenetically) inherited risk factors, have a secondary effect on life-span, e.g. in favoring the development of certain tumors. Studies of monozygotic (uniovular) twins have, however, shown that at least two thirds of variability of life-span is not genetically determined.

As one gets older, a reduction of bodily functions (\(\rightarrow C\)) occurs as, for example, of maximum breathing capacity, cardiac output (CO), maximal \(O_2\) uptake, and glomerular filtration rate (GFR). Muscle and bone mass decrease, while the amount of fat increases, largely due to endocrine factors (\(\rightarrow D\)). For these reasons it is their frailty that is the limiting factor for most (otherwise healthy) very old persons. This weakness of old age is characterized by diminished muscle power, slowed reflexes, impaired mobility and balance, and reduced stamina. The result is falls, fractures, reduced daily physical activity, and loss of independence. Muscle weakness is not only caused by physiological aging processes (\(\rightarrow D\)) and wear and tear (e.g., damage to joints), but also by lack of movement, leading to a vicious circle.

Purely age-related problems with memory (especially problems of orientation in an unacustomed environment) seem to be caused by a disturbed long-term potentiation in the cortex and hippocampus (reduced density of glutamate receptors, type NMDA, in the dentate gyrus). It is now doubted whether a significant loss of neurons, such as occurs in Alzheimer’s disease or atherosclerosis-induced reduction in cerebral blood flow, is part of the normal process of aging.
A. Life Expectancy

- % of survivors vs. Age (years)
- Graph showing survival rates for different regions and times:
  - 50,000 years ago (Africa)
  - 15,000 years ago (Europe)
  - 3,000 years ago (Europe)
  - 1970 (USA)

B. Dividing Capacity of Cultured Cells

- Number of cells vs. Division generations
- Pulmonary fibroblasts of:
  - Newborns
  - Progeria (Werner’s syndrome)
  - 100-year-old persons

C. Age-dependent Bodily Functions

- Nerve conduction velocity
- Max. breathing capacity
- Cardiac output
- Basal metabolic rate

D. Endocrinology of Aging

- Biological clock (?)
- Anterior pituitary
- 'Somatopause':
  - Skin thickness ↓
  - Muscle mass ↓
  - Bone mass ↓
  - Fat mass ↑
- 'Adrenopause':
  - ACTH ↓
  - Anterior pituitary
  - 'Andropause':
  - Free testosterone ↓
  - Muscle weakness
  - Anemia
  - Mood swings
- 'Somatopause':
  - DHEA (↓)
  - Cardiac output
  - Max. breathing capacity

- Increased risk of:
  - Coronary atherosclerosis
  - Osteoporosis
  - Alzheimer’s disease

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Fever

The aim of thermoregulation is to maintain the actual core temperature of the body at the set level of about 37 °C (with diurnal variations). In contrast to passive hyperthermia (→ p. 22), the set level is raised in fever, and the thermoregulatory mechanisms are thus responsible for maintaining the raised temperature (→ A5, green line). This becomes noticeable when the fever rises: because the actual level deviates from the suddenly raised set level, heat loss is reduced by a decrease in cutaneous blood flow, resulting in cooling of the skin (feeling cold). Additionally, heat production is increased by shivering (tremor). This lasts until the actual level (→ A5, red line) has approached the new set level (plateau). When the fever falls, the set level again falls, so that now the actual level is too high and cutaneous blood flow increases, resulting in the person feeling hot and sweating profusely (→ A5).

Fever is particularly common with infections in the course of the acute-phase reaction (→ p. 49ff.) in which fever-inducing substances (pyrogens) cause a change in the set point. Exogenous pyrogens are constituents of pathogens, among which the lipopolysaccharide complexes (endotoxins) of gram-negative bacteria are particularly effective. Such pathogens, or pyrogens, are opsonized by complement (→ p. 42ff.) and phagocytozed by macrophages, for example, Kupffer cells in the liver (→ A1). These release numerous cytokines, among them the endogenous pyrogens interleukin 1α, 1β, 6, 8, and 11, interferon α2 and γ, the tumor necrosis factors TNFα (cachectin) and TNFβ (lymphotoxin), the macrophage-inflammatory protein MIP 1 and many others. It is thought that these cytokines (Mr = ca. 15–30 kDa) reach the circumventricular organs of the brain which do not possess a blood-brain-barrier. The cytokines, therefore, can cause the fever reaction at these organs or nearby in the area preoptica and the organum vasculosum of the lamina terminalis (OVLT) by means of prostaglandin PGE2 (→ A2). Fever-reducing drugs (antipyretics) are effective here. Thus, acetylsalicylic acid, e.g., inhibits the enzymes that form PGE2 from arachidonic acid (cyclooxygenases 1 and 2).

As after i.v. injection of lipopolysaccharides the above-mentioned cytokines are found only 30 minutes after the onset of the fever and their appearance can be inhibited by subdiaphragmatic vagotomy, it seems that exogenous pyrogens activate the area preoptica and the OVLT also via afferent fibers from the abdomen. It is possible that signaling substances released from the hepatic Kupffer cells (? cytokines, ? PGE2) activate nearby vagal afferents that transmit the pyrogenic signal via the nucleus solitarius to the norepinephrine cell groups A1 and A2. These in turn project from the ventral norepinephrine tract to the fever-regulating neurons in the area preoptica and OVLT (→ A3). Norepinephrine that has been released there causes the formation of PGE2 and thus fever. This also brings about the release of adiuretin (ADH; V1 receptor effect), α-melanocyte-stimulating hormone (α-MSH), and the corticotropin-releasing hormone corticoliberin (CRH), which counteract the fever by means of a negative feedback loop in the form of endogenous antipyretics (→ A4).

As a consequence of fever, heart rate is increased (8–12 min⁻¹/C) and energy metabolism raised, resulting in fatigue, joint aches and headaches (see also p. 49ff.), increase in slow-wave sleep (which has a restorative function for the brain) as well as, in certain circumstances, disturbances of consciousness and of the senses (fever delirium) and seizures (see below).

The value of fever probably lies in its countering infection. The raised temperature inhibits the replication of some pathogens, while actually killing others. In addition, the plasma concentration of essential metals for bacterial reproduction, namely iron, zinc, and copper, is reduced. Furthermore, cells damaged by viruses are destroyed, so that viral replication is inhibited. For these reasons antipyretics should in general only be used if the fever leads to febrile convulsions, common in infants and young children, or rises so high (> 39 °C) that the onset of seizures is to be feared.
Feeling cold, little cutaneous blood flow, rigor
Feeling hot, high cutaneous blood flow, sweating

Core temperature °C

Energy metabolism
Heart rate (8 – 12 min⁻¹/°C)

Fever delirium
Slow-wave sleep
Febrile fits (infants, young children)
Headache, joint pain

Set level
Actual level

Fever

Exogenous pyrogens (lipopolysaccharides)
Macrophages
Kupffer cells of the liver

Endogenous pyrogens (= div. cytokines)
Norepinephrine
Arachidonic acid
PGE₂

Nucl. solitarius
Medulla oblongata
Noradrenergic tracts

Preoptic area, OVLT
Vagal nerve

Replication of pathogens
Virus replication

Adenosine
Noradrenergic tracts
Hyperthermia, Heat Injuries

On severe physical effort (increased heat production) and/or in a hot environment (decreased net heat loss) the thermoregulatory mechanisms of the organism are overtasked, especially when there is a lack of water and at high ambient humidity. In contrast to the situation in fever (→ p. 20), the body's core temperature can no longer be kept at the (unchanged) set level of ca. 37 °C and hyperthermia results (→ A, top). On standing upright, heat-induced vasodilation causes some of the blood to pool in the legs, and the extracellular volume is reduced by sweating. As a result, cardiac output (CO) and blood pressure fall, particularly because vasodilation in the skin reduces peripheral vascular resistance. Even at a core temperature below 39 °C, weakness, dizziness, nausea, and loss of consciousness may occur as a consequence of reduced blood pressure (heat collapse; → A1). Blood pressure will again rise on lying down and after taking fluids.

A much greater danger arises when the core temperature reaches 40.5 °C, because the brain cannot tolerate such temperatures. To protect itself against heat stroke the brain can temporarily be kept cooler than the rest of the body because a rising core temperature causes profuse sweating of the head (even with dehydration), especially the face (→ A2). Blood that has been cooled in this way reaches the endocranial venous system and the sinus cavernosus, where it lowers the temperature of the neighboring arteries. This would seem to be the only explanation for the fact that a marathon runner in whom a transient rise in core temperature to 41.9 °C had been measured did not suffer from heat stroke.

If there is a prolonged rise in core temperature to between 40.5 and 43 °C, the thermoregulatory center in the midbrain fails (→ p. 20) and sweating ceases. Disorientation, apathy, and loss of consciousness result (heat stroke). Cerebral edema with accompanying damage to the central nervous system will, without rapid help, lead to death; children are especially at risk because their surface area to body mass ratio is larger than adults’, and they produce less sweat. Treatment of heat stroke consists of bringing the person into a cooler environ-

ment and/or submerging them into cool water. However, the body surface must not be allowed to get too cold, because the resulting vasocostriction would delay the reduction in core temperature. Even successfully treated heat stroke may leave lasting damage in the thermoregulatory centers. This restricts future tolerance to extreme ambient temperatures.

Malignant hyperthermia (→ B) is the potentially lethal result of heterogeneous genetic defects of sarcoplasmic Ca2+ transport, in which the Ca2+-releasing channel (ryanodine receptor) is affected. Some inhalation anesthetics (halothane, enflurane, isoflurane) and depolarizing muscle relaxants (suxamethonium chloride) cause the sudden and excessive release of Ca2+ from the sarcoplasmic reticulum, so that generalized, uncoordinated muscle twitches occur with high oxygen consumption and enormous heat production. The result is acidosis, hyperkalemia, tachycardia, arrhythmia, and rapidly rising hyperthermia. If recognized in time, malignant hyperthermia can be successfully treated by discontinuing the anesthetics and/or muscle relaxants, administering dantrolene, which blocks Ca2+ release in skeletal muscle cells, as well as cooling the body.

Heat cramps occur with strenuous physical work in high ambient temperature (e.g., at a furnace) if only the loss of water, but not of salt, is replaced.

Sun stroke must be distinguished from hyperthermia. It is caused by direct sun radiation on head and neck and causes nausea, dizziness, severe headache, cerebral hyperemia, and serous meningitis and may end fatally.

Contact or radiant heat may cause first degree, second degree, or third degree burns (reddening, blisters, or necroses, respectively) to the skin. Frequent and intense exposure to the sun also increases the risk of melanoma.
A. Heat Collapse, Heat Stroke

Core temperature

Hyperthermic
Normothermic
Hypothermic

1. Vasodilation, sweating
   - Standing
   - Orthostasis
   - Recumbant

2. Dehydration
   - CO
   - Blood pressure

- Core temperature
- Reduced heat loss
- Increased heat production and uptake

- Brain temperature
- Cooling of the cerebral veins
- Failure of heat loss (dry skin)

- Brain temperature
- Heat stroke
- Cerebral edema
- CNS damage
- Death

- Weakness
- Nausea
- Dizziness
- Unconsciousness

B. Malignant Hyperthermia

Inhalation anesthesia, muscle relaxants

If genetically disposed

Generalized muscle contractions

Sarcoplasmic reticulum

Dantrolene

- Energy consumption
- Lactic acid
- Acidosis
- Vasodilation

- O₂ deficiency
- Cellular loss of K⁺
- Arrhythmias, heart failure
- Hyperkalemia

- Heat production
- Core temperature
- Coma

- Drop in blood pressure
- Coma
Hypothermia, Cold Injury

If there is a danger of the core temperature dropping, (counter)regulatory heat production results (muscle tremor and movement) (→ A). Its narrow limits are usually not overstepped, because the risk of cooling triggers behavioral changes, depending on the underlying cause(s) (protection against wind, added clothing, leaving swimming pool, etc.). If this reaction does not occur—either because it is not possible to escape the situation for physical reasons, the danger is not realized, or there are metabolic, hormonal, or neurological abnormalities—hypothermia develops, i.e., the core temperature drops below 35°C (→ A). Immersion in water at 5–10°C can lead to hypothermia after only 10 minutes (depending on the amount of “padding”). Wearing wet clothing in a strong wind and in an ambient temperature of 0°C can bring about hypothermia in less than one hour. Both the elderly (restricted thermoregulatory range) and infants (especially newborns), who have a relatively high body surface area to mass ratio, low resting heat production, and a thin subcutaneous fat layer are particularly at risk. While unclad young adults can maintain a constant core temperature even when the ambient temperature drops to ca. 27°C because of their resting heat production, hypothermia may develop in a newborn at an ambient temperature of <34°C.

The acute sequelae and symptoms of hypothermia can be divided into three stages (→ A, I–III):

◆ Stage of excitement (mild hypothermia, 32–35°C): maximal muscle tremor, resulting in a marked increase in resting metabolic rate, all sources of glucose are utilized (hyperglycemia), and O₂ consumption is increased up to sixfold. Tachycardia and vasoconstriction cause a rise in blood pressure; acral vasoconstriction causes pain. The person is at first fully awake, later confused and even apathetic, and ultimately judgment becomes impaired.

◆ Stage of exhaustion (moderate hypothermia, 32–28°C): the sources of glucose become exhausted (hypoglycemia); bradycardia, arrhythmia, and depressed breathing occur and the person begins to hallucinate and to behave perplexingly, soon losing consciousness and no longer feeling pain.

◆ Stage of paralysis (severe hypothermia, < ca. 28°C): coma; no pupillary reflexes (but no sign of brain death); ultimately ventricular fibrillation, asystole, and apnea. The lower the temperature until cerebral blood flow ceases, the longer the brain will tolerate circulatory arrest (30°C: 10–15 min; 18°C: 60–90 min). This is why some persons have survived extreme hypothermia (<20°C). The long time of circulatory arrest tolerated at low temperature is also of use in induced therapeutic hypothermia (during open-heart surgery and preservation of organs for transplantation).

Rewarming of hypothermic patients should still be attempted even if the core temperature has dropped below 20°C. However, rewarming may be associated with lethal complications, especially if it is done externally and too rapidly, i.e., more quickly than a few °C per hour (→ B). In stage I (>32°C), warming is done passively and externally (warm room, blankets, foil). In stage II, active warming must be undertaken (electric blankets, warm infusions, possibly hemodialysis with heat exchanger) under careful monitoring. In stage III hypothermia with circulatory arrest, active warming by means of extracorporeal circulation (heart-lung machine) is the most effective method of rewarming.

Long-term sequelae of successfully treated hypothermia include heart failure, liver and kidney failure, abnormal erythropoiesis, myocardial infarction, pancreatitis, and neurological disorders.

Frostbite. Even with mild hypothermia and/or low ambient temperature the perfusion of skin and limbs is markedly reduced, with intermittent and brief increases (Lewis reaction: about every 20 min at a skin temperature <10°C). None the less, frostbite may occur: 1st degree (at first pallor and loss of sensation; swelling and pain after rewarming); 2nd degree (blister formation after 12–24 h followed later by healing); 3rd degree (after days and weeks: extensive tissue necrosis with healing by scar).
A. Hypothermia

Hypothermia

Muscle tremors

Behavioral changes

Not possible/insufficient:

- Cold water (accident at sea, falling through ice), snow avalanche, fall into glacier crevasse, mountain accident
- Sleeping rough, malnutrition
- Shock, loss of consciousness, effect of alcohol or drugs, barbiturates (attempted suicide)
- Psychiatric illness, hypothyroidism, Parkinson’s disease

Predisposition:

- Infant, young child: Helpless, unable to appreciate danger, large surface to mass ratio, low heat production at rest, thin subcutaneous tissue
- In the elderly: Disorientation, narrow range of thermal regulation

Accidental hypothermia

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
<th>Metabolism</th>
<th>Level of consciousness</th>
<th>Cardiovascular system, respiration</th>
<th>Rewarming</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Cold tremors, pain (distal parts of limbs)</td>
<td>Metabolism ↑↑</td>
<td>Wide awake and agitated</td>
<td>Tachycardia, peripheral vasoconstriction</td>
<td>Warm room, blankets</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperglycemia ↑</td>
<td>Confused</td>
<td>Blood pressure ↑</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Muscle rigidity, pupillary reflex still active</td>
<td>Hypoglycemia ↓</td>
<td>Hallucinations, somnolent</td>
<td>Bradycardia, Depressed breathing</td>
<td>Electric blanket, warm infusion, hemodialysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Unconscious</td>
<td>Arrhythmias</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Wide, light insensitive pupils</td>
<td>Metabolism ↓</td>
<td>Coma</td>
<td>Ventricular fibrillation Asystole Apnea</td>
<td>Extracorporeal circulation</td>
</tr>
</tbody>
</table>

B. Complications of Rewarming

- Myocardial injury
- Hypovolemia

Peripheral vasodilation

Cold peripheral blood reaches body core

Hypothermia (after-drop)

Arrhythmia

Shock

Heart failure

Increased cardiac load

Acidic peripheral blood reaches body core

Acidosis

Blood pressure
Obesity, Eating Disorders

Several regulatory circuits are considered to be responsible for regulating body weight, each governed by the hypothalamus, for example, by its ventromedial nucleus as the “satiety center” and by the lateral hypothalamus as the “eating center”. The regulatory cycle that is probably decisive in the long term is the lipostatic mechanism: the body’s fat mass is recognized on a basis of a substance that is secreted by the fat cells (probably leptin, see below), and a feedback loop keeps this fat mass constant during changes in appetite and physical activity (→ A). Thus fat, even if surgically removed, is rapidly replaced.

Obesity (adiposity, excess weight) is a risk factor for hypertension, type 2 diabetes mellitus, hyperlipidemia, atherosclerosis as well as renal stones and gallstones. More than 40% excess weight is associated with a twofold risk of premature death. Obesity is partly of (poly)genetic, partly of environmental origin. Its causes are little known. Two defective genes have been discovered, one in two male mouse strains with extreme obesity and one in type 2 diabetes. If the ob[esity]-gene is defective, the 16-kDa protein leptin, coded by the ob-gene, is absent from plasma. Injection of leptin into mice with homozygotic ob mutation counteracts the symptoms of the gene defect. Its administration to normal mice leads to weight loss. But if the db-gene has mutated, the leptin receptor in the hypothalamus (in the arcuate nucleus, among other sites) is defective. While high concentrations of leptin circulate in plasma, the hypothalamus does not respond to them. Some obese persons also have a defective leptin gene, but in most others the plasma leptin concentration is high. In this case the feedback chain after leptin must have been interrupted somewhere (→ A, red X). Various possible defects have been postulated:

◆ Leptin can no longer overcome the blood-brain barrier (? defective transcytosis).
◆ The inhibitory effect of leptin on the secretion of neuropeptide Y (NPY) in the hypothalamus, which stimulates food intake and reduces energy consumption, is abnormal.
◆ Leptin does not cause the release in the hypothalamus of α-melanocortin (melanocyte-stimulating hormone [α-MSH]), which acts there via MCR-4 receptors and has the opposite effect of NPY.

Quite recently a homozygotic leptin receptor defect was found in three very obese sisters. As they had never gone through puberty and the secretion of both somatotropin hormone and thyrotropin-releasing hormone had been reduced, it seems that leptin also plays a part in other endocrine regulatory cycles.

In 90% of cases of eating disorders it is young women who are affected, bulimia nervosa (bouts of overeating followed by self-induced vomiting and/or purgative abuse) being more common than anorexia nervosa (self-induced weight loss through very restrictive diet). These eating disorders are characterized by a distorted body self-image (the patients feel “too fat” even though they have a normal or below normal weight) and an abnormal attitude toward eating (association between the sense of one’s own worth and body weight). There is a genetic disposition (50% concordance in monozygotic twins), without the primary genetic defect being known. Psychological factors, such as disturbed family interaction (overprotectiveness, avoidance of conflict, rigidity) and sexual-pubertal conflicts as well as socio-cultural influences (ideals of beauty, social expectations) are probably significant.

The disorder in anorexia nervosa (→ B) ranges from eating a very restrictive diet to complete refusal to eat, and often includes purgative abuse. This results in marked weight loss, even cachexia, which may require drip feeding. It leads to severe autonomic–hormonal disorders, for example, increased cortisol and diminished gonadotropin release (amenorrhea; loss of libido, and impotence in males), and even hypothermia, bradycardia, hair loss, etc. If the condition takes a prolonged course, the mortality rate can be up to 20%.

Bulimia is characterized by eating binges followed by self-induced vomiting; a reasonably normal body weight may be maintained.
A. Obesity

- Hypothalamus
- NPY
- α-MSH
- Arcuate nucleus, etc.
- MCR-4 receptor

- ‘Eating center’ etc.
- ‘Satiety center’ etc.

- NPY inhibition abnormal
- Leptin receptor defect
- Receptor defect
- Transcytosis defect

- Leptin in plasma
- Blood-brain barrier

- Obesity
- Hypertension
- Diabetes mellitus II
- Hyperlipidemia
- Atherosclerosis
- Renal stones
- Gallstones

B. Anorexia Nervosa

- Genetic predisposition
- Psychological factors
- Sociocultural factors

- Abnormal body image
- Deliberate vomiting
- Laxative abuse
- Extreme physical activity

- Weight loss (on average ~45%)

- Cortisol
- Gonadotropin
- Hypothermia
- Bradycardia
- Loss of hair etc.

- Malnutrition
- Cachexia

- Psychological changes

- Abnormal regulation of autonomic nervous system and hormones
Overview

Total blood volume correlates with the (fat-free) body mass (→ Table below) and averages 3.6 L in women and 4.5 L in men. The blood’s tasks include transporting various substances (O₂, CO₂, nutrients, metabolic products, vitamins, electrolytes, etc.), the transport of heat (heating, cooling), signal transmission (hormones), and buffering as well as defense against foreign materials and microorganisms. The blood cells (→ A and Table below) are involved in this, the erythrocytes being responsible for O₂ and CO₂ transport and a part of pH buffering. Among the leukocytes, the neutrophil granulocytes (neutrophils) are responsible for nonspecific immune defenses, and the monocytes and lymphocytes for specific immune reactions. The thrombocytes (platelets) are important for hemostasis. The ratio of blood cell volume to total blood volume is called hematocrit (Hct) (→ p. 31 A). More than 99% of the Hct is made up of erythrocytes.

In the fluid phase of blood, called plasma, electrolytes, nutrients, metabolic products, vitamins, gases and proteins are held in solution (→ Table). Among the tasks of the plasma proteins are humoral immune defense, maintenance of colloidal osmotic (oncotic) pressure, which is responsible for maintaining a constant blood volume, as well as the transport of water-insoluble materials and the protection of various substances against their breakdown in blood, and their excretion by the kidneys (e.g., heme). This protein-binding of small molecules lowers their osmotic power, while they can acquire an antigenic effect (→ p. 52 f.) as haptnets. The coupling of hormones, drugs, and toxins to plasma proteins reduces their signaling, therapeutic, or toxic action, while at the same time preventing their rapid excretion. Finally, numerous plasma proteins participate in blood clotting and fibrinolysis. When blood clots, the fibrinogen in plasma is used up and serum is formed.

Formation of blood cells (→ A). The hematopoietic tissue, i.e., red bone marrow in adults, the spleen and liver in the fetus, contain pluripotent stem cells that, under the effect of hematopoietic growth factors (see below), differentiate into myeloid, erythroid, and lymphoid precursor cells. These stem cells reproduce in such a way that their stock is maintained throughout life (→ p. 2 ff.). While the lymphocytes that originate from the lymphoid precursors still require further maturation (partly in the thymus, partly in the bone marrow) and are later on formed in the spleen and the lymph nodes (lymphopoiesis), all other precursor cells proliferate and mature up to their final stage in the bone marrow (myelopoiesis), until they finally pass from there into the blood (→ A). Among other factors, two renal hormones are involved in this, namely erythropoietin for the maturation and proliferation of erythrocytes (→ A and p. 32), and thrombopoietin for megakaryocytes and thrombocytes, respectively (→ A). There are additional paracrine factors that regulate blood cell formation in the bone marrow. Because of their action in cell culture, they are sometimes also called colony-stimulating factors (CSFs). Other stem cell growth factors are stem cell factor (SCF = steel factor = c-kit ligand) and fit3 ligand (FL). They trigger the release of synergistically active factors, such as CSF and interleukins (IL-3, IL-6, IL-11, IL-12) and are inhibited, among others, by transforming growth factor β (TGF-β) and tumor necrosis factor α (TNF-α).

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| Total Blood | Blood volume (L) | 0.041 · kgKG + 1.53; 0.047 · kgKG + 0.86 |
| Erythrocytes | Hematocrit (l_cells/l_blood) | 0.40 – 0.54; 0.37 – 0.47 |
| | Number (10¹²/l_blood = 10⁶/µl_blood) | 4.6 – 6.2; 4.2 – 5.4 |
| | Hemoglobin (g/l_blood) | 140 – 180; 120 – 160 |
| Leukocytes | Number (10⁹/l_blood = 10⁷/µl_blood) | 3 – 11 (of which 63 % granuloc., 31 % lymphoc., 6 % monoc.) |
| Thrombocytes | Number (10⁹/l_blood = 10⁷/µl_blood), 170 – 360; 180 – 400 |
| Plasmaproteins | (g/l Serum) | 66 – 85 (of which 55 – 64 % albumin) |
A. Maturation Sequence and Differentiation of Blood Cells

Pluripotent stem cells

Lymphoid precursor cells

Erythrocytic precursor cells

Myeloid precursor cells

Stem cell factor, interleukins
From stroma cells in bone marrow

Specific immune defense

Thymus

Bone marrow

T cells

B cells

Gas transport

Erythropoietin

Thrombopoietin

Kidney

Erythrocytes (RBCs)

Megakaryocytes

Hemostasis

Thrombocytes

Immune defense

Eosinophil leukocytes

Neutrophil leukocytes

Basophil leukocytes

Monocytes

Mast cells

Heparin, histamine

Tissue macrophages

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Erythrocytes

Erythrocytes (red blood cells [RBCs]) are formed in bone marrow from nucleus-containing erythroid precursor cells (→ B and p. 29 A) and reach the bloodstream as nucleus-free and mitochondria-free, disc-shaped cells (ca. 7.5 × 2 µm). They can be severely deformed within the blood capillaries, which greatly facilitates both their passage and the exchange of substances and gases with the surrounding tissues. RBCs that have recently entered the blood will retain net-like residues of organelles (reticulocytes) for another one or two days. With a normal life-span of RBCs of about 110–120 days, the proportion of reticulocytes is normally 1–2%.

Erythrocytes contain a large amount of hemoglobin (Hb), their mean corpuscular hemoglobin concentration (MCH) normally being 300–360 g per litre RBCs (→ A). Since a normal RBC has a volume (MCV) of 80–100 fl, it contains 26–35 pg Hb (MCH).

The high hemoglobin content largely contributes to intracellular osmolality so that, to avoid osmosis-induced entry of water, the intracellular ion concentration has to be held at a lower level than that in plasma. Na⁺-K⁺-AT-Pase is essential for this, the required ATP (adenosine 5'-triphosphate) in the RBCs (because of the absence of mitochondria) coming from anaerobic glycolysis. Volume regulation itself happens indirectly, especially via the volume-sensitive ion transporters that can lower the K⁺ and Cl⁻ content of RBCs (→ p. 10 f.). If ATP production ceases or the membrane is damaged, the RBCs swell and thus have a shorter survival time (premature hemolysis).

The RBCs regularly leave the arterioles in the pulp of the spleen and reach the small pores in the splenic sinuses. Old and abnormally fragile erythrocytes are separated out and destroyed in the region of these pores. The fragments are phagocytized by the macrophages in the spleen, liver, bone marrow, etc. and broken down (extravascular hemolysis in the reticuloendothelial system [RES], or more precisely, the mononuclear phagocytic system [MPS]; → p. 44). The liberated heme is broken down into bilirubin (→ p. 168), the liberated iron is reused (→ p. 38). If there is intravascular hemolysis, Hb that has been released can to a certain extent be bound to haptoglobin (→ p. 38). This reduces the glomerular filtration of Hb and thus its elimination (hemoglobinuria).

Erythropoiesis, Anemia

Anemia is the term given to the reduction in the number of erythrocytes, in the concentration of hemoglobin and/or in the hematocrit as long as the total blood volume is normal. Shortly after acute major blood loss, in dehydration, or in hyperhydration the blood volume must first be normalized before anemia can be diagnosed. Using the erythrocyte parameters mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH) (→ A), anemias can be classified according to cell volume (MCV: microcytic, normocytic, or macrocytic) and according to the ratio of Hb concentration/erythrocyte count (MCH: hypochromic, normochromic, or hyperchromic). Pathogenetic division of the anemias reflects the individual steps of erythropoiesis as well as the life-span of the erythrocytes circulating in blood (hemolytic anaemia; → B). Finally, acute or chronic blood loss can also lead to anemia.

Disorders of erythropoiesis (→ B) may occur as a result of 1) lack or absence of differentiation of pluripotent, hemopoietic stem cells (aplastic anemia in panmyelopathy or acute myeloid leukemia); 2) transient (viral infection) or chronic reduction of only the erythrocytic precursor cells (isolated aplastic anemia) due to autoantibodies against erythropoietin or against membrane proteins of the precursor cells; 3) erythropoietin deficiency in renal failure (renal anemia); 4) chronic inflammation or tumors that can activate, among others, erythropoiesis-inhibiting interleukins (secondary anemia); 5) abnormal cell differentiation (ineffective erythropoiesis), which in addition to gene defects may mainly be due to a deficiency in folic acid or vitamin B₁₂ (megaloblastic anemia; → p. 34); 6) abnormal Hb synthesis (microcytic hypochromic anemia; → p. 36 ff.).
A. The Erythrocyte Parameters MCH, MCV, and MCHC

Blood sample

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Formula</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCH (mean Hb mass/RBC)</td>
<td>( \frac{\text{Hb conc.} \times \text{No. RBC}}{\text{g/RBC}} )</td>
<td>~30 pg</td>
</tr>
<tr>
<td>MCV (mean volume of one RBC)</td>
<td>( \frac{\text{Hct} \times \text{No. RBC}}{\text{L/RBC}} )</td>
<td>~90 fl</td>
</tr>
<tr>
<td>MCHC (mean Hb conc. in RBCs)</td>
<td>( \frac{\text{Hb conc.}}{\text{Hct}} )</td>
<td>~320 g/L</td>
</tr>
</tbody>
</table>

Erythrocytes (RBC) (number/L blood)

Hemoglobin (Hb) concentration (g/L blood)

Erythrocyte

B. Forms of Anemia

- Defect of differentiation
- Virus infection
- Autoimmune reaction
- Gene defect
- Folic acid deficiency
- Iron deficiency
  - defects (membrane, metabolism)
  - damage (mechanical, immunological, toxic)
- Defect of globin synthesis
- Defect of heme synthesis
- Parasites (malaria etc.)
- Panmyelopathy
- Aplastic anemia
- Renal anemia
- Megaloblastic anemia
- Microcytic hypochromic anemia
- Hemolytic anemia

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Erythrocyte Turnover: Abnormalities, Compensation, and Diagnosis

Proliferation and differentiation of the erythroid precursor cells up to the mature erythrocytes takes barely a week. This time can be shortened to a few days if erythropoiesis is stimulated, for example, by an increase in cell loss (hemolysis or bleeding). As the average life-span of RBCs in peripheral blood is more than 100 days, a brief disorder of cell formation is not detectable, but increased cell loss quickly results in anemia. (With neutrophil leukocytes, whose differentiation time is roughly as long, the reverse is the case, because their life-span in peripheral blood is only about 10 hours: neutropenia occurs if there is an acute disorder of cell formation, but not after cell loss.)

With a survival time of ca. 10^7 sec and a total RBC count of ca. 1.6 x 10^13 in blood, the rate of formation is 1.6 million erythrocytes per second. If necessary, this production rate increases up to tenfold without causing bone marrow exhaustion. Life-long hemolytic anemia, for example, can thus largely be compensated.

Disorders of erythrocyte metabolism, be it abnormal erythropoiesis in its various steps (→ A), a shortened life-span, or chronic blood loss, can be differentiated by means of a number of diagnostic parameters:

- **Stem cells** obtained by bone marrow puncture can be stimulated to proliferate and differentiate by erythropoietin in a cell culture. Colonies of more or less differentiated, hemoglobin-containing cells (E) are formed in this way (burst-forming units [BFU-E] or colony-forming units [CFU-E]). Their number is decreased if the anemia is caused by abnormal cell formation; it is increased if the cells are lost in a late stage of differentiation (erythroblast, erythrocyte) (→ A1).
- **Erythroblasts** can be morphologically identified and quantified in a stained bone marrow sample. They decrease in number in aplasias and in defects of stem cell differentiation; they increase if erythropoiesis is stimulated, for example, by increased hemolysis (→ A2).
- The efficiency of the entire erythropoiesis can be measured by determining the number of reticulocytes (→ p. 30). If the number of reticulocytes is reduced, one must assume an abnormality of cell formation (→ A3) because the second, theoretically possible cause, a prolongation of RBC life-span, does not occur. On the other hand, a longer lasting increase in reticulocyte numbers (reticulocytosis) is evidence for a chronically shortened life-span in the circulation on the part of the RBCs (chronic bleeding or hemolysis). Transitory reticulocytosis is a sign of stimulated erythropoiesis, for example, after acute blood loss, after acute hemolysis, or after correction of abnormal cell formation (with a high level of erythropoietin; → B2, 3).
- When erythrocytes are broken down in macrophages (→ p. 30), bilirubin, formed from liberated heme, is excreted in the bile after conjugation in the liver. The concentration of unconjugated ("indirect") bilirubin in serum is increased in hemolysis (→ A4 and p. 164 ff.), but in some circumstances also if hemoglobin turnover is increased as a result of ineffective erythropoiesis.
- The life-span of RBCs (shortened in hemolytic anemia; → A5) as well as their total volume can be measured by marking the erythrocytes in vitro with radioactive ^{51}Cr (binding Cr to the Hb-β chain) and then re-infusing them. As ^{51}Cr is released in hemolysis and then excreted by the kidneys, the erythrocyte life-span can be calculated from the loss of radioactivity measured daily. Total erythrocyte volume can be determined from the amount of ^{51}Cr injected and the initial ^{51}Cr concentration in blood, using the principle of indicator dilution.
- Measuring erythropoietin (→ A6). Lowered concentration of plasma erythropoietin suggests the anemia is caused nephrogenically (→ B4). However, most anemias are associated with a (compensatory) increase in erythropoietin concentration (→ B2, 3).
A. Diagnostic Parameters in Anemia

<table>
<thead>
<tr>
<th>Defect of differentiation</th>
<th>Virus infection</th>
<th>Autoimmune reaction</th>
<th>Bone marrow</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFU-E, CFU-E</td>
<td>No. of erythroblasts</td>
<td>No. of retikulocytes</td>
<td>BFU-E, CFU-E</td>
<td>No. of erythroblasts</td>
</tr>
<tr>
<td>Erythropoietin</td>
<td>Erythrocyte life-span</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

B. Erythropoietin Concentration as Anemia Indicator

1. Normal regulation cycle
2. Abnormality of erythrocyte or hemoglobin formation
3. Hemolysis, blood failure
4. Renal failure
Megaloblastic Anemia Due to Abnormalities in DNA Synthesis

Some acquired forms of anemia are due to abnormalities in the absorption or metabolism of folate or cobalamin (vit. B₁₂) (→ A). The result is that DNA synthesis is inhibited and the cell cycle is slowed down during erythropoiesis. However, hemoglobin synthesis in the cytoplasm continues unchanged so that the erythroblasts increase in size (megaloblasts) and over-large, oval erythrocytes pass into the blood (megalocytes: MCV > 100 fl). The formation of granulocytes and megakaryocytes is also disturbed. In addition to the delay in proliferation, the anemia is aggravated by the premature destruction of megaloblasts in bone marrow (increased inefficient erythropoiesis; → p. 38) as well as by the shortened life-span of the megalocytes that have passed into the blood (premature hemolysis).

Folate. The folate metabolite N⁴, N¹⁰-methylene-tetrahydrofolate is necessary for the synthesis of deoxythymidylate (→ A₃), the only source of thymine, which is in turn necessary for DNA synthesis. Thus, a folate deficiency inhibits DNA synthesis. This particularly affects the rate of formation of rapidly proliferating cells, for example, during erythropoiesis and tumor formation. The folate requirement for two to four months is stored in the liver. Folate is largely present in food in the form of pteroylpolyglutamate, from which excess glutamate residues must be split off before it can be absorbed in the form of pteroylmonoglutamate in the upper small intestine (→ A₁). N⁵-methyltetrahydrofolate, the substrate for tetrahydrofolate formation (→ A₂), is then formed in the intestinal mucosa. Methylene-cobalamin is essential for this step (see below). N⁰, N¹⁰-methyltetrahydrofolate is formed from tetrahydrofolate, the former together with deoxyuridylate being metabolized through the action of thymidylate synthase to deoxythymidylate and 7,8-dihydrofolate. Finally, the used up tetrahydrofolate is regenerated from 7,8-dihydrofolate (→ A₃).

The following disorders of folate absorption or metabolism impair DNA synthesis, and thus erythropoiesis:

◆ Too little folate uptake with food (< 50 µg/d; overcooking food destroys folate);
◆ Increased requirement (pregnancy);
◆ Malabsorption, for example, in diseases of the small intestine, or inhibition of the folate carrier caused by methotrexate (→ A₁);
◆ Cobalamin deficiency (→ A₄);
◆ Inhibition of thymidylate synthase by the fluorouracil metabolite fluorodeoxyuridylate;
◆ Inhibition of dihydrofolate reductase by amnipterorin or methotrexate, whose affinity for the enzyme is 100 times that of the natural substrate 7,8-dihydrofolate (→ A₃).

As inhibition of folate metabolism also retards tumor growth, the drugs fluorouracil, methotrexate, and amnipterorin are used as cytostatic chemotherapeutics. Their side effect on erythropoiesis is usually undesirable and therefore often limits their dosage.

◆ Cobalamin (vitamin B₁₂) must be taken up by humans in their food (daily requirement: 3 – 5 µg). About a thousand times this amount is stored in the liver. Bound to different proteins, it is transported inside the organism from food to the site of its action where, in the form of methylcobalamin, it serves as coenzyme in demethylating N⁵-methyltetrahydrofolate (→ A₂). Among possible causes of cobalamin deficiency are (→ A₄):

◆ Too little uptake with food (e.g., a strict vegetarian diet);
◆ Intrinsic factor (IF) deficiency (in atrophic gastritis etc.; see p. 142): IF is essential for the binding and absorption of cobalamin. It is freed from its binding to salivary proteins in the lumen of the small intestine;
◆ Competition for cobalamin and splitting of IF from bacteria (blind-loop syndrome; → p. 148), or broad fish tapeworms in the intestinal lumen;
◆ Absence (congenital, after resection) or inflammation of the terminal ileum, i.e., at the site of absorption of cobalamin (→ p. 152f.);
◆ Defective transcobalamin II (TCII), which is responsible for cobalamin transport in plasma and for its uptake into cells.

Because of the great store of cobalamin in the liver, the symptoms of cobalamin deficiency (pernicious anemia, neurological abnormalities) occur only after years of blocked supply.
A. Anemias Caused by Disorders of DNA Synthesis

Folate deficiency

1. Mucosal cell (jejunum)
2. Cellular metabolism
3. Impaired folate metabolism

B. Cobalamin (vitamin B₁₂)

1. Gastric emptying
2. Intestinal absorption
3. Transport of cobalamin (vitamin B₁₂)
4. Intracellular localization

Homocysteine
Methionine

Methotrexate

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Anemias Due to Disorders of Hemoglobin Synthesis

Erythrocytes (RBCs) serve to transport $O_2$ and $CO_2$ and also as a buffer. Hemoglobin (Hb) is essential for all three functions. It is composed of four subunits ($2\alpha, 2\beta$) in HbA; see below), each of which is formed from three components: protoporphyrin, iron ($Fe^{2+}$) and globin ($\alpha$ or $\beta$). When $Fe^{2+}$ is built into protoporphyrin, heme is formed. If there is a deficiency or defect in one of the components, Hb synthesis is impaired. In this case the RBCs are usually small (MCV↓) and their Hb content decreased (MCH↓) (microcytic hypochromic anemia).

Disorders of protoporphyrin synthesis are due to inherited enzyme defects (→ p. 254), as for example, in hereditary sideroblastic anemia, in which the formation of δ-aminolevulinic acid (δ-ALA) from glycine and succinyl-CoA is reduced, and thus also heme synthesis (→ A1). Heme inhibits δ-ALA synthase in a negative feedback loop. If heme concentration is now reduced, inhibition of the enzyme is reversed and, despite the defect, sufficient amounts of heme are formed. Defects in subsequent enzymes lead to an increase in the concentration of intermediary products. While the rate of heme production is thus increased, these metabolites cause other disorders, namely porphyrias (→ p. 254).

Disorders of globin synthesis. Normally Hb is made up of 2 $\alpha$ chains of 141 amino acids each and 2 $\beta$ chains of 146 amino acids (HbA1 = HbA$\alpha_2\beta_2$). Only 2–3% of Hb contains so-called $\delta$-chains (HbA2 = Hb$\alpha_2\delta_2$) instead of the $\beta$-chains. Before birth a form of Hb is formed that has a higher $O_2$ affinity (adaptation to a lower $P_O_2$ in the placenta). This fetal Hb (HbF) contains so-called $\gamma$-chains (Hb$\alpha_2\gamma_2$) instead of the $\beta$-chains.

The properties of Hb (solubility, $O_2$ affinity, oxidizability, etc.) are dependent upon the particular amino acid sequence. However, most of the over 300 genetically-determined Hb variants which have been identified so far do not significantly impair function. On the other hand, even a single “false” amino acid (valine instead of glutamate in position 6 in the $\beta$-chain = HbS; → A2) can lead to extensive functional disorders, as seen in sickle cell anemia, which is caused by a homozygous gene defect. In the deoxygenated form, HbS aggregates in a way that results in sickle-shaped erythrocytes (→ A). These sickle cells cannot be further deformed and get stuck inside the capillaries, causing occlusion of smaller blood vessels. Aggregation of HbS takes a few minutes so that it is especially those capillaries through which the blood flows slowly which are affected (spleen; vasa recta of the renal medulla; → p. 106). If blood flow is slowed in general (shock) or if hypoxia occurs (at high altitude, during a flight, anesthesia), the abnormalities can spread to other organs (e.g., to the heart). Occlusion of the blood vessels further slows down blood supply in the affected regions and the $P_O_2$ is further reduced, so that a vicious circle results (crisis). Sickle cell anemia occurs nearly exclusively in blacks who themselves, or whose forbears, come from regions of Central Africa with a high prevalence of malaria. “Survival” of the defective gene in 40% of the population in Central Africa, despite the fact that until recently the disease was fatal in homozygous children, can be explained by the fact that heterozygous gene carriers are protected against the dangerous forms of malaria (selective advantage).

In β-thalassemia the production of $\beta$-chains is restricted, thus leading to a deficiency of HbA. It can be only partly compensated by an increased production of HbA2 and HbF. The incorporation of $Fe^{2+}$ is diminished so that it remains in the erythrocytes (siderochromasia) and may accumulate excessively in the body (secondary hemochromatosis; → p. 252). Although the RBCs’ osmotic resistance (→ p. 40) is actually increased, their mechanical vulnerability is increased (rapid breakdown in the spleen, early hemolysis). While the heterozygous form (T. minor) causes few symptoms, the homozygous form (T. major) may be fatal even before puberty. The rare α-thalassemia usually causes death of the fetus, because without α-chains no HbF can be formed either. Hb$\gamma_4$, produced in the fetus, and Hb$\beta_4$, occurring postnatally, are apparently inadequate substitutes for the normal Hb forms.
A. Defects of Hemoglobin Synthesis

1. Glycine, Succinyl-CoA → α-ALA synthase → δ-Aminolevulinic acid (δ-ALA) → Protoporphyrine → Heme → Globin synthesis → Heme 2 β-chains 2 α-chains

Gene defect

Hereditary sideroblastic anemia

Iron deficiency etc. (see next page)

Iron deficiency anemia

2. Gene defects

Hemoglobin A deficiency

α-Thalassemia (with Hbγ4, Hbδ4)

β-Thalassemia (with HbF = Hbα2γ2 and HbA2 = Hbα2δ2)

3. Gene defect

Hemoglobin S

False β-chain

Sickle-cell anemia

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Iron Deficiency Anemias

Of the iron (Fe) content in the body (2 g in females, 5 g in males) ca. \(\frac{2}{3}\) is bound to hemoglobin (Hb), \(\frac{1}{4}\) is stored iron (ferritin, hemosiderin), the rest is iron with diverse functions (myoglobin, Fe-containing enzymes). Loss of iron is ca. 1 mg/d in males and up to 2 mg/d in females (menstruation, pregnancy, birth). Of Fe taken up in food, 3–15% is absorbed in the duodenum (→A); in cases of Fe deficiency it can be up to 25% (see below). Iron intake with food should therefore be at least 10–20 mg/d (women > children > men).

Iron absorption (→A 1). Fe can be absorbed relatively efficiently as heme-Fe\(^{2+}\) (found in meat and fish). The Fe (split off from heme) gets into the blood or remains in the mucosa as ferritin-Fe\(^{2+}\) and returns to the lumen on mucosal cell disintegration. Non-heme Fe can be absorbed only in the form of Fe\(^{2+}\), which is absorbed by a Fe\(^{2+}\)-H\(^{+}\)-symport carrier (DCT1) (in competition with Mn\(^{2+}\), Co\(^{2+}\), Cd\(^{2+}\), etc.). A low pH of the chyme is essential for absorption, because it will 1) increase the H\(^{+}\) gradient that drives Fe\(^{2+}\) into the cell via DCT1, and 2) release Fe from compounds in food. Non-heme Fe\(^{2+}\) in food must be reduced by ferrireductase (+ ascorbate) to Fe\(^{2+}\) on the surface of the luminal mucosa (→A 1, FR). Fe uptake by blood is regulated by the intestinal mucosa: in Fe deficiency mucosal ferritin translation is inhibited by binding the Fe-regulating protein IRP1 to ferritin-mRNA, so that most of the absorbed Fe\(^{2+}\) can reach the blood. There it is oxidized by ceruloplasmin (+ copper) to Fe\(^{3+}\) and bound to apotransferrin, which transports Fe in plasma (→A). Transferrin (= apotransferrin with 2 Fe\(^{3+}\)) is taken up, via transferrin receptors, endocytotically in erythroblasts and in hepatic, placental, and other cells. After Fe has transferred to the target cells, apotransferrin again becomes available for Fe absorption from the intestine and macrophages (see below).

Iron storage (→A 2). Ferritin (in the intestinal mucosa, liver, bone marrow, erythrocytes, and plasma), which has a “pocket” for 4500 Fe\(^{3+}\) ions, is a rapidly available iron reserve (ca. 600 mg), while Fe from hemosiderin is more difficult to mobilize (250 mg Fe in macrophages from liver and bone marrow). Hb-Fe and heme-Fe, released from malformed erythroblasts (so-called inefficient erythropoiesis) and hemolysed erythroblasts, is bound to haptoglobin and hemopexin respectively, and taken up by the macrophages in bone marrow or by liver and spleen by endocytosis, 97% being reused.

Iron deficiency (serum Fe < 0.4 mg/L; serum ferritin ↓) inhibits Hb synthesis (→p.36) so that hypochromic microcytic anemia develops: MCH < 26 pg, MCV < 70 fl, Hb < 110 g/L. Its causes are (→A and Table):

- Blood loss (gastrointestinal tract, increased menstrual bleeding) in adults is the most common cause of iron deficiency (0.5 mg Fe lost with each mL of blood).
- Fe recycling is decreased; this form of anemia (the second most common worldwide) occurs with chronic infections. In this situation the Fe regained by the macrophages is no longer adequately released and thus cannot be reused.
- Fe uptake is too low (malnutrition, especially in the developing countries).
- Fe absorption is reduced due to: 1) achlorhydria (atrophic gastritis, after gastrectomy; →p.142, 148); and 2) malabsorption in diseases of the upper small intestine or in the presence of Fe-binding food components (phytate in cereals and vegetables; tannic acid in tea, oxalates, etc.).
- There is increased Fe requirement (growth, pregnancy, breast-feeding).
- An apotransferrin defect (rare).

If Fe overloading occurs in the body, damage is caused mainly to the liver, pancreas and myocardium (hemochromatosis) (→p.252).

<table>
<thead>
<tr>
<th>Normal</th>
<th>Fe deficiency</th>
<th>Apotransferrin defect</th>
<th>Fe utilization defect</th>
<th>Fe recycling defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Fe : Fe binding capacity</td>
<td>1 mg/L : 3.3 mg/L</td>
<td>↓ : ↑</td>
<td>↓ : ↓</td>
<td>↑ : normal</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>ca. 33%</td>
<td>&lt; 10%</td>
<td>0</td>
<td>&gt; 50%</td>
</tr>
</tbody>
</table>

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A. Iron (Fe) Deficiency Inhibits Hemoglobin Synthesis

1. Absorption

- Iron (Fe) deficiency anemia
- Fe deficiency
- Hb synthesis ↓

- Fe absorption ↓
- Growth, pregnancy, breast feeding
- Blood loss (GI-tract, menstruation)

2. Storage, loss and recycling

- Fe demand ↑
- Fe loss
- Chronic infections

- Fe recycling ↓
- Already in bone marrow
- Bone marrow
- Liver

Fe storage

- Ferritin
- Hemosiderin
- Fe uptake
- Heme

- Haptoglobin
- Hemopexin
- Erythrocytes
- Macrophages in spleen, liver and bone marrow (extravasal)
- Ferritin

- Systemic blood

- Already in bone marrow

- Normal Fe uptake: 10–20 mg/d
  - Female
  - 5–10 mg/d
  - Male

- Transferrin deficiency, transferrin defect

- Disease in upper small intestine, Fe-binding food

- Achlorhydria, gastrectomy

- Malnutrition etc.

- Nonabsorbed Fe in stool
  - normal: 85–97% of uptake

- Malabsorption

- Fe absorption: 3–15% of Fe uptake

- Fe deficiency

- Liver

- Blood

- Heme

- Fe uptake

- HCl

- Stomach
Hemolytic Anemias

Erythrocytes can only attain their normal life-span when their flexibility, their ability to withstand osmotic and mechanical stress, their reductive potential, and their energy supply are normal (→ p. 30). Defects in these properties lead to a shorter life-span (in some cases to just a few days [corpuscular hemolytic anemia]). There are, however, many other causes that shorten the life-span of normal erythrocytes (extracorpuscular hemolytic anemia). A common feature of these anemias is an increased concentration of erythropoietin, which provides compensatory stimulation of erythropoiesis (→ p. 33, A and B3).

Causes of corpuscular hemolytic anemia (→ A) are usually genetic defects:

- One of the membrane diseases is hereditary spherocytosis (spherocyte anemia). It is caused by a functional abnormality (defective ankyrin) or deficiency of spectrin, which, as an important constituent of the cytoskeleton, is essential for its stability (→ A1). The volume of spherocytes is normal, but the defect in the cytoskeleton results in erythrocytes being spherical, instead of having a normal flexible discoid shape. The osmotic resistance of these cells is reduced, i.e., they hemolysed when the hypotonicity of the external medium is still low. As they are prematurely segregated in the spleen, splenectomy is therefore therapeutically effective.

- Enzyme defects disturb the glucose metabolism of erythrocytes (→ A2): 1) if pyruvate kinase is affected, ATP to Na⁺-K⁺-ATPase supply is stopped, the cells swell up so that they become vulnerable and hemolysed early; 2) defective glucose-6-phosphate dehydrogenase (gluc-6-PDH; → A3) slows the pentose phosphate cycle, so that oxidized glutathione (GSSG), formed under oxidative stress, can no longer be adequately regenerated to the reduced form (GSH). As a result, free SH groups of enzymes and membrane proteins as well as phospholipids are no longer sufficiently protected against oxidation, leading to premature hemolysis. Eating horsebeans (vicia faba major, causing favism) or certain drugs (e.g., primaquin or sulphonamides) increase oxidative stress and thus aggravate the situation; 3) a defect of hexokinase results in a deficiency of both ATP and GSH (→ A2, 3).

- Sickle cell anemia and thalassemias (→ p. 36) also have a hemolytic component (→ A4).

- In (acquired) paroxysmal nocturnal hemoglobinuria (PNH) some of the erythrocytes derived from somatically mutated stem cells have increased complement sensitivity. It is based on a defect of certain membrane proteins that are involved in regulating the complement system (especially the decay accelerating factor [DAF]; → A5). Complement activation then leads to perforation of the erythrocyte membrane. It is not clear why this usually occurs during sleep.

Examples of the causes of extracorpuscular hemolytic anemia are:

- Mechanical causes, such as damage to the erythrocytes by collision with artificial heart valves or vascular prostheses, especially if cardiac output (CO) is raised;

- Immunological causes, for example, in ABO blood group transfusion mismatches, or Rh incompatibility between mother and fetus;

- Toxins, for example, certain snake poisons.

In most hemolytic anemias the erythrocytes will, as would occur normally, be phagocytized and “digested” in bone marrow, the spleen and liver (extravascular hemolysis), and Fe is reused (→ p. 38). A small amount of Hb released intravascularly is bound to haptoglobin (→ p. 38). In massive acute intravascular hemolysis (→ B) haptoglobin is, however, overloaded and free Hb is filtered in the kidneys. This results not only in hemoglobinuria, but can also through tubular occlusion lead to acute renal failure (→ p. 108). Chronic hemoglobinuria additionally causes Fe deficiency anemia, cardiac output rises and the resulting mechanical hemolysis creates a vicious circle (→ B). Finally, the erythrocytic fragments produced in intravascular hemolysis may cause thrombi and emboli, which can result in ischemia in the brain, cardiac muscle, kidneys, and other organs.
A. Causes of Corpuscular Hemolytic Anemia

1. Osmotic resistance
   - Hereditary spherocytosis

2. Enzyme defects
   - ATP deficiency
   - Cell swelling

3. Defect
   - Oxidative stress
   - Paroxysmal nocturnal hemoglobinuria (PNH)

4. Sickle-cell anemia
   - Thalassemia

5. Complement activation
   - DAF defect
   - Hereditary spherocytosis

B. Causes and Consequences of Acute Intravascular Hemolysis

Corpuscular causes (e.g. PNH)
- Erythrocyte fragments
- Thrombosis, embolism
- Ischemia

Extracorpuscular causes
- Immunological (e.g. transfusion reaction)
- Toxic (e.g. snake poison)
- Mechanical (e.g. artificial heart valve)

Acute intravascular hemolysis

Free Hb↑
- Haptoglobin overload
- Renal filtration of Hb

CO↑
- Hb deficiency
- Fe deficiency
- Hemoglobinuria

Acute renal failure
Immune Defense

The body possesses nonspecific, congenital, and (interlinked) specific, acquired, or adaptive immune defenses against microorganisms (bacteria, viruses, fungi, parasites) and against macromolecules identified as being “foreign”. Fragments of pathogens and large-molecular foreign bodies represent antigens to which the specific defense system reacts with the activation and proliferation of monospecific T and B lymphocytes (T cells and B cells). B cells differentiate to plasma cells which produce antibodies (immunoglobulins, Ig, with the subgroups IgA, IgD, IgE, IgG, IgM). It is their task to: 1) neutralize, 2) opsonize antigens, and 3) activate the complement system (see below). These highly specific mechanisms of the immune defense serve to recognize the particular antigens whose elimination is then accomplished in a relatively nonspecific way. In addition, the antigen (with B and T memory cells) is held “in memory” (immunological memory).

At their maturation in the thymus (T cells) and bone marrow (B cells), respectively, a repertoire of > 10^9 different monospecific lymphocyte types (each against a specific antigen) is formed from lymphatic precursor cells that do not possess any antigen receptors. Such as yet naive lymphocytes circulate through the organism (blood and lymph → lymphatics → blood and lymph). When they discover “their” antigen, as usually happens in lymphatic tissue, exactly this lymphocyte type proliferates (clonal selection and proliferation), and numerous monospecific daughter cells are formed. These differentiate into armed T cells and plasma cells, respectively, which are responsible for elimination of the antigen.

Lymphocytes with receptors against endogenous tissue are prematurely eliminated in the thymus or bone marrow after recognizing their antigen. This clonal deletion thus results in (central) immunological tolerance. The immune system learns around the time of birth to distinguish between foreign and endogenous antigens. Normally it continues to recognize throughout life those that it came into contact with at this time as endogenous; all those that come later are recognized as being foreign. If this distinction fails, autoimmune disease occurs (→ p. 56).

The nonspecific system is rarely able, for example, when a measles infection occurs for the first time, to single-handedly prevent the virus replicating and spreading in the body, i.e., illness follows. The specific immune defense with killer T cells (→ B2; p. 46f. B) and immunoglobulins (at first IgM, then IgG; → B5) goes into action only slowly (primary response or sensitization), but then manages to neutralize the pathogen, i.e., the measles infection is conquered. If the infection reoccurs, antibody production (especially IgG) sets in abruptly (secondary response), the virus is eliminated straightaway, and a renewed infection fails to occur (immunity). (A primary response with ensuing immunity can also be achieved by immunization with pathogen antigen [active immunization]).

Nonspecific defense (→ A) is served by dissolved or humoral defense substances, such as lysozymes and complement factors (→ A1) as well as phagocytes, i.e., especially macrophages (formed in tissue from immigrating monocytes) and neutrophil leukocytes, or neutrophils (→ A2). The latter are formed, like monocytes and eosinophil leukocytes, or eosinophils, in bone marrow, pass through the body and are finally attracted by chemokines (chemotaxis) to sites of pathogens. There they set in motion the inflammatory processes through the release of mediators (→ A2, 4 and p. 48ff.).

The phagocytes take up the pathogen (endocytosis), damage it (especially after its activation; see below and B6) by means of lysozymes, oxidants such as hydrogen peroxide (H_2O_2) and oxygen radicals (O_2^-, OH, ^1O_2), nitrogen monoxide (NO), etc. and “digest” the pathogen with their lysosomal enzymes (lysis). If the antigen is too large (as is the case with worms, for example) the above-mentioned defense substances are also exported (exocytosis; in this case mainly from eosinophils). Normally the concentration of the above-mentioned oxidants is held at a low level by reducing enzymes, such as catalase and superoxide dismutase. This “reining in” is given up when the phagocytes are activated: the bactericidal action of the oxidants can then take its full effect so that the phagocytes themselves and, in
A. Nonspecific Immune Defense (Enhanced by Specific Antibodies)

**Humoral**
- Lysozyme
- Damaged membranes
- Interferons (IFN)
  - IFNα, β, γ inhibit virus proliferation
  - IFNγ activates macrophages, killer cells, B and T cells
- Complement activation
  - alternative C3
  - classical C1q
  - Micro-organisms
  - C3b → Antigen opsonification
    - Antigen: pathogen, foreign cell, virus infected body cell
    - Oxidants
    - Proteases
    - Na⁺, H₂O
    - Perforins
    - Natural killer cell
  - ADCC
  - Fc receptor

**Cellular**
- Neutrophil leukocytes, monocytes → macrophages
- Phagocytosis
- Membrane attack complex (C5–C9)
  - Lysis
  - Liberate: oxidants, proteases, inflammation mediators
  - Membrane damage
  - Activated macrophages (see B6)
- Inflammation
  - Mast cells, basophil leukocytes
  - Eosinophil leukocytes
  - Antigen: pathogen, foreign cell, virus infected body cell
  - Immunglobulins
    - IgE, IgA, IgG, IgM
    - IgE
  - Fc receptor

**Antigen opsonification by Ig and C3b**
certain circumstances, even other endogenous cells are unfavorably affected.

Phagocytosis and lysosomal digestion are increased (and made possible in those bacteria with polysaccharide capsules) when the antigen surface is “larded” with IgM, IgG, or complement component C3b (opsonification; \(\rightarrow A1, 2\)). Phagocytes have receptors for the antigen-independent Fc part of the immunoglobulins and for C3b, through which they can attach themselves to the opsonized antigen (especially important for TI antigens; see below). In this way the phagocytosis, which is actually nonspecific, participates in specific immune defense. Furthermore, the mannose-binding protein (MBP), which binds to mannan groups (polymers of mannose) on the surface of bacteria and some viruses, seems to have an opsonizing effect as a “nonspecific antibody”.

In addition, pathogens that are opsonized with Ig (so-called classical path), but also those that are not opsonized (so-called alternative path) and possibly also MBP, set in motion the complement cascade \(\rightarrow A1\). At the end of this the membrane attack complex is formed from the complement components C5–C9. This complex perforates the outer wall of (Gram-negative) bacteria, which causes their death. At the same time, lysozyme (also present in plasma, lymph, and secretions) breaks down the wall of bacteria enzymatically (cytolysis; \(\rightarrow A3\)).

The so-called natural killer cells (NK cells, NKC) specialize in nonspecific defense, particularly against viruses, mycobacteria, and tumor cells. They identify their “victims”, the pathogen, the virus infected cell or the tumor cell, by their foreign surface (lack of own HLA type; cf. below) or couple to their Fc receptors on IgG-opsonized antigens on the surface of the victim (antigen-dependent cell-mediated cytotoxicity [ADCC]; \(\rightarrow A3\)). In each case the killer cells perforate the victim’s membrane with exocytic perforins and thus cause the death of the cell being attacked (cytolysis; \(\rightarrow A3\)). This takes away not only the invading viruses’ ability to multiply (the cell’s enzyme apparatus), but makes them (and also other intracellular pathogens that are still alive) more vulnerable to attack from other defense systems. The NK cells are activated by interferons (IFN), namely by IFN-α and IFN-β, which are released by leukocytes and fibroblasts, as well as by IFN-γ, which is released from activated T cells and from the NK cells themselves. IFNs, which are released especially from infected cells, also induce increased virus resistance in cells which have not yet been infected. Defensins are peptides (with ca. 30 amino acids) that are released by phagocytes and act (among other methods, by forming ion channels in the target cell membrane) in a nonspecific cytotoxic manner, even on pathogens that are resistant to NK cells.

Macrophages are formed from monocytes that have immigrated or stay at one site (but move freely there), such as the liver sinuses (Kupffer cells), pulmonary alveoli, splenic sinuses, peritoneal lining, lymph nodes, skin (Langerhans cells), joints (synovial A cells), brain (microglia), and epithelium (e.g., renal glomeruli). Together they are referred to as the mononuclear phagocytic system (MPS) or reticuloendothelial system (RES). Macrophages can recognize relatively nonspecific carbohydrate components on the surface of bacteria and thereupon phagocytize and digest them. Macrophages have to be activated in order to be able to deal with those pathogens that survive in the phagosomes (see below and B6).

The specific cellular immune defense by armed T effector cells that are activated relatively slowly (taking days [delayed immune response]) presupposes that the prepared antigen (peptide fragments) is presented to the passing naive T cells by “professional” antigen-presenting cells (APC) (presentation; \(\rightarrow B1\)). As a result the antigen is built into MHC class I and MHC class II proteins, in humans also called HLA class I or II, respectively (HLA = human leukocyte antigen). (The appropriate gene locus is the major histocompatibility complex [MHC]). It is especially dendritic cells, to be found mainly in lymphatic tissue, which act as APCs. For presentation (\(\rightarrow B1\)), ICAM is bound on the APC surface to lymphocyte function-associated antigen 1 (LFA1) on the T-cell membrane. When a T cell that is specific for the antigen docks, the binding is strengthened and the T cell is activated by a double signal that triggers clone selection (\(\rightarrow B1\)). The double signal consists of: 1) recognition of the (HLA I–bound or HLA II–bound)
antigen by the T-cell receptor with its coreceptor (CD8 in cytotoxic T cells and CD4 in helper T cells [see below]), and 2) the costimulation signal, i.e., the binding of the B7 protein (on the APC) to the CD28 protein of the T cell. (If antigen binding occurs without costimulation [e.g., in the liver, where there are usually no APCs], the lymphocytes are actually inactivated, i.e., they become anergic [peripheral immune tolerance]). The T cell can also obtain the APC double signal from infected macrophages or from B cells that have taken up the antigen with their receptors (e.g., insect or snake poisons, allergens). The APC double signal starts the expression of interleukin 2 (IL-2) in the T cell as well as the incorporation of the appropriate IL receptor into the cell membrane. IL-2 (or IL-4, IL-7, IL-15) is the actual (autocrine and paracrine active) signal for clonal expansion of these monospecific T cells. In this process the T cells differentiate into three armed types (killer T cells, Th1-cells and Th2-cells) that no longer require costimulation and express new adhesion molecules (VLA-4 instead of L-selectin), so that they are now “anchored” on the endothelium of inflammatory tissue portions (and not in lymphatic tissue as are their naive mother cells). The importance of the IL signal can also be judged from the fact that highly effective immune suppression can be achieved with IL inhibitors such as cyclosporin A or rapamycin (e.g., in organ transplantations).

Cytotoxic T cells (killer T cells) originate from naive CD8 T cells after HLA I–associated antigen presentation, HLA I having mostly taken its antigen from the cytosol (viruses, cytosolic proteins, endogenous antigen presentation). Through their CD8-associated T-cell receptors, the cytotoxic T cells then recognize the corresponding HLA I–bound antigen on the surface of (virus) infected body cells, tumor cells, and cells of transplanted organs, and kill them (→ B 2). Perforins form pores through which granzyme B (protease) reaches the inner cell and cause both apoptosis and cytolysis. Apoptosis is also caused by binding of the CD95 ligand of the T cell to CD95 (= Fas) of the target cell (→ B 2 and p. 12).

After HLA II–associated presentation of the antigen (from intracellular vesicles, e.g., phagocytized bacteria or proteins of the viral membrane), the CD4-T cells change into immature effector T cells (T 1H0). Through differentiation these turn into helper T cells, either inflammatory T cells (Th1), which activate macrophages by means of IFN-γ (→ B 6), or Type 2 helper T cells (Th2), which are essential for B cell activation (→ B 4). These two cell types inhibit each other (suppression), so that only one type predominates once the course is set (→ B 6).

The specific humoral immune defense originates in B lymphocytes (→ B 3). IgD and monomers of IgM are anchored on their surface (dissolved IgM is present in the form of pentamere); several of which bind to the appropriate antigen. The resulting antigen cross-linkage causes internalization and processing of the antigen–antibody complex. However, a second signal is essential for the subsequent activation of the B cells. In the case of the so-called thymus-independent (TI) antigens this can come from the antigens themselves (e.g., bacterial polysaccharides); in the case of thymus-dependent (TD) antigens it comes from Th2 cells to which the B cells present the HLA II–associated TD antigen (→ B 4). Should the T-cell receptor of the Th2 cell “recognize” the antigen, it expresses the CD40 ligand (which binds to the CD40 protein of the B cell) on the surface and also secretes IL-4. CD40 ligand and IL-4 (later also IL-5 and IL-6) trigger clonal selection of the B cells, secretion of monospecific IgM, and differentiation to plasma cells. Depending on recoding for the Fc region (class jump, switch), these now produce IgA, IgG, or IgE in such a way that all Ig originating from one B cell clone is specific for the same antigen.
B. Specific Immune Defense

Presentation of antigen by APC:
- macrophages
- dendritic cells
- B cells

T lymphocytes

CD8+ type (identifies antigen in HLA I)
CD4+ type (identifies antigen in HLA II)

Antigen

T-cell receptor

Double signal

CD8/HLA I
CD4/HLA II

T-cell proliferation
(clonal expansion and differentiation)

APC

HLA I or HLA II

B7

ICAM

LFA1

IL-2

IL-2 receptor

Antigen

T-cell receptor

Double signal

CD8/HLA I

CD4/HLA II

‘Naive’ T cell

Infected cell, tumor cell, foreign cell

Cytotoxic T cell

Infected cell

ICAM

HLA I

Antigen

CD8
T-cell receptor

CD95 ligand

Perforins

Granzyme B

Apoptosis

Proteolysis

Cytolysis

H2O, NaCl

Macrophage activation

Macrophage

Inflammation

‘Th1’ cell

IL-10, TGFβ

‘Th2’ cell

IFNγ

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Immune Defense II + III

B lymphocytes

Antigen binding

‘Naive’ B cell

Cooperation of Th2 cell and B cell

CD4
T-cell receptor

CD40 ligand

IL-4
IL-5
IL-6

TD antigen
HLA II

Presentation

Proliferation

Plasma cell

Differentiation

IgM
IgG
IgA
IgE

According to class jump

Immune globulins

Specific humoral immune defense (see A)

Preparation

Internalization

Activation

Antibody enmeshing

IgD-, IgM-monomer

Immune globulins

Specific humoral immune defense (see A)

Preparation

Internalization

Activation

Antibody enmeshing

IgD-, IgM-monomer

Immune globulins

Specific humoral immune defense (see A)
Inflammation

Inflammation is a defense reaction of the organism and its tissues to injurious stimuli. The aim is to repair the damage or at least to limit it, and also to remove the cause, for example, bacteria or foreign bodies.

Causes of an inflammation can be:

- **Microorganisms** (→ A), such as bacteria, viruses, fungi, or parasites;
- **Foreign bodies** (foreign protein, e.g., pollen; asbestos or silicon crystals); or
- **Tissue destruction** with formation of tissue debris, for example, through mechanical damage such as cuts, stabs, scratches or foreign bodies, chemical compounds such as acids or alkalis, physical influences such as cold, heat, radiation (UV, X-rays, radioactivity), and endogenous causes such as disintegrating tumor cells, extravascular blood, autoimmune reactions (→ p. 56), or crystals of substances precipitated in the body (uric acid, calcium oxalate, calcium phosphate, and cholesterol).

An acute inflammation expresses itself as a local reaction associated with the symptoms, known since antiquity, of pain (dolor), swelling (tumor), reddening (rubor), and warmth (calor). In addition, there are general inflammatory reactions (acute-phase response; see below).

Rapid activation of mast cells (in tissue) or their counterparts in blood, the basophil leukocytes, or basophils, is an example of the occurrence of a very strong acute inflammatory reaction (→ A) on which especially type I hypersensitivity reactions are based (→ p. 52). If the body has previously been in contact with an antigen (antigen in cases of hypersensitivity), for example, with bee-poison protein, B cells will have been sensitized as a reaction to it (cooperation with Th2 cells; → p. 47, B4). The ensuing plasma cells produce IgE that binds to the Fc receptors of the mast cells. On renewed contact with the antigen this is now bound to the antigen-specific Fab-ends of IgE. It seems to be important for further reactions of the mast cells that the allergen is bound to several IgE molecules (antibody cross-linking); large antigens that can repeatedly act antigenically with different molecular parts (polyvalence) are especially effective (e.g., parasites with several bound haptenes).

Cross-linking of the antibodies by the antigen sets free second messengers in the mast cell (cGMP, inositol phosphate, Ca2+) that trigger a rapid degranulation of the mast cells, i.e., exocytosis of the inflammation mediators and chemokines stored within the granules (histamine, interleukin 8(IL-8), eosinophil neutrophil chemotactic factor [NCF], etc.). Ca2+ also activates phospholipase A2 that splits off arachidonic acid from the phospholipids in the cell membrane. This is the starting substance for other important inflammation mediators, namely prostaglandins (E2 etc.) and leukotrienes (C4, D4 and E4; together also called slow reacting substance of anaphylaxis [SRS-A], as well as B4). The ether phospholipid platelet activating factor (PAF), another important inflammation and hemostatic mediator, is liberated from the cell membrane of mast cells.

In the further course of inflammatory reaction leukotrienes and PAF (platelet–activating factor) are also released from eosinophils and neutrophils, from macrophages as well as PAF from thrombocytes. This contributes significantly to strengthening the reaction and to the inclusion of the hemostatic system. These cells are attracted by chemotaxis. Eotaxin, PAF, and leukotriene B4 act chemotactically on eosinophils (and Th2 cells). As PAF also activates the mast cells, the two cell types cooperate. Neutrophils and monocytes are attracted by leukotriene B4, C5 a (see below), NCF, tumor necrosis factor (TNF-α), IL-1, IL-4, and several chemokines, such as IL-8 (→ A).

Histamine, PAF, and the leukotrienes C4, D4, and E4 act together with other mediators (prostaglandin E2, bradykinin) to cause: 1) vasodilation, 2) an increased paracellular permeability of the endothelium, and 3) stimulation of nociceptors (→ A).

Vasodilation is the cause of the reddening and warming at the site of inflammation (see above) and of reduced blood flow velocity which makes it possible for the chemotactically attracted leukocytes to swim to endothelium–near regions. Endothelium that has been activated in the inflammatory area by, among others, IL-4 (from Th2-lymphocytes) pushes selectins out into the lumen. These selectins, in
A. Acute Inflammation

**Mast cell**
- Previous antigen contact → T\(^2\) cells → IL-5 → Bone marrow → Eosinophil leukocytes
- Fc\(_\varepsilon\) receptor → IL-4

**Immunglobulin synthesis**
- Fc\(_\varepsilon\) receptor
- Fc\(_\gamma\) receptor

**Renewed antigen contact**
- Many hours

**Histamine**
- Eotaxin
- IL-8
- NCF

**Chemotaxis**
- TH2 cells (see above)

**Vessels**
- Permeability ↑
- Vasodilation ↓
- Diapedesis

**Exudation**
- Eosinophils
- Neutrophils
- Monocytes

**Local reaction**
- Pain
- Swelling (edema)
- Reddening
- Warming

**Acute phase response**
- IL-1, IL-6, TNF\(\alpha\) etc.
- Brain
- Hypothalamus: Tiredness, fatigue, Fever

**Bone marrow**
- Leukocytosis
- Ferritin ↑

**Liver**
- Immune defense ↑
- CRP, SAA ↑

**Immune system**
- Fat tissue
- Muscles

**Exudation**
- Histamine
- PAF
- Leukotrienes
- Nociceptors

**Oxidants**
- Activation by:
  - Endo- and exotoxines
  - immune complex, C5a
  - crystals (urate, silicate, asbestos)

**Phagocytosis**
- Macrophage

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the guise of adhesion molecules, cause the leukocytes to roll along the endothelium and thus activate other adhesion molecules (integrins; ICAM-1, VCAM). This enables the leukocytes to adhere to the vessel wall (margination). The increased endothelial permeability (loosening of endothelial cell connections) allows the leukocytes to slip through into the extravascular space (diapedesis; \( \rightarrow A \)). Furthermore, more protein-rich fluid (inflammatory exudate) reaches the interstitial spaces and leads to edematous swelling. In extreme cases even the erythrocytes leave the blood vessels (hemorrhagic inflammation). Finally, pain arises, which brings the injury into consciousness (changed behavior), and stimulates a reflex action to nurse the inflamed region (e.g., a limb).

The neutrophils that have migrated to the site of inflammation and the macrophages that have differentiated from the immigrant monocytes now try to phagocytize the pathogens causing the inflammation and to digest them by means of their lysosomes. Their “appetite” is increased by opsonification with IgG or C3b (\( \rightarrow p. 44 \)).

The complement system is also activated by the inflammation, in the classical way in the presence of antigen–antibody complexes or in the slower, so-called alternative way through less specific binding to bacteria-infected or virus-infected cells. In both cases complement C3b is formed. It not only opsonizes antigens, but also causes polymerization of other components (C5–C9) on the cell membrane of the attacking pathogen which forms the membrane-attack complex and thus triggers lysis of the pathogen (\( \rightarrow p. 44 \)). The complement system can, in addition, break up virus particles and antigen–antibody complexes. Side products of the complement system (C3a, C4a and C5a, so-called anaphylaxins) act chemotactically and activate macrophages.

Macrophages are activated mainly by pathogen exotoxins and endotoxins and by antigen–antibody complexes, C5a, crystals (see above), and by phagocytosis, whereupon oxidants like \( O_2^{-} \), \( OH^- \), \( ^{1}O_2 \), and \( H_2O_2 \) are liberated and damage the pathogens (\( \rightarrow A \)). The macrophages also release inflammation mediators, for example, PAF, leukotrienes, prostaglandins, IL-1, IL-6, and TNF-\( \alpha \). The latter do not only act locally and chemotactically, but also include the entire organism in the inflammation reaction (acute-phase response; \( \rightarrow A \)). Mediated by IL-1, IL-6, and TNF-\( \alpha \), the following occurs via specific receptors:

- Sleep reactions are initiated in the brain (fatigue, tiredness);
- The set point of the body temperature shifted towards higher levels (fever; \( \rightarrow p. 20 \));
- Bone marrow is stimulated to release more leukocytes;
- The liver is stimulated to absorb more iron (taking it from the bacteria in plasma) and to produce so-called acute-phase proteins (among them C reactive protein (CRP) and serum amyloid A [SAA]);
- The immune system is stimulated (e.g., antibodies are formed); and
- Lipolysis and catabolism are initiated (weight loss).

Tissue repair. After transient formation of cellular granulation tissue (macrophages etc.), characterized by budding blood vessels, platelet-derived growth factor (PDGF) and other mediators stimulate the proliferation and immigration of fibroblasts. They produce glycosaminoglycans that swell and deposit themselves on collagen fibers. New collagen is also formed; shrinking of this collagen closes the wound margins.

Finally, the collagen fibers (scar) are replaced by normal tissue for that site (restitutio ad integrum; \( \rightarrow B \)). This latter event is, however, true only for small, noninfected tissue injuries. If the cause of the inflammation (e.g., foreign bodies or wound infection) cannot be removed at once, wound healing is delayed and the defense response by the phagocytes is intensified. Much energy is expended in this (increased warming), the synchronously activated hemostatic system occludes vessels in the surrounding area so that ATP also becomes deficient due to a lack of \( O_2 \), and the pH value falls (anaerobic lactic acid formation). The liberated oxidants also damage the body’s own cells. When these die, lysosomal enzymes are freed so that finally the leukocytes and cells of the inflamed tissue themselves also die. This tissue death (necrosis), which can progress to abscess formation (\( \rightarrow B \)), is the price paid for preventing the spread of inflamma-
tion and usually results in a permanent scar. This also occurs when the defect is too large (e.g., a gaping wound).

A disorder of wound healing (→ B) occurs when the inflammatory and healing processes balance each other out (chronic inflammation; e.g., in smoker’s bronchitis, or liver damage caused by alcohol). If particularly large amounts of collagen are formed, the outcome is fibrosing inflammation (e.g., liver cirrhosis; → p. 172 ff.), while excessive formation of granulation tissue is characteristic of granulomatous inflammation (e.g., in tuberculosis, foreign bodies).

If the scar tissue is of inferior quality, for example, when collagen synthesis is impaired by corticoids or there is an abnormality of collagen cross-linking in vitamin C deficiency, local stress can cause a re-opening of the wound, as in the much-feared abdominal dehiscence after abdominal operations. Larger scars, especially in the face, can lead to cosmetic problems, especially in cases of excessive scarring (keloid; → B). In some cases scars can lead to significant functional disorders, for example, on the cornea (visual impairment), on cardiac valves (stenosis, regurgitation; → p. 194 ff.), or in the abdomen (adhesions or strictures of the gut; → p. 156).

If it proves impossible to locally delimit a pathogen-caused inflammation, it will spread to the entire organism, usually via the lymphatic system and sepsis sets in. This also occurs if, for example, the large area of the peritoneum is acutely overwhelmed by pathogens (gut rupture, burst abscess).
Hypersensitivity Reactions (Allergies)

An allergy is a specific overreaction of the immune system to a substance that is foreign to the body but otherwise harmless, i.e., an antigen (→ p. 42), which now becomes an allergen. By binding to small-molecule foreign substances (so-called haptens), endogenous proteins can have the same effect as an allergen. While normally the increased immune (secondary) reaction can act protectively on repeated antigen contact (immunization; → p. 42 ff.), in an allergy it will lead to the destruction of intact tissue via immune mechanisms that are in principle quite similar. Thus, the primary contact will have initiated an allergizing process. However, similar destruction can also occur when the immune system fails to recognize endogenous proteins as being endogenous and autoantibodies are formed (→ p. 54). In each case it is inflammatory reactions (→ p. 48 ff.) that do the damage.

Hypersensitivity reactions are divided into (sometimes overlapping) types I–IV. Type I (immediate) reaction is common. It is preceded by allergization: when B and T, cells cooperate, the allergen is presented, and, among others, IL-4 and IL-5 are liberated. Under the influence of IL-4, antigen-specific B cells proliferate (→ IgE formation; → p. 47 B4), and eosinophils in bone marrow are stimulated by IL-5 to differentiate and then enter the bloodstream (→ p. 49, top). On second contact, immediate reaction (anaphylaxis) occurs within seconds to minutes and may be followed in a few hours by a late reaction. The immediate reaction is based on rapid liberation and new formation of vasoactive inflammation mediators from IgE-coupled mast cells, while the late reaction is mediated by attracted eosinophils and neutrophils and IgG (→ p. 49, top).

A type I (immediate) reaction can, depending on allergen exposure, be local or to a variable extent generalized. Allergens in the air (e.g., pollen, mite dust, animal hair) precipitate reactions in the respiratory tract, where mucosal edema with hypersecretion (e.g., hay fever) and bronchospasm (asthma) may occur, while food allergens (e.g., constituents of milk, fruit, or fish) result, in the first instance, in gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea. Nevertheless, hypersecretion in the respiratory tract as well as any vomiting or diarrhea actually help to remove the allergen. The skin reacts to allergens (e.g., to bee-poison protein) with itching, swelling, urticaria, and atopic dermatitis. If the allergen gains direct access into blood through injection (e.g., serum or haptens such as penicillin), a immediate systemic reaction occurs and the resulting liberation of vasoactive mediators can lead to a life-threatening drop in blood pressure (anaphylactic shock; → p. 230 ff.). It may also occur, although slightly delayed, after strong gastrointestinal or respiratory exposure to allergens. Similarly, urticaria may develop in cases of food allergy.

In type II, or cytotoxic hypersensitivity (→ A), the focus is usually on antigen-effective cells or extracellular matrix proteins, in that either haptens (e.g., drugs) bind to endogenous (blood) cells, or foreign blood cells enter the organism. After allergization on first contact with the allergen, subsequent antigen exposure results in large amounts of allergen-specific IgM and IgG being formed and being densely bound (10^4–10^5 per cell) to the allergenic cell surface (opsomization; → A). In this way the complement system is activated (→ p. 43, A1), and natural killer cells unfold their cytotoxic action (antibody-dependent cell-mediated cytotoxicity [ADCC]; → p. 43, A3). Both produce destruction of the allergenic cell within a few hours (cytolysis; → A). Hapten binding to endogenous erythrocytes thus results in hemolytic anemia (→ p. 40), and hapten binding to thrombocytes results in thrombocytopenia. (The two cell types are especially exposed to complement attack, because they possess only a few complement-regulating proteins; see also p. 40). Foreign erythrocytes (e.g., in ABO incompatibility) are agglutinated, i.e., they are bound together via IgM and are quickly hemolyzed (acute transfusion accident; → p. 41, B). In a basically similar (but not as yet fully clarified) way, autoimmune mediate against the basement membrane lead to tissue destruction in the kidneys and lung (Goodpasture’s syndrome). IgG is deposited along the capillaries of the renal glomeruli, where they cause a strong inflammatory reaction (rapidly progressive glomerulonephritis with impend-
A. Cytotoxic (Type II) Hypersensitivity to Cellular Antigens

- Previous antigen contact
- Sensitization
- Re-exposure to antigen
- B lymphocyte
- Haptens
- Antigen-carrying cell
- IgM
- IgG
- ADCC
- Plasma cells
- Natural killer cell
- Perforins
- Fc receptor
- Membrane attack complex
- Cytolysis
- Basal membrane (kidney, lungs)
- Goodpasture’s syndrome, RPGN

B. Type III Hypersensitivity to Antigen-Antibody Complexes

- Antibodies (IgG)
- C1q
- Complex deposition in capillaries
- Complement activation
- Phagocytes
- Chemotaxis
- Basal membrane
- Endothelium
- Inflammation
- Tissue damage
- Serum illness
- Kidney
- Bone
- Skin
- Fever, myalgia, lymphadenopathy

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<th>Haptens + erythrocyte</th>
<th>Haptens + granulocyte</th>
<th>Haptens + thrombocyte</th>
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ing renal failure [RPGN]; → p.102 ff.), while pulmonary involvement is characterized by life-threatening bleeding.

A type III reaction (→ B) is due to the formation and deposition of immune complexes (antigen–antibody complexes), the antigens frequently being connected to one another via the participating immunoglobulins (IgM, IgG). Such immune complexes not only activate the complement system (→ p. 43, A1), but also macrophages, granulocytes, and thrombocytes (via their Fc receptors). It is especially when the antigen is in excess that small, soluble immune complexes circulate in blood for long periods (→ B, curves) and are only slowly broken down. They are mainly deposited in the capillaries of the glomeruli (granular) but can also be found in joints, skin, and elsewhere. The capillary wall will now be attacked by the complement system as well as by phagocytes that have been chemotactically attracted and then activated. The phagocytes liberate proteases, oxidants, and inflammation mediators, so that (immune complex) glomerulonephritis, joint pains, urticaria, lymphadenitis, and fever develop. These are symptoms that used to occur on passive immunization with vaccines made from animal serum (cattle, sheep, horses) and were called serum sickness.

A type III reaction can also be caused by infections, if the immune system is unable to eliminate the pathogens completely (e.g., streptococci or certain malaria protozoa), but enough antibodies are formed to maintain a high concentration of immune complexes in the blood. Systemic lupus erythematoses is a type III reaction of unknown etiology.

A local type III reaction can develop in the skin, for example, after vaccination (Arthus’ phenomenon), or it can occur in the lung after small amounts of antigen have been repeatedly inhaled. On further contact, large amounts of IgG are released (antigen excess) and complexes are formed that are precipitated in the lung (exogenous allergic alveolitis). Examples are bird fancier’s lung (antigens in bird excreta) and farmer’s lung (mold antigens in hay).

A type IV reaction (→ C, D) is borne mainly by T\textsubscript{H} cells, killer T cells and macrophages, reaching its maximum effect in two to four days (delayed reaction type or delayed hypersensitivity type [DHT]). It is triggered mainly by proteins from pathogens (viruses, tuberculosis, lepra, bilharziasis, leishmaniasis, listeriosis, fungal infections), other foreign proteins (e.g., the wheat protein gliadin that causes celiac disease), and haptens, for example, drugs, metals (e.g., nickel; → D), cosmetics, plant constituents (e.g., pentdekacetechol in poison ivy [Rhus radicans], or poison oak [Rhus toxicodendron]). Primary rejection of transplanted organs is also a type IV reaction.

The antigen is phagocytized by macrophages, processed and presented to the (DHT-) T\textsubscript{H} cells (→ C). Sensitization takes more than five days. On renewed contact, numerous T cells are activated into T\textsubscript{H} cells (→ p. 45 ff.). These stimulate monocyte formation in bone marrow via IL-3 and granulocyte-macrophage colony stimulating factor (GM-CSF), attract monocytes and macrophages via chemokines, e.g., MCPs (monocyte chemoattractant proteins) and MIPs (macrophage inflammatory proteins), activate them via interferon γ (IFN-γ) and with them (as well as with TNF-β) cause a strong inflammatory reaction in which endogenous or transplanted tissues may be extensively destroyed (tuberculosis, lepra, organ rejection).

Often haptens on the skin are responsible for a type IV reaction in the form of contact dermatitis. Nickel in jewellery or watches can get into the skin where, bound to endogenous protein, it is phagocytized as an antigen by the skin macrophages (Langerhans cells) and processed (→ D). Subsequently, the macrophages migrate to the regional lymph nodes and there (after transformation to dendritic, B7-positive cells) present the antigen to antigen-specific T cells from the blood and lymph. The latter proliferate and differentiate (to killer T cells and T\textsubscript{H} cells) and in this way reach the site of antigen exposure in large number (mainly via the blood; → C, D).

Type V reactions are caused by autoantibodies against transmitter receptors or hormone receptors (→ p. 56).
C. Delayed Hypersensitivity (Type IV)

- Insect poisons
- Pathogen proteins (e.g., tuberculin, lepromin)
- Haptens (metals, drugs, cosmetics, plant constituents, etc.)
- Endogenous proteins

Macrophage

- Phagocytosis
- Initial contact
- Sensitization
  - 5 days
  - Sensitized T cells
- Repeated contact
- Chemokines (attraction)
- IFNγ
- IL-3/GM-CSF
- TNFβ
- MHC II

Presentation to and activation of inflammatory T cells

Macrophage

TH1 cell

Tissue damage

Macrophage activation

D. Development of Contact Dermatitis

Watch

Hapten contact

Nickel (hapten)

Skin

Protein

Chemokines

Monocyte

TNFβ

Chemokines

IFNγ

Macrophage

TH1 cell

Contact dermatitis

TH1 cell circulation (via blood) to site of antigen exposure

TH1 cell

Macrophage activation

Migration to regional lymph nodes (and transformation into dendritic cells)

Collection of antigen-specific T cells (from blood and lymph)

Presentation to, proliferation and differentiation of TH1 cells

TH1 cell

Langerhans cell

Phagocytosis and processing

Monocyte

Monocytes

IFNγ

TNFβ

Contact dermatitis

Contact dermatis (see D), tuberculosis, leprosy, allergic encephalitis, thyroiditis, mycosis, bilharziasis, primary transplant rejection

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Autoimmune Diseases

When the immune system continuously forms autoantibodies (AAB) or activates T cells against endogenous antigens, this may cause damage to tissues or organs (autoimmune disease [AID]). (The occurrence of AAB is by itself no proof of AID, because AAB can be demonstrated as a transient response to tissue damage.)

AID is normally prevented, because

- immature T cells, which recognize the most common, ubiquitous autoantigens (AAG), are subject to clonal deletion in the thymus (→ p. 42);
- mature T cells are clonally inactivated (anergy; → p. 45). The reason for this is that cells in tissue do not give off any costimulation signals (e.g., B7-protein; → p. 46, B1);
- AAG-specific T cells are not activated in certain circumstances, despite recognition (immunological ignorance; see below, point 3).

The etiology and pathogenesis of AID has not been adequately clarified, yet the formation of AAB and T cell activation are based on the same mechanisms that operate in immune reactions to foreign bodies (→ p. 42 ff. and 52 ff.). The following causes may be fully or in part responsible for the development of AID (→ A):

1. Genetic predisposition is due to certain HLA-II alleles: carriers of the HLA-II allele DR3 + DR4 are, for example, 500 times more likely than carriers of DR2 + DR2 to develop type I diabetes mellitus (→ p. 286).

2. A sex linkage that is especially marked in puberty points to hormonal influences. For example, the female to male ratio in systemic lupus erythematoses is 10 : 1, while in ankylosing spondylitis it is 1 : 3.

3. AAG from immunologically privileged regions (brain, eye, testis, uterus) may leave these (via blood vessels, but not via lymphatics) and interact with T cells, but this does usually not trigger AID, because AAGs are accompanied by TGFβ. This is probably responsible for TH2 cells being activated (instead of the destructive TH1 cells). None the less, it is precisely from these regions that AAGs cause AID, for example, myelin base protein (MBP) of the brain causing multiple sclerosis, one of the most common AIDs. It has been shown in animal experiments that MBP produces no toler-
A. Causes of Autoimmune Disease

- Genetic predisposition, mainly HLA-II genotype
- Hormonal influences
  - Sex prevalence
- Psychological factors
- Altered immune regulation, e.g. altered activity of T-suppressor cells (?)
- Cancellation of immunological ignorance of autoantigens from immunologically privileged regions, e.g. eye, brain, uterus, sperm, thyroglobulin
- Cross-reaction of antiforeign antibodies, e.g. anti-streptococcal antibodies against endocardium and myocardium
- Mutation of immunocompetent cells (?), e.g. lymphoma cells

B. Organ-Specific and Tissue-Specific Autoimmune Diseases

- Organ-specific autoantibodies or T cell activation against
  - Acetylcholine receptors of skeletal musculature
  - Adrenal cortex
  - Acetylcholine receptors of skeletal musculature
  - Pancreatic B cells
  - Parietal cells; intrinsic factor
  - Thyroglobulin
  - TSH receptor

- Tissue-specific autoantibodies against
  - Basal membranes
  - Acetylcholine receptors of skeletal musculature
  - Adrenal cortex
  - Acetylcholine receptors of skeletal musculature
  - Pancreatic B cells
  - Parietal cells; intrinsic factor
  - Thyroglobulin
  - TSH receptor

- Idiopathic Addison’s disease
- Myasthenia gravis pseudoparalytica
- Diabetes mellitus
- Atrophic gastritis, pernicious anemia
- Graves’ disease
- Hashimoto’s thyroiditis
- Glomerulonephritis
- Pulmonary bleeding
- Goodpasture’s syndrome
Immune Defects

Immune defects express themselves through frequent, prolonged, and often life-threatening infections (also caused by otherwise harmless infectious agents) and through certain tumors.

Among defects of nonspecific defense are those of the complement system (infection with extracellular pathogens, e.g., the Neisseria), of the NK cells (infection with intracellular pathogens, e.g., listeria or herpes virus) as well as of mannose-binding proteins ([MBP] → p. 44). Disorders of phagocytosis can concern the cell number (e.g., leukopenia due to G-CSF deficiency; agranulocytosis due to radiotherapy or chemotherapeutic agents), or may be functional. In leukocyte adhesion defect (LAD), a defect of the integrin subunit (CD18) prevents margination; in lazy leukocyte syndrome, migration is slowed down; in chronic (or septic) granulomatosis oxidants are not formed; and in Chediak-Higashi syndrome the fusion of phagosomes with lysosomes is abnormal.

Humoral immune defects can be caused by disorders of maturation, function, or activation of B cells. Without antibodies the organism is powerless, especially against pus-forming pathogens, because their polysaccharide membrane cannot be phagocytized without opsonification. Examples are 1) selective IgA deficiency (very common, with an incidence of 1 in 700), in which a lack of mucosal protection frequently leads to respiratory and gastro-intestinal infections and to an increased incidence of susceptibility to allergies; 2) congenital agammaglobulinemia, in which a (X-linked) defect of Bruton-type tyrosine kinase hinders the maturation of B cells; 3) hyper-IgM syndrome, in which IgM concentration is greatly increased, but that of IgG and IgA is reduced (no class jump due to defect of CD40 ligands; → p. 47, B4); and 4) so-called variable immune defect (deficient stimulation of B cells by CD4-T cells).

Disturbances of cellular immune defense occur in thymus aplasia (DiGeorge’s syndrome) and in combination with humoral immune defects. They extend from abnormal stem cell differentiation (reticular dysgenesis) via defective HLA formation (naked lymphocytes syndrome) to the life-threatening combined B- and T-cell disorder (severe combined immunodeficiency disease [SCID], e.g., due to a deficiency of adenosine deaminase or purine nucleoside phosphorylase).

AIDS (acquired immunodeficiency syndrome) is caused by HIV-1 or HIV-2 (HIV = human immunodeficiency virus) (→ A). The genome of these retroviruses is coded in two almost identical molecules of a single-strand RNA (ssRNA). Built into the virion (complete virus particle) cover is the gp120-protein (→ A 1) that docks simultaneously on CD4 and on a chemokine receptor (CCR5 at the beginning of an infection; = CXCR4 at the final stage) of the host cell membrane, thus eliciting membrane fusion and virion endocytosis (→ A 2). (People with a CCR5 defect are largely protected against an HIV infection). In addition to CD8 cells, it is mainly the CD4-T cells that are affected. In the latter, ssRNA is transcribed to cDNA by a virion-endogenous reverse transcriptase, finally being incorporated as a double-strand dsDNA (provirus) into the host cell’s genome (latent stage). Activation of the CD4 cells (at the onset of infection and the late stage) triggers expression of the provirus. The proteins that result from this, tat and rev as well as Nfkβ from the host cell, take part in the formation of new virions that are exocytosed (viremia; → A 3, 4). The CD4 cell may be destroyed during these stages (see photograph), particularly as it is attacked by its own immune defenses (anti-gp120-IgG + complement; viral peptide recognition by cytotoxic T cells). Noninfected CD4 cells may also die (HLA-independent apoptosis) so that in the late stage a serious CD4 cell deficiency develops (→ A 4). The changes in cytokine concentration (→ A 5) decimate Th1 cells and cytotoxic T cells. The body is now ever more helplessly exposed to other, normally harmless, pathogens (e.g., fungi) and certain tumor cells (Kaposi’s sarcoma, lymphoma) (< 500 CD4 cells/μl blood: ARC = AIDS-related complex); < 200: full-blown AIDS). Many years can pass from the initial viremia (high p24-antigen level with IgM formation) and the ARC with renewed viremia (no more IgM) (→ A 4), during which the proviruses survive in relatively few (10²), inactive CD4 cells (mostly in lymph nodes).
A. AIDS

1. HIV

2. Nucleus
   - CD4-T cell
   - CD4 Chemokine receptor

3. HIV ssRNA
   - tat
   - NFκB

4. Infection
   - Viremia
   - CD4-T cells
   - IgM (Anti-p24)
   - IgG (Anti-gp120)
   - p24-Antigen

5. Cytokine concentration
   - IL-2
   - IL-4
   - IL-10
   - IFNγ

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Hemostasis and Its Disorders

The hemostatic system protects the organism against bleeding and blood loss. It involves plasma factors, thrombocytes (platelets), and the vessel wall. Their interaction locally guarantees the sealing of leaks in the vessel when platelets temporarily “glue” it together (white thrombus), and subsequently the plasma coagulation system forms a firm fibrin tangle (red thrombus) and thus a stable closure is formed. However, excessive clot formation (thrombi) with consequent occlusion of larger blood vessels (thrombosis) and the migration of thrombi (emboli; p. 240) must be avoided.

To keep this balance the hemostatic system, if required, is rapidly activated locally (a matter of minutes), but an extension of hemostasis is prevented by inhibitory factors (in part through a feedback mechanism). The fibrinolysis system is responsible for dissolving excessive fibrin clots.

Thrombocytes (TCs or platelets; 170–400 × 10^9/µL blood) are nucleus-free cytoplasmic bud-like particles split off from the megakaryocytes in bone marrow (p. 28). Endothelial damage leads, via the von Willebrand factor (vWF) to immediate adhesion of TCs to exposed collagen, which requires, among other factors, glycoprotein Ib on the TC surface (F1). Adhesion activates the TCs, i.e., it causes their aggregation (aided by thrombin), changes their form and releases vasoconstrictive (PDGF, thromboxan A_2) and aggregation-promoting substances (fibronectin, vWF; fibrinogen). In addition, thromboxan A_2 together with ADP (adenosine 5’-diphosphate) that has also been released, and the inflammation mediator PAF (p. 48) enhance TC activation. When aggregating, TCs contract and greatly change their shape (formation of microvilli), during which the glycoproteins Iib/IIia (among others) are exposed on the platelet surface. This serves the adhesion on fibronectin of the subendothelial matrix as well as of fibrinogen that links the platelets together in a net-like structure (F).

The coagulation system is made up of numerous factors. They include (D):
- factor I (fibrinogen)
- factor II (prothrombin)
- factor III (tissue thromboplastin)
- factor IV (Ca^{2+})
- factors VII–XIII
- prekallikrein ([PKK]; Fletcher factor)
- high-molecular kininogen ([HMK]; Fitzgerald factor)
and the inhibitory factors (E):
- antithrombin III
- α_2-macroglobulin
- α_1-antitrypsin
- protein C^k, and
- protein S^k

With the exception of Ca^{2+}, they are all globular proteins with a molecular mass between 54 kDa (α_1-antitrypsin) and 2 000 kDa (factor VIII), most of which are synthesized in the liver (I, II^k, V, VII^k, IX^k, X^k, XIII, kininogen). Vitamin K is essential for the formation of those factors and proteins marked with a ^k. The vitamin is important in the posttranslational γ-carboxylation of a number of glutamyl residues at the N-terminal of the peptide chains. These γ-carboxyglutamyl groups are necessary for Ca^{2+}-mediated fixing to phospholipids, for example, of the thrombocyte membrane (formation of complexes).

Coagulation (D, E). Most coagulation factors are normally not active. They are activated (Index a) by a cascade. Usually the particular factor is converted from its inactive form (= proenzyme =zymogen) to an active endopeptidase which in turn activates the subsequent factor in the same way. The cascade starts in the environment of the endothelial defect (negative charge of subendothelial collagen and sulfatid groups) with contact activation of factor XII to XIIa (endogenous activation). Factor XIIa then activates PKK to kallikrein (KK), which enhances factor XII activation (contact phase with positive feedback for enhancement). Factor XIIa activates Factor XI to Xla, the latter activating IX to IXa etc., until finally fibrin monomers are formed from fibrinogen (factor I), these monomers being bound together covalently by factor XIII (transamidase) into a fibrin net. If the injury is large, tissue thrombokinase (factor III) comes into contact with the blood and activates factor VII, which in a complex with Ca^{2+} and phospholipids in turn activates factor X (exogenous activation).
A. Causes and After-effects of Bleeding Tendency

- Lack of plasma factors
- Vascular disorder
- Thrombocyte deficiency or defect

Mainly joint bleedings and blue-black spots

Bleeding tendency (hemorrhagic diathesis)

Mainly petechial hemorrhages

B. Clotting Tests for Diagnosing Plasmatic Hemorrhagic Diatheses

Exogenous system: factor VII

Quick value

Partial thromboplastin time (PTT)

Fibrinogen

Thrombin time

Endogenous system: factors VIII, IX, XI, XII as well as HMK and prekallikrein

Common pathway for both systems: factors II, V, X as well as Fibrinogen

C. Interpretation of Clotting Test Results

<table>
<thead>
<tr>
<th>Quick value</th>
<th>PTT</th>
<th>Thrombocyte count</th>
<th>Bleeding time</th>
<th>Probable causes of hemorrhagic diathesis (applied to moderate to severe disorders)</th>
</tr>
</thead>
<tbody>
<tr>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>Vascular cause, factor XIII deficiency</td>
</tr>
<tr>
<td>reduced</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>Factor VII deficiency</td>
</tr>
<tr>
<td>normal</td>
<td>normal</td>
<td>reduced</td>
<td>normal</td>
<td>Heparin administration, deficiency of factor VIII, IX, XI, XII, HMK or prekallikrein</td>
</tr>
<tr>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>reduced</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>Administration of coumarin derivatives, vitamin K deficiency, factors I, II, V, X deficiency</td>
</tr>
<tr>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>v. Willebrand’s disease</td>
</tr>
<tr>
<td>reduced</td>
<td>normal</td>
<td>normal</td>
<td>normal</td>
<td>Liver damage, consumption coagulopathy, sepsis</td>
</tr>
</tbody>
</table>

(after E. Lechler)
A bleeding tendency (hemorrhagic diathesis [HD]) may be caused by disorders of the coagulation or fibrinolysis system (plasma HD) as well as disorders of TC (thrombocytic HD), or of vascular defects (vascular HD). While in plasma disorders minimal mechanical injury result in hematomas (bruses) and bleeding into joints, thrombocytic and vascular HDs are characterized by punctuate, tiny insect bite–like cutaneous bleedings (petechiae; →A, photo).

The probable cause of a more serious HD can be elucidated with a few simple clotting tests (→B). In the Quick test, plasma is transiently made incoagulable with substances that form complexes with Ca²⁺ (citrate, oxalate, or EDTA); an excessive amount of Ca²⁺ and tissue thrombokinase are then added and the resulting clotting time is compared with serial dilutions of normal plasma. If, for example, the test plasma coagulates after the same time interval as 1:1 diluted normal plasma, the Quick value is 50% (normal range: 70–125%). Low Quick values denote that either factor VII (exogenous system) or the cascade initiated by factor X is abnormal or is influenced by vitamin K antagonists (→B, C, D). To measure partial thromboplastin time (PTT), kephalin, kaolin (substitute for contact activation), and Ca²⁺ are added to the citrated plasma and the time until clotting (→PTT) is measured (normal: 25–38 s). If it is increased, the disorder lies either in the endogenous activation or in the common final pathway from factor X onward (→B, C). To measure (plasma) thrombin time, thrombin is added to the citrated plasma and the clotting time determined (normal: 18–22 s); the result can reveal fibrinogen deficiency (→B), or can be used to monitor treatment with heparin, which enhances the inhibitory action of antithrombin III on thrombin (→E). An abnormality in the platelets usually goes hand in hand with prolonged bleeding time (bleeding >5 min after, e.g., a prick into the ear lobe). A TC deficiency (thrombocytopeny; <50 × 10⁹/µL blood) can be distinguished from an abnormality of platelet function (thrombocytopeny) by means of a platelet count (→C).

Plasma hemorrhagic diathesis (coagulopathies) are caused by congenital or acquired clotting factor deficiency. The hereditary coagulopathies (→D1) can affect practically each of the plasma factors, but deficiency of some of the factors may produce relatively few symptoms (e.g., factors of the contact phase, factor XI). The most common (one of 10,000 newborn boys of the the X-chromosomal recessive forms is classical hemophilia (Type A). This was, for example, inherited from Queen Victoria by numerous male descendants of European royal houses (women are carriers). The most common bleeding sites are the muscles and the large joints of the leg, the latter becoming markedly deformed with time (hemophilic arthropathy). Hemophilia A is due to the absence, reduced formation, or defect of factor VIII. The fivefold rarer hemophilia B (factor IX deficiency) is similar in its mode of inheritance and symptoms to hemophilia A. The rare homozygous hereditary deficiency of factor I (afibrinogenemia), of factor II (hypoprothrombinemia), of factors V, VII, and X leads especially to marked bleeding after severe injury or operations. Homozygous deficiency of α₂-antiplasmin, an important inhibitor of fibrinolysis (→D3) also results in a hemophilia-like bleeding tendency. Factor XIII deficiency is characterized by fibrin instability so that bleedings occur only after a long interval (up to 1½ days). The routine clotting tests are usually normal in factor XIII deficiency, because actual clotting is unchanged.

Acquired coagulopathies (→D2) occur when formation of the various factors is reduced, when they are inhibited (e.g., by administration of heparin [→E] or by immune coagulopathies, e.g., factor VIII antibodies), or if their consumption is high (consumption coagulopathy). As most of the clotting factors are formed in the liver, liver damage (in particular liver cirrhosis; →p. 172 ff.) results in clotting disorders. Simultaneously occurring portal hypertension further increases the risk of hemorrhages (mainly from esophageal varices; →p. 170 ff.) because platelets are sequestered in the enlarged spleen, resulting in thrombocytopenia (see below). As several clotting factors are vitamin K–dependent (see above), a coagulopathy can also be caused by deficiency or inhibition of vitamin K (→D2).

Causes of vitamin K deficiency are:
- obstructive jaundice, in which fat-soluble vitamins (e.g., vitamin K₁ from green plants
D. Angeborener und erworbener Faktormangel als Ursache einer Blutungsneigung

1 angeborener Faktormangel
- Faktor VII
- Faktor XII
- Faktor IX: Hämophilie B
- Faktor X
- Faktor VIII: Hämophilie A
- Faktor V
- Faktor II: Hypoprothrombinämie
- Faktor XIII
- Faktor I: Acharinogenämie
- α₂-Antiplasmin

2 erworbener Faktormangel durch:
- Vitamin-K-Mangel
- Leberschäden
- Verbrauchskoagulopathie
- Curarine
- Vitamin-K-Wirkung

3 Fibrinolyse
- α₂-Antiplasmin
- Plasminogen
- Gewebeplasminogenaktivator
- Plasmin
- Urokinase
- Streptokinase
- Trastanxamsäure
- Staphylokinase
- lösliche Fibrinopeptide

Plate 3.18 Hemostasis II

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or synthetic vitamin K₃ fail to be absorbed due to the lack of bile salts (→ p. 168);
- generalized malabsorption (→ p. 152 ff.);
- destruction by antibiotics of the intestinal flora, which through its synthesizing vitamin K₂ contributes significantly to supplying the body with this substance.

The inhibition of the vitamin K effect by coumarin derivatives (phenprocoumon, warfarin, acenocumarol) is used for oral prophylaxis of thrombosis (anticoagulant treatment).

*Consumption coagulopathy (= disseminated intravascular coagulation; → D2) is a coagulation disorder caused by acute or chronic activation of thrombin with clot formation and platelet activation that secondarily results in hyperfibrinolysis. It is caused by large amounts of tissue thromboplastin entering the bloodstream, for example, in amniotic fluid embolism, extensive brain injury, malignant disease (e.g., leukemia), or sepsis (e.g., petechiae in meningococcal septicemia [Waterhouse–Friedrichsen syndrome]). Vascular causes are seen, for example, in aortic aneurysm (→ p. 236 ff.), or in vascular malformations as well as in ABO blood group mismatches, and due to enzyme action with certain snake poisons.*

The two groups of *hemorrhagic diathesis caused by platelet abnormalities* are thrombocytopenias and thrombocytopenopathies. *Acquired thrombocytopenias (TCPs)* are the most common HD. TCP is due to *diminished platelet formation* (aplastic TCP, e.g., in bone marrow tumors, radiation damage, or cobalamin or folate deficiency), to *increased platelet destruction* (thrombocytoclastic TCP), or *platelet sequestration* in an enlarged spleen. Markedly increased bleeding tendency occurs when the number of platelets falls below 20 × 10⁹/μL. Idiopathic TCP (Werlhof’s disease) is relatively frequent, its acute form developing one to three weeks after a viral infection (shortened platelet survival time due to immune complexes). The chronic form occurs as an autoimmune disease. Drug allergy can produce TCP through the action of drugs (e.g., quinine or sulfonamides) as haptons (→ p. 52). *Acquired thrombocytopenias* occur in uremia and dysproteinemia (platelet coating). They can also be caused by such drugs as acetylsalicylic acid via their inhibitory effect on cyclo-oxygenase, an effect that is used in *thrombosis prophylaxis*.

*Congenital thrombocytopenic HDs* are the autosomal-dominant and autosomal-recessive hereditary thrombocytopenias (abnormal platelet production) with the following functional disorders:

- *Membrane defects* such as 1) deficiency of platelet glycoprotein Ib (→ F1) that disturb adhesion (Bernard–Soulier syndrome); 2) deficiency of glycoprotein complex IIa/IIIb (→ F2), which inhibits aggregation and adhesion (Glanzmann–Naegeli thrombasthenia);
- *Diverse defects of storage or secretion*, for example, deficiency of cyclo-oxygenase and thromboxane synthetase, in which ADP release is reduced (storage pool deficiency); (→ F3).

Among the forms of HD of *vascular cause* are the different kinds of hereditary von Willebrand’s (vW) disease, a defect of vascular endothelium in which the vW factor is reduced or defective (→ F4). This weakens platelet adhesion and secondarily leads to factor VIII deficiency, because the vW factor acts as a kind of carrier for this factor (complex formation). Finally, there are a number of functional disorders and tissue changes in the vascular wall and connective tissue that are either congenital (purpura simplex; Osler–Weber–Rendu disease; Schönlein–Henoch disease), or acquired (scurvy in vitamin C deficiency; drug-mediated immune reactions).
E. Inhibition of Blood Clotting System

Exogenous activation

Endogenous activation

PL–Ca$^{2+}$–VIIa

PL–Ca$^{2+}$–IXa–VIIIa

PL–Ca$^{2+}$–Xa–Va

Prothrombin

Thrombin

Negative feed-back

Thrombomodulin

Fibrin

$\alpha_2$ macroglobulin
$\alpha_1$ antitrypsin

Fibrinopeptides

Heparin

Antithrombin III

α2 macroglobulin
α1 antitrypsin

F. Causes of Thrombocytic and Vascular Bleeding Tendency

1. Ilb reduced
   - Bernard-Soulier syndrome
   - Adhesion
   - vWF reduced
   - Thrombocyte adhesion
   - v. Willebrand’s disease

2. Ilb/Ilia reduced
   - Glanzmann-Naegeli thrombasthenia
   - Aggregation
   - ADP

3. Thromboxan synthetase and cyclooxygenase deficiency
   - Storage pool deficiency
   - Defects of storage and secretion

4. vWF reduced
   - Endothelial defect
   - F VIII deficiency

Causes:
- thrombocytic
- vascular
- various
Overview

Breathing through the lungs has two functions: firstly, to supply O₂ to the blood and, secondly, to regulate the acid–base balance via the CO₂ concentration in the blood. The mechanics of breathing serve to ventilate the alveoli, through whose walls O₂ can diffuse into the blood and CO₂ can diffuse out. Respiratory gases in the blood are largely transported in bound form. The amount transported depends, among other factors, on the concentration in blood and on pulmonary blood flow (perfusion). It is the task of respiratory regulation to adapt ventilation to the specific requirements.

A number of disorders can affect breathing in such a manner that ultimately sufficient O₂ uptake and CO₂ release can no longer be guaranteed.

In obstructive lung disease (→ p. 76) flow resistance in the respiratory tract is raised and ventilation of the alveoli is thus impaired (→ A1). The primary consequence is hypoventilation in some alveoli (abnormal distribution; → p. 72) or of all alveoli (global hypoventilation). If alveolar ventilation ceases completely, a functional arteriovenous shunt occurs. However, hypoxia leads to constriction of the supplying vessels, thus diminishing blood flow to the underventilated alveoli.

In restrictive lung disease (→ p. 74) the loss of functioning lung tissue reduces the area of diffusion and in this way impairs gaseous exchange. There is also a reduced area of diffusion in emphysema (→ p. 78), a condition characterized by alveoli that have a large lumen but are also diminished in number. Disorders of diffusion can also be caused by an increased distance between alveoli and blood capillaries (→ A2; → p. 70, 80). If alveoli and capillaries are completely separated from one another, this results in both a functional dead space (nonperfused alveoli) and an arteriovenous shunt.

Restrictive and obstructive lung disease as well as cardiovascular disease may affect lung perfusion (→ A3; → p. 80). Decreased perfusion results in a reduced amount of gases being transported in blood, despite adequate O₂ saturation and CO₂ removal in the alveoli. If flow resistance is increased, severe consequences for the circulation are possible, because the entire cardiac output (CO) must pass through the lungs (→ p. 80).

Breathing is also impaired in dysfunction of the respiratory neurons (→ p. 82) as well as of the motoneurons, nerves, and muscles that are controlled by them (→ p. 68). The changes in breathing movement that occur when the breathing regulation is abnormal (→ Table 1) do not, however, necessarily lead to corresponding changes of alveolar ventilation.

Consequences of inadequate breathing can be hypoxemia (→ A5; → p. 84), hypercapnia or hypocapnia (increased or decreased CO₂ content, respectively; → A4; → p. 86 ff.) in arterialized blood. The supply of O₂ to the cells as well as the removal of CO₂ from the periphery do not only depend on adequate respiration but also on unimpaired oxygen transport in the blood (→ chap. 3) and on intact circulation (→ chap. 7).

Table 2 Definition of Some Parameters of Ventilation

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tidal volume (Vₜ)</td>
<td>volume of normal inspiration and expiration</td>
</tr>
<tr>
<td>Vital capacity (VC)</td>
<td>volume of maximal expiration after maximal inspiration</td>
</tr>
<tr>
<td>Maximal breathing capacity (Vₘₐₓ)</td>
<td>maximal ventilation (L/min) achieved in a short period of time (usually 10 s)</td>
</tr>
<tr>
<td>Compliance (C)</td>
<td>lung distensibility</td>
</tr>
<tr>
<td>Forced expiration volume (FEVₜ)</td>
<td>maximal volume expired in 1 second</td>
</tr>
<tr>
<td>Functional residual capacity (FRC)</td>
<td>total residual volume after normal expiration</td>
</tr>
</tbody>
</table>
A. Pathophysiology of Respiration (Overview)

1. Abnormal regulation of breathing
2. Obstructive lung diseases, increased flow resistance
3. Restrictive lung diseases, loss of tissue
4. Abnormal oxygen transport

![Diagram of respiratory system with labels](image)

- **Abnormal ventilation**
- **Abnormal diffusion**
- **Abnormal perfusion**

**Graphs**

- **Graph 4**: 
  - Y-axis: \([\text{HCO}_3^- \text{mmol/L in blood}]\)
  - X-axis: \(P_{CO_2} \text{ (kPa in blood)}\)
  - Key points:
    - Hypocapnia
    - Hypercapnia

- **Graph 5**: 
  - Y-axis: \([O_2 \text{ mL/L in blood}]\)
  - X-axis: \(P_{O_2} \text{ (kPa in blood)}\)
  - Key points:
    - Hypoxemia
    - Hyperoxemia (at >50 kPa)

1 kPa = 7.5 mmHg
Ventilation, Perfusion

To reach the alveoli, inspired air must pass through those respiratory pathways in which no gaseous exchange takes place (dead space), i.e., normally the mouth, pharynx and larynx, trachea, bronchi and bronchioles. On its way the air will be warmed, saturated with water vapor, and cleansed.

The tidal volume (VT) contains, in addition to the volume of air that reaches the alveoli (VA), the volume of air that remains in the dead space (VB). If tidal volume is less than VB (normally ca. 150 ml), the alveoli are not ventilated with fresh air (→ A, right). When tidal volume is greater than VB, the proportion of alveolar ventilation rises with increasing VT. Alveolar ventilation may even be reduced during hyperpnea, if the depth of each breath, i.e., VT, is low and mainly fills the dead space.

Increased ventilation can occur as a result of either physiologically (e.g., during work) or pathophysiological (e.g., in metabolic acidosis; → p. 88) increased demand, or due to an inappropriate hyperactivity of the respiratory neurons (→ p. 82).

Decreased ventilation can occur not only when the demand is reduced, but also when the respiratory cells are damaged, or when neural or neuromuscular transmission is abnormal. Further causes include diseases of the respiratory muscles, decreased thoracic mobility (e.g., deformity, inflammation of the joints), enlargement of the pleural space by pleural effusion or pneumothorax (→ p. 74) as well as restrictive or obstructive lung disease (→ p. 74ff.).

Changes in alveolar ventilation do not have the same effect on O₂ uptake into the blood and CO₂ release into the alveoli. Because of the sigmoid shape of the O₂ dissociation curve, O₂ uptake in the lungs is largely independent of alveolar partial pressure (PAO₂). If there is only minor hypoventilation, the partial pressure of O₂ in the alveoli and thus in blood is reduced, but the O₂ dissociation is at the flat part of the curve, so that the degree of hemoglobin saturation and thus O₂ uptake in blood is practically unchanged (→ B, right). On the other hand, the simultaneous increase in CO₂ partial pressure in the alveoli and blood leads to a noticeable impairment of CO₂ release (→ B, left).

Massive hypoventilation lowers the O₂ partial pressure in the alveoli and blood, so that oxygen is at the steep part of the O₂ binding curve of hemoglobin and O₂ uptake is therefore impaired much more than CO₂ release is. Hyperventilation increases the O₂ partial pressure in the alveoli and blood, but cannot significantly raise the level of O₂ uptake into the blood because the hemoglobin is already saturated. However, hyperventilation boosts CO₂ release.

Lung perfusion is increased, for example, during physical work. It can be reduced by heart or circulatory failure (→ p. 224), or by constriction or occlusion of pulmonary vessels (→ p. 80).

A moderate increase in lung perfusion while ventilation remains unchanged increases O₂ uptake virtually in proportion to the amount of blood flow (→ C, right). Even though the alveolar O₂ partial pressure falls slightly because of the increased O₂ uptake from the alveoli into the blood, this has little influence on O₂ saturation in the blood (see above). It is only when the alveolar partial pressure of O₂ falls into the steep part of the O₂ dissociation curve that a decrease of alveolar O₂ partial pressure significantly affects O₂ uptake into blood. At those O₂ partial pressures a further increase in lung perfusion only slightly increases O₂ uptake. Furthermore, at very high lung perfusion flow, the contact time in the alveoli is not sufficient to guarantee that partial O₂ pressure in blood approaches that in the alveoli (→ p. 70). If lung perfusion is reduced, O₂ uptake is proportionally decreased.

CO₂ removal from blood is dependent on lung perfusion (→ C, left) to a lesser extent than O₂ uptake. In case of reduced lung perfusion (but constant ventilation and venous CO₂ concentration) the CO₂ partial pressure in the alveoli falls and thus favors the removal of CO₂ from the blood. This, in turn, attenuates the effect of the reduction in perfusion. At raised lung perfusion an increase of alveolar CO₂ concentration prevents a proportional rise in CO₂ release.
A. Dead Space ($V_D$), Alveolar Volume ($V_A$) and Tidal Volume ($V_T$)

- Tidal volume ($V_T$)
- Dead space ($V_D$)
- Alveolar proportion of $V_T$ ($V_A$)

$V_A = V_T - V_D$

- $V_D > V_T$
- $V_T = V_D$

B. $O_2$ and $CO_2$ of Arterial Blood in Abnormal Ventilation

Hyper-ventilation vs. Hypo-ventilation

- $CO_2$ blood
- $P_{CO_2}$ blood (kPa)

- Normal
- Hypocapnia
- Severe hypercapnia

- $O_2$ uptake
- $P_{O_2}$ blood (kPa)

- Normal
- Severe hypoxia
- $HbO_2$ practically unchanged

C. $CO_2$ Release and $O_2$ Uptake at Different Perfusion Levels

- Reduced perfusion
- Increased perfusion

- Normal
- Marked effect on $O_2$ uptake
- Minor effect on $CO_2$ output
Diffusion Abnormalities

O₂ has to diffuse from the alveoli to hemoglobin in the erythrocytes, and CO₂ from the erythrocytes into the alveoli. The amount of gas (M) that diffuses across the diffusion barrier between alveoli and blood per unit time is proportional to the diffusion area (A) and the difference in partial pressure between alveolar gas (Pᴬ) and blood (Pblood), and inversely proportional to the length of the diffusion pathway (d):

\[ M = K \times F (P_A - P_{blood})/d. \]

Krogh’s diffusion coefficient K is about 20 times greater for CO₂ than for O₂. The diffusion capacity D (K × F /d) is about 230 mL × min⁻¹ × kPa⁻¹ (1.75 L × min⁻¹ × mmHg⁻¹) in a healthy person.

A diffusion abnormality exists when the ratio of diffusion capacity to lung perfusion (or cardiac output) is reduced.

The diffusion capacity may be reduced by increased distance (→ A). When a pulmonary edema occurs (→ p. 80), raised intravascular pressure means plasma water is exuded into the interstitial pulmonary tissue or into the alveoli, and thus increases the diffusion distance. Inflammation causes a widening of the space between alveoli and blood capillaries as a result of edema and the formation of connective tissue. In interstitial lung fibrosis (→ p. 74), the connective tissue forces alveoli and blood capillaries apart. It is the distance between hemoglobin and alveolar gas which matters. Thus, the distance can also be slightly increased by vessel dilation (inflammation) or anemia.

A diminished diffusion capacity may also be caused by a reduction of the diffusion area (→ A), as after unilateral lung resection, loss of alveolar septa (pulmonary emphysema; → p. 78), or in loss of alveoli in pneumonia, pulmonary tuberculosis, or pulmonary fibrosis (see above). The diffusion area can also be reduced by alveolar collapse (atelectasis; → p. 72), pulmonary edema, or pulmonary infarction (→ p. 80).

Diffusion abnormalities become obvious when cardiac output is large (→ A), blood flows rapidly through the lungs, and the contact time of blood in the alveoli is thus quite brief. In effect, diminution of the diffusion area (e.g., after unilateral lung resection) also means a shorter contact time in the remaining lung tissue, because the same amount of blood will now pass through a reduced amount of lung tissue per unit of time. An increased O₂ demand during physical exercise forces an increase in cardiac output and can thus reveal a diffusion abnormality.

Abnormal diffusion primarily affects O₂ transport. In order for the same amount of gas to diffuse per time, the O₂ gradient must be twenty times greater than the CO₂ gradient. Should the diffusion capacity in an alveolus be diminished while ventilation remains constant, O₂ partial pressure will fall in the blood leaving the alveolus. If all alveoli are similarly affected, O₂ partial pressure will fall in the pulmonary venous (and thus systemic arterial) blood. If O₂ consumption remains constant, O₂ partial pressure will necessarily be lower also in deoxygenated (systemic venous) blood (→ B2). For this reason patients with a diffusion abnormality get blue lips on physical exertion (central cyanosis; → p. 84). The primary effects of abnormal diffusion on CO₂ transport and acid–base metabolism are much less marked. Hypoxia stimulates the respiratory neurons, and the resulting increase in ventilation can produce hypocapnia. However, the hypoxemia due to abnormal diffusion can only be slightly improved by hyperventilation. In the example given (→ B3), doubling of the alveolar ventilation at unchanged O₂ consumption increases alveolar O₂ partial pressure by only 4 kPa to 17 kPa (30 mmHg to 129 mmHg), but the increased O₂ gradient does not normalize the O₂ saturation of the blood. At the same time, respiratory alkalosis develops, despite the abnormal diffusion, because of the increased CO₂ removal (→ p. 86). Hypoxemia due to abnormal diffusion can be neutralized with O₂–enriched inspiratory air (→ B4). The degree of hypoxemia can be lessened by decreasing O₂ consumption.
A. Development of Diffusion Abnormalities

Lung resection, emphysema, tuberculosis, etc.

Edema, inflammation, vessel dilation

Diffusion area
Diffusion distance
Permeability
Cardiac output

\[
\frac{K \cdot F}{d \cdot CO} \quad \text{Diffusion abnormality}
\]

\[
\frac{[O_2] \text{ ven.} - [O_2] \text{ art.}}{P_{O_2} \text{ cap.} - P_{O_2} \text{ alv.}}
\]

B. Abnormal Diffusion: Concentrations of CO₂ and HbO₂ in Blood

1 Normal diffusion capacity

2 Diffusion abnormality

3 Abnormal diffusion with hyperventilation

4 Abnormal diffusion with O₂ ventilation

Venous blood
Arterial blood

7 6 13 4 6.5 13 5
3
17

6 10 4
5
30
7 6.5 24 5.5
B. Abnormal Diffusion: Concentrations of CO₂ and HbO₂ in Blood

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Distribution Abnormalities

The concentration of $O_2$ and $CO_2$ in an alveolar space and the related capillary are dependent on the ratio of ventilation ($VA$) to perfusion ($Q$). In the ideal case this relationship ($VA/Q$) and thus the $O_2$ and $CO_2$ concentration is identical in all alveoli. Pulmonary vessels contract in hypoxia and thus normally guarantee extensive adaptation of perfusion to ventilation of individual alveoli. In an upright position ventilation and perfusion in the basal lung segments are greater than in the apical ones. Perfusion is more strongly affected and $VA/Q$ is thus normally slightly higher apically than basally.

The term “abnormal distribution” describes the condition when the ratio of ventilation to perfusion in individual alveoli deviates to a functionally significant extent from that in the whole lung. In principle there are two possibilities:

- **Impaired perfusion** of individual alveoli in relation to perfusion occurs in vascular occlusion, for example, in pulmonary embolism ($\rightarrow p. 80$). In addition, capillaries can be separated from their related alveoli by proliferating connective tissue, as is the case in pulmonary fibrosis ($\rightarrow p. 70, 74$). Lastly, capillary supply to the alveoli may also fade away if the alveolar septa are destroyed, as is the case in pulmonary emphysema ($\rightarrow p. 78$).

The impaired perfusion of ventilated alveoli **increases the functional dead space**, because the air in these alveoli no longer takes part in the gaseous exchange. This condition can be compensated by deeper breathing (increased $VT$). If a large proportion of alveoli are not perfused, the **diffusion area** also decreases ($\rightarrow p. 70$), and this can no longer be compensated by deeper breathing.

- **In impaired ventilation** of perfused alveoli ($\rightarrow A$) the blood is no longer adequately saturated with $O_2$ and rid of $CO_2$. In an extreme case a functional arteriovenous shunt develops. In obstructive lung disease, such as asthma and chronic bronchitis ($\rightarrow p. 76$), some of the bronchi are narrowed and preclude normal ventilation of their alveoli. Ventilation of individual bronchi (or bronchioles) can also be prevented by occlusion through tumor. The opening up and therefore ventilation of parts of the lung can be prevented by local scarring such as pleural thickening. Diaphragmatic paralysis has the same effect by preventing expansion of basal lung segments. Functional arteriovenous shunts can also occur in pulmonary fibrosis.

Perfusion of inadequately ventilated alveoli leads to an admixture of nonarterIALIZED blood with pulmonary venous blood. This results in hypoxemia ($\rightarrow A$; $P_A = $ partial pressure in alveolar gas mixture), which cannot be compensated by hyperventilation of “intact” alveoli (this is because $O_2$ uptake by the blood that passes along ventilated alveoli can be increased only minimally by hyperventilation; $\rightarrow p. 68$). On the other hand, hypercapnia hardly ever occurs because the reduced $CO_2$ release from underventilated alveoli ($\rightarrow A$, right) can be well compensated by increased release into hyperventilated alveoli ($\rightarrow A$, left). On the contrary, the hypoxemia frequently leads to excess hyperventilation, and the development of hypercapnia. If considerable venous admixture occurs, the arterial hypoxemia cannot be stopped even by breathing pure $O_2$.

If the supplying airway is completely occluded, the alveoli collapse (atelectasis). Normally more $O_2$ is taken up in tissue than $CO_2$ is released, so that there is a greater decrease in $O_2$ partial pressure than increase in $CO_2$ partial pressure ($\rightarrow B$1). The blood therefore takes more $O_2$ from the alveoli than it adds $CO_2$, resulting in a decrease of the alveolar volume. As a consequence $N_2$ in the alveoli is concentrated and, following its gradient, also diffuses into the blood. Eventually, the entire alveolar volume is reabsorbed. The process is delayed by a fall in alveolar $O_2$ concentration and subsequent vascular contraction (see above). Ventilation with $O_2$ can favor the development of atelectases ($\rightarrow B$2), because $O_2$ uptake is increased by the high alveolar $O_2$ partial pressure and there is no constriction of the supplying vessels.
A. Effects of Abnormal Distribution on O₂ Uptake and CO₂ Release

![Diagram showing effects of abnormal distribution on O₂ and CO₂]

B. Development of Atelectasis

1. With air
   - O₂ 14%
   - CO₂ 5%
   - N₂ 75%
   - H₂O 6%

2. With oxygen
   - O₂ 89%
   - CO₂ 5%
   - N₂ 75%
   - H₂O 6%

![Diagram showing development of atelectasis]

- After blockage
  - Normal O₂ difference
  - Alveolus shrinks slowly

- Large O₂ difference
  - Alveolus shrinks rapidly
Restrictive Lung Disease

Restrictive lung disease is a term given to an anatomical or functional loss of gaseous exchange area.

An anatomical loss occurs after removal (resection) or displacement (e.g., by a tumor) of lung tissue. Atelectasis (→ p. 72) may also lead to a decrease in diffusion area.

A functional decrease in exchange area occurs if plasma water is exuded into alveoli, for example, in pulmonary edema (→ p. 80) or in inflammation (increased vascular permeability, e.g., in pneumonia). In pulmonary fibrosis proliferating connective tissue displaces intact pulmonary parenchyma (decrease in diffusion area), infiltrates between capillaries and alveoli (increase in distance), and prevents the normal expansion of the lung (impairment of alveolar air exchange). Pulmonary fibrosis can be caused by inflammatory reaction against connective tissue (so-called collagen disease) or by inhalation of dust which contains silicate or asbestos. Sometimes no cause is found (idiopathic pulmonary fibrosis [Hamman–Rich syndrome]). Local or generalized impairment of lung expansion can also occur in thoracic deformities, diaphragmatic paralysis, or adhesion of both pleural layers (as a result of inflammation [pleural fibrosis]).

Pneumothorax is also a restrictive lung disease (→ B). If there is an open connection between the pleural space and outside air (thoracic injury; → B, top) or the alveoli (torn alveolar wall due to overdistension), air enters and the ipsilateral lung collapses. Breathing is also impaired in the other lung, because the pleural pressure on the healthy side falls on inspiration and as a result the mediastinum is displaced to the healthy side. On expiration the pressure rises and the mediastinum moves toward the collapsed side. This mediastinal flutter reduces the breathing excursion (\(V_T\)) of the healthy lung. If a valve-like mechanism develops on the injured side, allowing air into the pleural space but not out of it, tension pneumothorax develops (→ B, bottom). It is especially the burst alveoli that often act like valves: the collapsed lung expands on inspiration, allowing air to enter the pleural space through the damaged alveolus, but when lung and alveolus collapse during expiration the escape of air is prevented. The mediastinum is massively displaced by the increasing pressure toward the healthy side and breathing correspondingly impaired. The increase in intrathoracic pressure also reduces the venous return and thus right ventricular filling, as a consequence of which cardiac output falls.

In whole-body plethysmography the air in the pleura is indistinguishable from that in the alveoli, because both are equally reduced on expiration. However, inspired test gas is distributed only throughout the lung. In pneumothorax, the intrathoracic volume measured by whole-body plethysmography is thus greater than the alveolar volume obtained with a test gas.

Restrictive pulmonary disease causes a fall in compliance (C), vital capacity (VC), functional residual capacity (FRC), and diffusion capacity (→ p. 66). The latter leads to diffusion abnormality (→ p. 70) and thus to hypoxemia (→ A; \(S_{O_2}\) = oxygen saturation of blood). Maximum breathing capacity (\(V_{max}\)) and forced expiration volume in 1 second (FEV\(_1\)) are usually reduced, but relative forced expiration volume (normally 80% of VC) is generally normal. To inspire a certain volume, greater negative pressure than normal is required in the pleural space (\(P_{pl}\)) and more energy thus has to be expended during breathing (increased work of breathing; → A; \(\dot V = \) ventilation flow). Reduction of the vascular bed by removing lung tissue or by compressing blood vessels increases vascular resistance. Greater pressure is required to pump the blood through the pulmonary vascular bed, pressure which must be generated by the right heart. The consequence is a raised load on the right ventricle (cor pulmonale; → p. 214).
A. Causes and Effects of Restrictive Lung Diseases

- Fibrosis
- Pulmonary edema, pneumonia
- Atelectasis
- Carcinoma

Restrictive lung diseases

<table>
<thead>
<tr>
<th>Diffusion surface</th>
<th>Loss of parenchyma</th>
<th>Vascular cross sectional area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffusion abnormality</td>
<td>Compliance</td>
<td>Vascular resistance</td>
</tr>
</tbody>
</table>

Hypoxemia

\[ S_{O_2} \]

\[ P_{O_2} \]

Dyspnea

\[ \text{Work of breathing} \]

\[ \dot{V} \]

\[ P_{pl} \]

Pulmonary hypertension

B. Pneumothorax

- Normal
- Mediastinal flutter
- Open pneumothorax
- Hole with valve-like effect
- Tension pneumothorax
Obstructive Lung Disease

In order to reach the alveoli air must pass through the respiratory tract or airways (→ p.68), which present a resistance to the flow. This resistance is determined by the lumen in the tract. In particular the narrow lumen of the bronchioles can be further narrowed by mucus and the contraction of the bronchial musculature. Mucus is secreted in order to trap pathogens and dirt particles. It is transported toward the mouth by the cilia of the lining epithelium and then swallowed. As the cilia cannot propel very sticky mucus, an electrolyte solution is usually secreted that lifts the mucus from the cilia, so that mucus moves toward the mouth on a thin fluid layer. The lumen can be narrowed by the action of the bronchial muscles, which increases the likelihood of pathogens being caught in the mucus. The disadvantage, however, is that narrowing raises flow resistance. Obstructive lung diseases are characterized by an increased flow resistance.

Intrathoracic increase in resistance is usually due to a narrowing or obstruction of the bronchi, by either external compression, contraction of bronchial muscles, thickening of the lining mucus layer, or obstruction of the lumen by mucus. Most of these changes are the result of asthma or chronic bronchitis. In asthma there is an allergy to inhaled antigens (e.g., pollen). These antigens cause an inflammation of the bronchial mucosa leading to the release of histamine and leukotrienes (called slow reacting substances in anaphylaxis [SRSA]). The bronchial muscles contract and mucus secretion as well as vessel permeability (mucosal edema) are increased (→ A, top) under the influence of these mediators. In addition to the inhaled antigens, microorganisms in the mucosa may also act as antigens (infectious–allergic asthma). Here there is no clear-cut distinction between asthma and bronchitis. Obstructive lung disease can also be the result of cystic fibrosis (CF). As the result of an autosomal recessive genetic defect of the CF transmembrane regulator (CFTR; → p.162) there is decreased secretion and hyperreabsorption of fluid, and mucus can no longer be cleared from the airways. The result is obstructive lung disease. The lung’s reduced ability to retract (flaccid lung, → p.78) can also lead to obstructive lung disease, because reduced elastic recoil (increased compliance) of the lung requires an increase in pressure during expiration, resulting in compression of the intrathoracic airways (see below).

Extrathoracic increase in resistance occurs, for example, in paralysis of the vocal chords, edema of the glottis, and external tracheal compression (e.g., by tumor or goitre; → p.282 ff.). In tracheomalacia the tracheal wall is softened and collapses on inspiration.

The effect of obstructive lung disease is reduced ventilation. If extrathoracic obstruction occurs, it is mainly inspiration that is affected (inspiratory stridor), because during expiration the pressure rise in the prestenotic lumen widens the narrowed portion. Intrathoracic obstruction mainly impairs expiration, because the falling intrathoracic pressure during inspiration widens the airways. The ratio of the duration of expiration to that of inspiration is increased. Obstructed expiration distends the alveolar ductules (centrilobular emphysema; → p.78), lung recoil decreases (compliance increases), and the midposition of breathing is shifted toward inspiration (barrel chest; → p.78). This raises the functional residual capacity. Greater intrathoracic pressure is necessary for expiration because compliance and resistance are increased. This causes compression of the bronchioles so that the airway pressure increases further. While the effort required to overcome the elastic lung resistance is normal or actually decreased, the effort required to overcome the viscous lung resistance and thus the total effort of breathing is greatly increased (→ A, middle). The obstruction reduces maximum breathing capacity (Vmax) and FEV₁ (→ table 2 on p.66), and the differing ventilation of various alveoli results in abnormal distribution (→ p.72). The hypoxia of underventilated alveoli leads to vasoconstriction, increased pulmonary vascular resistance, pulmonary hypertension, and an increased right ventricular load (cor pulmonale; → p.214).
A. Obstructive Lung Diseases

- Cartilage
- Ciliated cells
- Goblet cells
- Bronchial glands
- Muscles

**Bronchioles (section)**

- Mucus secretion
- Mucosal edema
- Muscle contraction

**Increased resistance to breathing**

**Work of breathing**

- Hypoxia
- Dyspnea

- Constriction of pulmonary vessels
- Compression of blood vessels

- Pulmonary hypertension
- Emphysema

- Right heart failure

**Abnormal ventilation**

- Dyspnea

- Emphysema

- Right heart failure
Pulmonary Emphysema

Emphysema is characterized by an increase in the volume of the airways distal to the bronchioles. **Centrilobular emphysema**, with predominant distension of the alveolar ducts and respiratory bronchioles, is distinguished from **panlobular emphysema**, in which the terminal alveoli in particular are distended (→ A). In **flaccid lung** there is merely a loss of elastic recoil. The disease can affect a circumscribed area (local emphysema), or the entire lung (generalized emphysema). Emphysema is one of the most frequent causes of death.

Centrilobular emphysema is caused mainly by **obstructive lung disease**: in flaccid lung there is a loss of connective tissue of unknown cause; in panlobular emphysema there is additional loss of alveolar septa. In **the elderly** an increase in alveolar volume in relation to alveolar surface regularly occurs. In some patients (ca. 2%) there is a **deficiency in α₁-proteinase inhibitor** (α₁-antitrypsin), which normally inhibits the action of proteinases (e.g., leukocyte elastase). This enzyme is produced in the liver; its mutation can affect its secretion and/or function. In either case decreased inhibition of the proteinases leads to a breakdown and thus a loss of lung tissue elasticity. If secretion is disturbed, the accumulation of the defective protein in the liver cells can additionally lead to liver damage. Finally, a lack of proteinase inhibition can also affect other tissues, for example, renal glomeruli and the pancreas may be damaged. α₁-antitrypsin is oxidized and thus inhibited by smoking, which thus promotes the development of emphysema even in someone without a genetic predisposition.

In addition to a lack of inhibitors, **increased elastase production** may be a cause of emphysema (e.g., of a serine elastase from granulocytes, a metalloelastase from alveolar macrophages, and various proteinases from pathogens). The excess of elastases in chronic inflammatory disease leads, for example, to a breakdown of elastic fibers in the lung.

When considering the effects of pulmonary emphysema, the consequences of **reduced elastic recoil** are important. In the end the lung's elastic recoil generates the positive pressure in the alveoli in comparison to ambient air necessary for normal expiration. Although positive pressure in the alveoli can also be produced by external compression, i.e., by contraction of the expiratory muscles, this will also compress the bronchioles and thus bring about a massive increase in flow resistance. Maximal expiratory flow rate ($V_{\text{max}}$) is thus a function of the ratio between elastic recoil (K) and resistance ($R_L$) (→ A, right). Reduced elastic recoil can thus have the same effect as obstructive lung disease (→ p. 76). Elastic recoil can be raised by increasing the inspiratory volume (→ A, right), eventually leading to a **shift in the resting position** toward inspiration (barrel chest; → B). If tidal volume remains constant, both the functional residual capacity and the residual volume are increased, sometimes also the dead space. However, vital capacity is diminished because of the reduced expiratory volume. The loss of alveolar walls leads to a **diminished diffusion area** (→ p. 70); the loss of pulmonary capillaries to an **increase in functional dead space** as well as increased pulmonary artery pressure and vascular resistance with the development of **cor pulmonale** (→ p. 214). In centrilobular, but not panlobular, emphysema a **distribution abnormality** develops, too (→ p. 72), because of differing resistances in different bronchioles. The abnormal distribution results in **hypoxemia**. Patients with centrilobular emphysema due to obstructive lung disease are called “blue bloaters” (→ A). In contrast, patients with panlobular emphysema at rest are called “pink puffers”, because enlargement of the functional dead space forces them to breathe more deeply. It is only when diffusion capacity is greatly reduced or oxygen consumption is increased (e.g., during physical work) that diffusion abnormality will result in hypoxemia (→ p. 70).
A. Emphysema

Chronic obstructive lung disease

Breakdown of connective tissue in the lung

Elastase excess

Centrilobular

Panlobular

Emphysema

Bronchial obstruction

Loss of diffusion area

Capillary destruction

Loss of retractability (recoil)

Bronchioles

Respiratory bronchioles

Alveolar ducts

Alveoli

Flaccid lung

B. Development of Barrel Chest in Emphysema

Tidal volume

Residual volume

Functional residual capacity

Total capacity

Normal inspiratory position

‘Barrel chest’ in emphysema

Increased dead space

Compensation through inspiration

\[ \frac{V_{\text{max}}}{T} = \frac{T}{R_L} \]

‘Blue bloater’

‘Pink puffer’

‘Barrel chest’

Hypoxemia

Pulmonary vasoconstriction

Pulmonary hypertension

Work: Cardiac output (CO)

Abnormal distribution

Abnormal diffusion

Increased dead space

Deepened breathing

Right heart failure ‘cor pulmonale’

‘Barrel chest’
Pulmonary Edema

In pulmonary capillaries, as in systemic capillaries, filtration is determined by the effective filtration pressure, i.e., the difference between the hydrostatic and oncotic pressure gradients. An increase in effective filtration pressure in the pulmonary vessels leads to pulmonary congestion, filtration of plasma water into the interstitial space results in interstitial pulmonary edema, and the passage of plasma water into alveoli causes alveolar pulmonary edema (→A, middle).

A rise in hydrostatic pressure in the pulmonary capillaries occurs when the left ventricle’s forward pumping action is inadequate (→A, right). Causes are reduced myocardial power or excess demand on it (heart failure; → p.224), mitral valve stenosis or regurgitation (→ p.194 ff.). The resulting increase in left atrial pressure is transmitted backward into the pulmonary vessels.

The development of pulmonary edema is facilitated by abnormal lymphatic drainage (→A, left). Normally, an excess of filtered fluid is removed via the lymphatics. However, the capacity of the pulmonary lymphatic system is low even under physiological conditions. If right heart failure occurs together with left heart failure, the systemic venous pressure rises and thus also the pressure at the point of drainage of the lymphatic vessels into the veins at the venous angle, so impairing lymphatic drainage.

The oncotic pressure in the capillaries is reduced by hypoproteinemia (→A, left), favoring the development of pulmonary edema. Hypoproteinemia is usually the result of hyperhydration, for example, an inappropriately high supply of fluids to patients with reduced renal excretion (e.g., due to renal failure; → p.110 ff.). A reduction in plasma protein formation in the liver (liver failure; → p.174) or loss of plasma proteins, for example, via the kidneys (nephrotic syndrome; → p.104), also decreases plasma protein concentration.

Finally, increased capillary permeability can result in pulmonary edema (→A, right). Increased permeability of the capillary wall for proteins reduces the oncotic pressure gradient and thus increases the effective filtration pressure. Capillary permeability is increased by, for example, inhalation of corrosive gases or prolonged inspiration of pure O₂ (→ p.84).

Effects of pulmonary congestion are reduced pulmonary perfusion, and thus impaired maximal O₂ uptake. The distension of the congested vessels prevents enlargement of the alveoli and decreases lung compliance. In addition, the bronchi are narrowed by the distended vessels and resistance to breathing increases (→ p.76), discernable through diminution of the maximal breathing capacity and of FEV₁ (→ table 2 on p.66).

In interstitial pulmonary edema the interstitial space between capillary and alveolus is increased. As a result, diffusion is disturbed with impairment mainly of O₂ uptake (→ p.70). If, due to physical activity, O₂ consumption rises, O₂ concentration in blood falls (hypoxemia, cyanosis: →A, bottom).

Any further pressure increase and damage to the alveolar wall causes the passage of filtrate into the alveolar space. The fluid-filled alveoli are no longer involved in breathing (gaseous exchange) and a functional venoarterial (pulmonary arterial to pulmonary venous) shunt occurs along with a decrease in O₂ in the systemic arterial blood (central cyanosis). Fluid enters the airways and thus also increases airway resistance. Increased filtration of fluid into the pleural space (pleural effusion) also impairs breathing.

Pulmonary edemas force the patient to breathe in the upright position (orthopnea). On sitting or standing up after being recumbent (orthostasis) venous return from the lower part of the body falls (even more in the fully upright position), and thus right atrial pressure and the right cardiac output decrease. Less blood flows through the lungs, causing a fall in hydrostatic pressure in the pulmonary capillaries at the same time that pulmonary venous flow from the upper parts of the lung is increased. Moreover, the decrease of central venous pressure facilitates lymphatic drainage from the lung. As a result, pulmonary congestion as well as interstitial and alveolar edemas regress.
A. Pulmonary Edema

- e.g. Hyperinfusion
- Increased hydrostatic pressure
- Left heart failure
- Increased vascular permeability
- Reduced vital capacity
- Increased central venous pressure
- Abnormal lymphatic drainage
- Reduced oncotic pressure

Interstitial pulmonary edema

- Abnormal diffusion

Alveolar pulmonary edema

- Narrowing of alveoli and bronchi
- Abnormal ventilation

- Dyspnoea
- On physical work

- Hypoxemia

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Pathophysiology of Breathing Regulation

Numerous factors influence the respiratory neurons in the medulla oblongata (→ A):

**Ventilation is increased** by acidosis, hypercapnia, hypoxia, and a decrease of Ca$^{2+}$ and Mg$^{2+}$ in cerebrospinal fluid (CSF). Pain, intensive cold or heat stimuli to the skin, an increase or moderate fall in body temperature, a drop in blood pressure, and muscular activity (joint innervation) all increase ventilation. Other stimulating factors are epinephrine and norepinephrine in the blood, histamine, acetylcholine and prostaglandins in the central nervous system (CNS), progesterone, testosterone, and corticotropin.

Conversely, **ventilation is reduced** by alkalosis, hypocapnia, peripheral hyperoxia, and Ca$^{2+}$ and Mg$^{2+}$ increase in the CSF. Hypoxia in the CNS, deep hypothermia, rise in blood pressure, ganglion blockers as well as high concentrations of atropine, catecholamines, endorphins and glycine in the CNS also diminish ventilation.

Normally the **pH around the respiratory neurons** or the pH in the CSF has a decisive influence on ventilation. A shift in pH in the brain following rapid changes in P$_{CO_2}$ is accentuated by the low buffering power of CSF (low protein concentration). Because CO$_2$, but not HCO$_3^-$ or H+, quickly passes through the blood–CSF and blood–brain barriers, changes in CO$_2$ concentration in the blood result in very rapid adaptation of ventilation, while adaptation after changes in blood pH or blood HCO$_3^-$ occurs only after a delay of several days. If sudden **metabolic acidosis** occurs (→ B, top; see also p. 88 ff.), respiratory compensation will thus occur only slowly. Conversely, treatment of a partly compensated respiratory acidosis, for example, by infusion of HCO$_3^-$, often leaves behind **respiratory alkalosis** (→ B, bottom). Also, with a sudden fall of O$_2$ partial pressure in inspiratory air (at high altitude) ventilation is not immediately and adequately raised. The onset of hyperventilation leads to hypocapnia, and the resulting intracerebral alkalosis will then transiently inhibit any further rise in ventilation. Complete adaptation of breathing to a reduced O$_2$ supply requires an increase in renal HCO$_3^-$ excretion with subsequent decrease in HCO$_3^-$ concentration in plasma and (after a delay) in CSF.

**Barbiturates** (soporific drugs) and **chronic respiratory failure** decrease the sensitivity of the respiratory neurons to pH or CO$_2$ in CSF. **Lack of O$_2$** thus becomes the **most important stimulus to breathing**. In both cases the supply of O$_2$-enriched air leads to hyperventilation and respiratory acidosis (→ p. 88 ff.). This response is increased by, for example, uremia (→ p. 110 ff.) or sleep. Because O$_2$ uptake varies within a wide range independently of alveolar ventilation (→ p. 68), breathing is stimulated only when there is a marked diminution in alveolar O$_2$ partial pressure and a fall in O$_2$ saturation in the blood. The resulting increase in ventilation will again cease as soon as O$_2$ saturation in the blood is normal; breathing is therefore irregular.

The reduced sensitivity of the respiratory neurons to CO$_2$ can also result in **sleep apnea**, an arrest of breathing during sleep lasting a few seconds. It is more likely in the presence of a metabolic alkalosis.

Damage or massive stimulation of the respiratory neurons can cause **pathological breathing** (→ C):

- **Kussmaul breathing** (→ C 1) is an adequate response of the respiratory neurons to metabolic acidosis. The depth of the individual breaths is greatly increased but breathing is regular.
- **Cheyne–Stokes breathing** (→ C 2) is irregular. The depth of breathing periodically becomes gradually deeper and then gradually more shallow. It is caused by a delayed response of respiratory neurons to changes in blood gases resulting in an overshooting reaction. It occurs when there is hypoperfusion of the brain, or when breathing is regulated by a lack of oxygen (see above).
- **Blot breathing** (→ C 3) consists of a series of normal breaths interrupted by long pauses. It is an expression of damage to respiratory neurons. **Gasping** (→ C 4) also signifies a marked disorder in the regulation of breathing.
A. Modulators of Respiratory Neurons

- **Excitatory**
  - Acidosis (pH↓)
  - Hypercapnia (CO₂↑)
  - Hypoxia (O₂↓)
  - Calcium and magnesium in CSF↓
  - Body temperature↑
  - Pain, anxiety
  - Blood pressure
  - Muscle work
  - Hormones
  - Transmitters

- **Inhibitory**
  - Alkalosis (pH↑)
  - Hypocapnia (CO₂↓)
  - Central hypoxia
  - Calcium and magnesium in CSF↑
  - Severe hypothermia
  - Blood pressure↑
  - Sleep
  - Transmitters

B. Effects of Blood-Brain Barrier

1. Normal 
   - pH 7.4
   - [HCO₃⁻] 25 mmol/L
   - CO₂ 5 kPa
   - Blood
   - CSF

2. Loss of bicarbonate in blood
   - pH 7.1
   - [HCO₃⁻] 12 mmol/L
   - Delayed [HCO₃⁻] adjustment
   - Acute metabolic acidosis

3. Hyperventilation, therefore CO₂ given off
   - pH 7.7
   - [HCO₃⁻] 25 mmol/L
   - Hypertonic [HCO₃⁻] correction
   - Respiratory compensation

C. Pathological Patterns of Breathing

1. Kussmaul breathing
2. Cheyne-Stokes breathing
3. Biot breathing
4. Severe abnormal regulation

- e.g. Metabolic acidosis
- e.g. Sleep, drugs, hypoxemia

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Hypoxia and Hyperoxia

**Hypoxia** occurs when O₂ transport from ambient air to the cell is impaired. There may be several causes: (→ A):

- **Hypoventilation** reduces the diffusion gradient to venous blood and thus impairs O₂ uptake. However, ventilation has to be markedly reduced before O₂ uptake is noticeably decreased (→ p. 68).
- **Reduced diffusing capacity** (→ p. 70) prevents equilibration of gas concentrations in alveoli and capillary blood.
- **Reduced O₂ uptake capacity of the blood** occurs in anemia (→ p. 30ff.) or can be caused by the inability of hemoglobin to bind or release O₂. Carbon monoxide (CO), for example, binds to hemoglobin with an affinity that exceeds that of O₂ by a factor of 200. CO bound to one heme group raises the affinity of the other three heme groups of the affected hemoglobin molecule so that it not only binds less O₂ but is also less ready to release the oxygen bound to it. Increased O₂ affinity with reduced peripheral O₂ release also occurs in a deficiency of 2,3-bisphosphoglycerate (2,3-BPG) or alkalosis.
- **Circulatory failure** (→ p. 224) impairs O₂ transport in the cardiovascular system.
- **Tissue diffusion** is impaired if the distance between a cell and its nearest capillary is increased, as in tissue hypotrophy without accompanying increased capillary formation, or edema. The diffusion distance is also increased when the precapillary sphincter of the nearest capillary contracts, because the O₂ supply must then come from the second nearest capillary.
- Several **poisons of the respiratory chain** can inhibit O₂ utilization.

The most important **effect** of all the above-mentioned causes is the impairment of the cells’ aerobic energy supply.

If the O₂ supply is deficient, some cells are able to meet their energy needs by breaking down glucose into lactic acid. However, the energy gain from this is small (2 molecules of ATP per molecule of glucose compared with 36 ATPs in oxidative metabolism), and the dissociation of lactic acid results in metabolic (not respiratory) **acidosis** (→ p. 88). The lack of energy at first causes a reversible impairment of function, but ultimately leads to irreversible cell damage.

Hypoventilation, abnormal pulmonary diffusion, and circulatory failure cause **cyanosis** (blue discoloration of the skin and mucous membranes) if the average concentration of deoxygenated hemoglobin in the capillaries is lower than ca. 0.7 mmol/L (5 g/100 mL) (→ A). In hyperventilation and disorders of pulmonary diffusion the arterialized blood is hypoxic (central cyanosis). It must be stressed that cyanosis is not always due to O₂ deficiency. If the hemoglobin concentration in blood is increased, cyanosis may occur even though there is no lack of O₂ (**pseudocyanosis**). Conversely, an O₂ deficiency may occur in hemoglobin deficiency (anemia), without the concentration of deoxygenated hemoglobin reaching the level required for cyanosis.

The organism can be damaged not only in hypoxia but also in **hyperoxia**, the latter as a result of the reactivity of O₂ (→ B). Hyperoxia, for example, produced by hyperbaric ventilation with a breathing apparatus during diving or by inhalation of pure O₂ over many days, can inhibit the cellular **oxidation of glucose**. High O₂ partial pressure lowers cardiac output and blood flow through the kidneys and brain, the latter resulting in **dizziness and cramps**. In the lung, irritation of the airway can cause **coughing and pain**, while oxidative damage to the alveolar epithelium and endothelium lead to increased permeability, and to the development of **pulmonary edemas** (→ p. 80). Oxidation can inactivate surfactant, the fluid that normally reduces surface tension in the alveoli and ensures they unfold evenly. The lack of surfactant may lead to different sizes of alveoli with subsequent abnormal distribution of ventilation (→ p. 72). Artificial ventilation with O₂ also facilitates the collapse of alveoli (**atelectasis**; → p. 72). In neonates mixtures containing over 40% O₂ lead to the development of **hyaline membranes** in the lung and thus impair gaseous exchange. In the vitreous body and cornea, vascular and connective tissue proliferates, possibly leading to blindness (**retrolental fibroplasia**).
A. Causes of Oxygen Deficiency

- O₂ deficiency in inspiratory air
- Abnormal ventilation
- Abnormal diffusion
  - Decreased transport capacity (e.g., anemia)
  - Increased O₂ affinity of hemoglobin
  - Abnormal diffusion in tissues (e.g., edema)
  - Abnormal O₂ utilization (e.g., mitochondrial poison)
- Circulatory failure
- Vasoconstriction

B. Effects of Hyperoxia

- Oxidation of surfactant
- Oxidation of lipids
- Membrane damage
- Damage to alveolar membrane
- Formation of hyaline membranes
- Blood flow (brain)
- Energy supply abnormal (e.g., CNS)
- Inhibition of glucose metabolism
- In infants: proliferation of vascular and connective tissues in vitreous body

- Abnormal distribution
- Cough
- Edema
- Abnormal diffusion
- Dizziness, seizures
- Retrolental fibroplasia
Development of Alkalosis

The pH of blood depends on the ratio of HCO$_3^-$ to CO$_2$ concentration:

$$\text{pH} = \text{pK} + \log \frac{\text{HCO}_3^-}{\text{CO}_2}$$

pK contains the dissociation constant of H$_2$CO$_3$ and the reaction constant of CO$_2$ to H$_2$CO$_3$. Alkalosis (pH > 7.444) thus occurs either when the CO$_2$ concentration in blood is too low (hypocapnia, respiratory alkalosis), or that of HCO$_3^-$ is too high (metabolic alkalosis).

**Respiratory alkalosis** occurs in hyperventilation (→ A3 and p. 82). Causes include emotional excitement, salicylate poisoning, or damage to the respiratory neurons (e.g., by inflammation, injury, or liver failure). Occasionally a lack of O$_2$ supply in the inspiratory air (e.g., at high altitude) causes increased ventilation resulting in an increased amount of CO$_2$ being expired.

Numerous disorders can lead to metabolic (i.e., non-respiratory) alkalosis:

- In **hypokalemia** the chemical gradient for K$^+$ across all cell membranes is increased. In some cells this leads to hyperpolarization, which drives more negatively charged HCO$_3^-$ from the cell. Hyperpolarization, for example, raises HCO$_3^-$ efflux from the proximal (renal) tubule cell via Na$^+$/(HCO$_3^-$)$_3$ cotransport (→ A4). The resulting intracellular acidosis stimulates the luminal Na$^+$/H$^+$ exchange and thus promotes H$^+$ secretion as well as HCO$_3^-$ production in the proximal tubule cell. Ultimately both processes lead to (extracellular) alkalosis.

- In **vomiting of stomach contents** the body loses H$^+$ (→ A6). What is left behind is the HCO$_3^-$ produced when HCl is secreted in the parietal cells. Normally the HCO$_3^-$ formed in the stomach is reused in the duodenum to neutralize the acidic stomach contents and only transiently leads to (weak) alkalosis.

- Vomiting also **reduces the blood volume**. Edemas as well as extrarenal and renal loss of fluid can similarly result in volume depletion (→ A4; see also p. 122). Reduced blood volume stimulates Na$^+$/H$^+$ exchange in the proximal tubules and forces increased HCO$_3^-$ reabsorption by the kidneys even in alkalosis. In addition, aldosterone is released in hypovolemia, stimulating H$^+$ secretion in the distal nephron (→ A5). Thus, the kidneys’ ability to eliminate HCO$_3^-$ is compromised and the result is volume depletion alkalosis. Hyperaldosteronism can lead to alkalosis without volume depletion.

- Parathyroid hormone (PTH) normally inhibits HCO$_3^-$ absorption in the proximal tubules. **Hypparathyroidism** can thus lead to alkalosis.

- The liver forms either glutamine or urea from the NH$_4^+$ generated by amino acid catabolism. The formation of urea requires, in addition to two NH$_4^+$, the input of two HCO$_3^-$ that are lost when urea is excreted. (However, NH$_4^+$ is split off from glutamine in the kidney and then excreted as such). In **liver failure** hepatic production of urea is decreased (→ A7), the liver uses up less HCO$_3^-$, and alkalosis develops. However, in liver failure respiratory alkalosis often predominates as a result of damage to the respiratory neurons (see above).

- An increased supply of **alkaline salts** or mobilization of alkaline salts from bone (→ A2), for example, during immobilization, can cause alkalosis.

- Metabolic activity may cause the accumulation of **organic acids**, such as lactic acid and fatty acids. These acids are practically completely dissociated at blood pH, i.e., one H$^+$ is produced per acid. If these acids are metabolized, H$^+$ disappears again (→ A1). Consumption of the acids can thus cause alkalosis.

- The breakdown of cysteine and methionine usually produces SO$_4^{2-}$ + 2 H$^+$, the breakdown of arginine and lysine produces H$^+$. Reduced protein breakdown (e.g., as a result of a protein-deficient diet; → A8), reduces the metabolic formation of H$^+$ and thus favors the development of an alkalosis.

The extent to which the blood’s pH is changed depends, among other factors, on the **buffering capacity** of blood, which is reduced when the plasma protein concentration is lowered.
A. Causes of Alkalosis

1. Consumption of organic anions
   - Lactate, dissociated fatty acids, etc.

2. Demineralization
   - $\text{CO}_3^{2-}$
   - $\text{PO}_4^{3-}$
   - $\text{H}_2\text{PO}_4^-$
   - $\text{HCO}_3^-$

3. Hyperventilation
   - CO$_2$ output with expiration
   - $\text{H}_2\text{O}$
   - $\text{CO}_2$

4. Hypokalemia

5. Hypovolemia

6. Vomiting
   - $\text{H}^+$
   - $\text{HCO}_3^-$

7. Liver failure
   - Urea
   - $\text{NH}_4^+$

8. Protein deficiency
   - Cys
   - Met
   - Lys
   - Arg
   - $\text{SO}_4^{2-}$

H$^+$ consumption $\uparrow$

Metabolism

H$^+$ excretion $\uparrow$

HCO$_3^-$ production $\uparrow$

$\text{H}^+ = \text{pK} + \log \frac{[\text{HCO}_3^-]}{[\text{CO}_2]} > 7.45$ Alkalosis

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Development of Acidosis

The pH of blood is a function of the concentrations of HCO$_3^-$ and CO$_2$ (→ p. 86). An acidosis (pH < 7.36) is caused by too high a concentration of CO$_2$ (hypercapnia, respiratory acidosis) or too low a concentration of HCO$_3^-$ (metabolic acidosis) in blood.

Many primary or secondary diseases of the respiratory system (→ p. 66 – 80) as well as abnormal regulation of breathing (→ p. 82) can lead to respiratory acidosis (→ A3). This can also be caused by inhibition of erythrocytic carbonic anhydrase, because it slows the formation of CO$_2$ from HCO$_3^-$ in the lung and thus impairs the expiratory elimination of CO$_2$ from the lungs.

There are several causes of metabolic acidosis:

- **In hyperkalemia** (→ A4) the chemical gradient across the cell membrane is reduced. The resulting depolarization diminishes the electrical driving force for the electronegotic HCO$_3^-$ transport out of the cell. It slows down the efflux of HCO$_3^-$ in the proximal tubules via Na$^+$/HCO$_3^-$ cotransport. The resulting intracellular alkalosis inhibits the luminal Na$^+$/H$^+$ exchange and thus impairs H$^+$ secretion as well as HCO$_3^-$ production in the proximal tubule cells. Ultimately these processes lead to (extracellular) acidosis.

- Other causes of reduced renal excretion of H$^+$ and HCO$_3^-$ production are renal failure (→ p. 110 ff.), transport defects in the renal tubules (→ p. 96 ff.), and hypoaldosteronism (→ A5). (Normally aldosterone stimulates H$^+$ secretion in the distal tubules; → p. 270).

- PTH inhibits HCO$_3^-$ absorption in the proximal tubules; thus in hyperparathyroidism renal excretion of HCO$_3^-$ is raised. As PTH simultaneously promotes the mobilization of alkaline minerals from bone (→ p. 132), an acidosis only rarely results. Massive renal loss of HCO$_3^-$ occurs if carbonic anhydrase is inhibited, because its activity is a precondition for HCO$_3^-$ absorption in the proximal tubules.

- Loss of bicarbonate from the gut (→ A6) occurs in vomiting of intestinal contents, diarrhea, or fistulas (open connections from the gut or from excretory ducts of glands). Large amounts of alkaline pancreatic juice, for example, can be lost from a pancreatic duct fistula.

- As the liver needs two HCO$_3^-$ ions when incorporating two molecules of NH$_4^+$; in the formation of urea (→ p. 86), increased urea production can lead to acidosis. In this way the supply of NH$_4$Cl can cause acidosis (→ A7).

In certain circumstances the infusion of large amounts of NaCl solution can lead to an acidosis, because extracellular HCO$_3^-$ is “diluted” in this way. In addition, expansion of the extracellular space inhibits Na$^+$/H$^+$ exchange in the proximal tubules as a result of which not only Na$^+$ absorption in the proximal tubules but also H$^+$ secretion and HCO$_3^-$ absorption is impaired.

- **Infusion of CaCl$_2$** results in the deposition of Ca$^{2+}$ in bone in the form of alkaline salts (calcium phosphate, calcium carbonate). H$^+$ ions, formed when bicarbonate and phosphate dissociate, can cause acidosis.

- **Mineralization of bone**, even without CaCl$_2$, favors the development of acidosis (→ A2).

- Acidosis can also develop when there is increased formation or decreased breakdown of organic acids (→ A1). These acids are practically fully dissociated at the blood pH, i.e., one H$^+$ is formed per molecule of acid. Lactic acid is produced whenever the energy supply is provided from anaerobic glycolysis, for example, in O$_2$ deficiency (→ p. 84), circulatory failure (→ p. 224), severe physical exercise, fever (→ p. 20 ff.), or tumors (→ p. 14 ff.). The elimination of lactic acid by gluconeogenesis or degradation is impaired in liver failure and some enzyme defects. Fatty acids, β-hydroxybutyric acid and acetacetic acid accumulate in certain enzyme defects but especially in increased fat mobilization, for example, in starvation, diabetes mellitus (→ p. 286 ff.), and hyperthyroidism.

- A protein-rich diet promotes the development of metabolic acidosis, because when amino acids containing sulfur are broken down (methionine, cystine, cysteine), SO$_4^{2-}$ + 2 H$^+$ are generated; when lysine and arginine are broken down H$^+$ is produced (→ A8).

The extent of acidosis depends, among other factors, on the blood’s buffering capacity.
A. Causes of Acidosis

1. Formation of organic acids
   - Lactate, dissociated fatty acids, acetic acids, etc.
   - H⁺ formation ↑↑

2. Mineralization
   - CO₂ output with expiration ↓↓

3. Hypoventilation
   - CO₂ output with expiration ↓↓

4. Metabolism
   - H⁺ formation → H⁺

5. Renal failure
   - HCO₃⁻ absorption and formation ↓↓
   - H⁺ excretion ↓
   - HCO₃⁻ excretion ↑

6. Diarrhea
   - HCO₃⁻ uptake
   - NH₄⁺ uptake
   - HCO₃⁻ consumption ↑↑

7. Diarrhea
   - Urea
   - NH₄⁺ uptake
   - HCO₃⁻ consumption ↑↑

8. Protein excess
   - Cys, Met
   - Lys, Arg
   - SO₄²⁻ → H⁺

9. pH = pK + log \( \frac{[HCO₃⁻]}{[CO₂]} \) < 7.35 Acidosis
Effects of Acidosis and Alkalosis

It is through changes in breathing and renal functions that the body tries to compensate for abnormalities of acid–base metabolism, thus to keep blood pH constant. Changes in pH as well as HCO₃⁻ and CO₂ concentrations in blood, when acid–base balance is abnormal, and how they are compensated can be demonstrated in graphs. HCO₃⁻ concentration, for example, is plotted as a function of P CO₂ (→ A, left) or the logarithm of P CO₂, is plotted as a function of pH (→ A, right; Sigggaard-Andersen nomogram: gray lines = CO₂ equilibration lines). These graphs illustrate the following abnormalities and mechanisms for compensating them:

- **Respiratory alkalosis** (→ A 1) is compensated by decreased reabsorption of HCO₃⁻ in the kidneys.
- **Metabolic alkalosis** (→ A 2) can theoretically be compensated by hypoventilation. But the need to take up sufficient O₂ sets narrow limits to this form of compensation.
- **Respiratory acidosis** (→ A 4) is compensated by increased renal excretion of acids (or through forming HCO₃⁻). The increased plasma HCO₃⁻ results in more HCO₃⁻ being filtered at the glomeruli. The kidney must therefore continually reabsorb an increased amount of filtered HCO₃⁻ if renal loss of HCO₃⁻ is to be avoided.
- **Metabolic acidosis** (→ A 3) can be compensated by respiratory reduction in plasma CO₂ concentration. However, the lower the plasma CO₂ concentration the less CO₂ is given off with each breath. Thus, in order to exhale the particular amount of CO₂, hyperventilation must be maintained until the plasma HCO₃⁻ concentration is again normal, either through raised renal excretion of acid or through the breakdown of organic acids (→ p. 86).

The effect of alkalosis is usually hypokalemia, because the cells release less HCO₃⁻, depolarize less, and thus lose less K⁺. If H⁺ is removed from the cell by Na⁺/H⁺ exchange, Na⁺ gains access to the cell, but is again pumped out of the cell in exchange for K⁺ (→ B).

In addition, more Ca²⁺ is bound to plasma proteins in alkalosis (→ B, right). As a result, there is a fall in the concentration of ionized Ca²⁺ in plasma. As part of Ca²⁺ in plasma is also bound to HCO₃⁻, the concentration of free Ca²⁺ falls more in metabolic than in respiratory alkalosis. Effects, especially of respiratory alkalosis (hypocapnia), include among others raised neuromuscular excitability with cramps, in part due to reduced plasma Ca²⁺ concentration, but is in the first instance the result of constriction of the cerebral vessels and thus hypoperfusion of the brain. Intracellular alkalosis can inhibit neuromuscular excitability by activating the K⁺ channels. Hypocapnia also stimulates contraction of the bronchial musculature and thus increases airway resistance. Alkalosis inhibits gluconeogenesis and promotes glycolysis so that hypoglycemia and lactic acidemia may occur. Finally, intracellular alkalosis favors cell division.

The effects of respiratory and metabolic acidosis (→ B, red arrows) are largely similar. In extracellular acidosis the cells lose HCO₃⁻; through depolarization they also lose K⁺. In addition, acidosis inhibits Na⁺/K⁺-ATPase. Hyperkalemia develops (→ p. 124). On the other hand, acidosis stimulates Na⁺/H⁺ exchange. The result is not only Na⁺ uptake but also cell swelling.

Furthermore, intracellular acidosis inhibits K⁺ channels and has a negative inotropic effect as well as (by blocking the intercellular connections) a negative dromotropic effect on the cardiac muscle (→ B, right). Hypercapnia induces vasodilation (fall in blood pressure, rise in intracerebral pressure) and relaxation of the bronchial musculature. Intracellular acidosis inhibits the pacemaker enzymes of glycolysis and hyperglycemia occurs. Prolonged acidosis promotes demineralization of bone (→ B, right), because alkaline bone salts are dissolved by acids (→ p. 132). In intracellular acidosis H⁺ is taken up by the mitochondria in exchange for Ca⁺. H⁺ also inhibits adenylylcy clase and thus impairs hormonal effects. Finally, cellular acidosis inhibits cell division and favors apoptotic cell death.
A. Abnormal pH and its Compensation

B. Effects of Acidosis and Alkalosis
Overview

Renal damage can impair renal perfusion as well as glomerular and/or tubular functions (→ A). In addition, abnormal urine composition can lead to precipitations (urolithiasis) that inhibit the free flow of urine. Abnormal renal function can be caused by reduced renal excretion of useless or harmful substances (e.g., uric acid, urea, creatinine, vanadate [VN₄], foreign substances [xenobiotics], and so-called uremic substances) whose plasma concentration then rises correspondingly (→ A3).

Conversely, a defective glomerular filter can lead to renal loss of protein, while impaired tubular reabsorption can result in the increased excretion of substances which are important for the body (electrolytes, minerals, bicarbonate, glucose, amino acids). Reduced renal excretory function affects the kidney’s decisive contribution to the regulation of the metabolism of water, electrolytes, minerals, and acid–base balance (→ p.122 ff.). Through its regulation of water and electrolyte metabolism the kidney is also important for long-term blood pressure regulation (→ p.208 ff.).

The capacity of the kidney to regulate the composition of extracellular fluid is a function of volume, which, per unit time, is under the control of its epithelia. For substances that are not secreted by tubular cells, the controlled volume corresponds to the glomerular filtration rate (GFR). All substances that are dissolved in the filtrate can either be reabsorbed or excreted by the tubular epithelium. For substances that are secreted by the tubular epithelium (e.g., potassium), the controlled volume is ultimately the entire blood plasma that flows through the kidney (renal plasma flow [RPF]).

Renal excretion is regulated or governed by hormones (e.g., antidiuretic hormone [ADH] or arginine vasopressin [AVP], aldosterone, atrial natriuretic factor [ANF], parathyroid hormone [PTH], calcitriol [1,25(OH)₂D₃], calcitonin, cortisol, prostaglandin E₂, insulin, progesterogens, estrogens, thyroxine, somatotropin) and is thus adapted to requirements. Thus, disorders of hormone release also impair renal excretory functions.

Normally the amount of filtered water and solutes is a multiple of what is actually excreted: all of the plasma water passes across the renal epithelia within 20 minutes; the total extracellular volume within three hours. The excretory capacity of the kidney is thus by no means exhausted. For this reason GFR, i.e., the volume controlled by the kidney, can be greatly impaired without there being any harmful effect on the body. However, a reduction in GFR will from the very beginning go hand in hand with a diminished regulatory range that will become apparent when there is an increased load.

The kidney is not only the target organ for hormones, but also, by forming hormones, it influences its own function as well as extrarenal elements of mineral metabolism (calcitriol) and blood pressure regulation (renin/angiotensin) (→ A2). The prostaglandins and kinins formed in the kidney primarily serve to regulate renal function. If the kidney is damaged, the effects of abnormal renal excretory function are added to those of abnormal renal excretion of hormones. The hormone erythropoietin, formed in the kidney, regulates erythropoiesis; its absence thus causes anemia (→ p.32).

Lastly, the kidney fulfills metabolic tasks (→ A1). Thus, for example, in acidosis it splits ammonia from glutamate (ammonia is excreted as NH₄⁺; → p.86) and forms glucose from the carbohydrate skeleton (gluconeogenesis). Glucose is also formed in the proximal tubules from absorbed lactate, and additionally fatty acids are broken down in the tubules. The kidney plays an important role in the inactivation of hormones. About 40% of insulin inactivation takes place in the kidney, which also breaks down steroid hormones. Filtered oligopeptides (e.g., hormones) are broken down in the tubular lumen and the amino acids are reabsorbed. Reduction of functional renal tissue necessarily impairs the above-mentioned metabolic tasks.
A. Pathophysiology of the Kidney (Overview)

1. Metabolism
   - Gluconeogenesis
   - Fatty acid breakdown
   - Hormone inactivation
   - Ammonia production

2. Hormone release
   - Erythropoietin
   - Calcitriol
   - Renin, angiotensin
   - Kinins
   - Prostaglandins

3. Regulation
   - Loss of useful substances:
     - H₂O
     - K⁺
     - Na⁺/Cl⁻
     - H⁺/HCO₃⁻
     - Ca²⁺/HPO₄²⁻
     - Mg²⁺

   - Blood pressure
   - Erythropoiesis
   - Water, electrolyte and mineral balance
   - Excretion
   - Elimination
     - Retention of useless or harmful substances:
       - Uric acid
       - Urea
       - Creatinine
       - VnO₄
       - Xenobiotics
       - Uremia toxins

- Plate 5.1 Overview
Abnormalities of Renal Excretion

The elimination of a given substance is impaired if filtration and tubular secretion are reduced; conversely, it is increased when tubular reabsorption is decreased and/or tubular secretion is increased. This can change the plasma concentration of the substance, although the latter depends on extrarenal factors (→ A), such as production or breakdown, enteric absorption or extrarenal excretion (e.g., via gut or sweat), deposition or mobilization. The amount of substance that results per unit time from the sum of extrarenal processes is the so-called prerenal load.

The right interpretation of changed plasma concentrations presupposes a knowledge of the quantitative correlation between plasma concentration and renal excretion (→ B).

This correlation is simple with substances that are filtered but not significantly secreted or reabsorbed (e.g., creatinine). The excreted amount (Mₑ) is identical to the filtered amount (Mᵢ) and thus equal to the product of plasma concentration (P) and the GFR: Mₑ = Mᵢ = P·GFR (→ B 1, green line). The clearance (Mₑ/P) is identical to the GFR and thus independent of the plasma concentration (→ B 2, green line). If the production of creatinine is constant, a reduction in GFR transiently leads to a reduction in creatinine excretion (→ B 3 a). The amount produced is thus greater than that excreted, so that the plasma concentration and also the excreted amount of creatinine per unit time rises (→ B 3 b) until as much creatinine is excreted as is produced by the body. In equilibrium, the renal excretion mirrors the prerenal load. With substances which are filtered but neither reabsorbed nor secreted there is a linear correlation between plasma concentration and renal excretion and thus between prerenal load and plasma concentration (→ B 4, green line).

In reabsorption by transport processes with high affinity (e.g., glucose, most amino acids, phosphate, sulfate) practically the entire filtered amount is reabsorbed and nothing eliminated, as long as the plasma concentration is low (→ B 1, blue curve). If the filtered amount exceeds the maximal transport rate, the whole of the excess filtered amount is excreted. The plasma concentration at which the filtered amount and the transport maximum are the same is called the renal threshold (→ B 1, red portion of the blue curve).

In transport processes with low affinity (e.g., uric acid, glycine) not everything is reabsorbed even at low plasma concentration, so that both the reabsorption rate and the renal excretion increase with increasing plasma concentration (→ B 1, yellow curve).

In secretion (e.g., of p-aminohippuric acid [PAH]) not only the filtered by also the secreted substance is excreted (→ B 1, violet curve). In high affinity of the transport system and low plasma concentration, the entire amount reaching the kidney will be excreted. Renal clearance thus corresponds to renal plasma flow, i.e., the amount of plasma flowing through the kidney per unit of time. If the amount of substance that is presented exceeds the maximal transport rate, excretion can be raised only by an increase in the amount filtered, and renal clearance is reduced (→ B 2).

An abnormality of prerenal factors can, despite unimpaired tubular transport, raise the excretion of the affected substance via an increase in its plasma concentration and the amount filtered. Thus, glycosuria may occur even when renal transport of glucose is normal, if the plasma concentration of glucose is higher than its renal threshold, as is the case in diabetes mellitus (overflow glycosuria). Similarly, impaired breakdown of amino acids leads to overflow aminoaciduria. Conversely, a change in plasma concentration in the presence of an abnormal renal transport can be prevented by extrarenal regulatory mechanisms (→ A). Thus, hypocalcemia due to impaired renal reabsorption of Ca²⁺ is prevented by the release of PTH which mobilizes Ca²⁺ from bone and increases enteric absorption of Ca²⁺ via the release of calcitriol (→ p. 128). The result is hypercalciuria but not hypocalcemia.
A. Determinants of Plasma Concentration

Prerenal

Food

Hormonal regulation

Deposition

Mobilization

Metabolism

Liver

Gut

Bones, joints

Plasma concentration

Renal

Excretion

Kidney

B. Plasma Concentration, Renal Excretion, Clearance

1

Renal excretion $M_e$

PAH

Creatinine

Glucose

Uric acid

0

0

Plasma concentration $P$

2

Renal clearance

RPF

PAH

Creatinine

Glucose

Uric acid

0

0

Plasma concentration $P$

3

Renal excretion $M_e$

GFR normal

a

b

GFR reduced

0

0

Plasma concentration $P$

4

Renal excretion $M_e$

Uric acid

Glucose

Creatinine

PAH

0

0

Prerenal load

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Pathophysiology of Renal Transport Processes

Genetic or toxic causes, drugs, or hormonal abnormalities can impair tubular transport processes.

At least two luminal transporters are responsible for the reabsorption of glucose in the proximal tubules. A genetic defect of the renal and intestinal Na+-glucose/galactose transporter (→ A1) results in glucose-galactose malabsorption. A defect of the second renal glucose transporter leads to classical renal glucosuria in which either the maximal transport rate (type A) or the affinity (type B) is impaired (→ D3). If in type A plasma concentration exceeds the lowered renal threshold, this results in the quantitative excretion of the additionally filtered glucose; if the plasma concentration is below the renal threshold, all of the glucose is reabsorbed. However, in type B renal glucosuria, glucose is excreted even at low plasma concentrations.

The Na+-phosphate cotransporter (→ A2) can be impaired if there is a genetic defect (renal phosphate diabetes) or a deficiency of calcitriol. The reduced renal phosphate reabsorption causes demineralization of bone via a deficiency of phosphate (rickets; → p. 132). Raised renal phosphate reabsorption in PTH deficiency (hypoparathyroidism) or abnormal PTH action (pseudohypoparathyroidism), for example, leads to hyperphosphatemia (→ p. 130).

A defect of Na+ cotransport of certain neutral amino acids (→ A3) in kidney and gut results in Hartnup disease, in which increased amino acid excretion occurs. As tryptophan is necessary for nicotinic acid synthesis, nicotinic acid deficiency, and thus damage to the nervous system and the skin may occur.

A defect of the amino acid exchanger for neutral and dibasic amino acids (→ A4) increases the excretion of ornithine, lysine, arginine, and cystine (cystinuria). The poorly soluble cystine is precipitated and forms urinary stones (→ p. 120). In familial protein intolerance the reabsorption of dibasic amino acids is abnormal.

A defect of the Na+ cotransporter for acidic amino acids (→ A5) leads to harmless acid aminoaciduria; a defect of the carrier for cyclic amino acids such as proline, results in harmless iminoglycinuria (→ A6).

Decreased activity of the Na+/H+ exchanger (→ A7), of the Na+-3HCO3- cotransporter (→ A8), or inhibition of carbonic anhydrase (CA) results in proximal-tubular acidosis (→ p. 88 ff.). As the reduced HCO3- reabsorption in the proximal tubules cannot be compensated by the (normally small) distal-tubular transport capacity, bicarbonate is excreted in the urine even when the HCO3- load is normal (→ E2). Nevertheless, if the plasma concentration of HCO3- is reduced, the proximal tubules can reabsorb the bulk of filtered bicarbonate, and the distal tubules will then produce urine of normal acidity.

Na+-3HCO3- cotransport is largely dependent on the membrane potential, and thus on K+ flux via K+ channels (→ A15), and on extracellular K+ concentration. Hyperkalemia depolarizes the cell membrane and inhibits HCO3- reabsorption in the proximal tubules, while HCO3- reabsorption is increased by hypokalemia. The renal excretion of H+ and thus the acid-base metabolism is thus a function of the extracellular K+ concentration (→ p. 86 ff.).

Dehydration stimulates the activity of the Na+/H+ exchanger (→ A7) and thus proximal tubular HCO3- reabsorption. This results in a volume depletion alkalosis. Inhibition of the Na+/H+ exchanger or of carbonic anhydrase increases salt excretion (natriuresis). The inhibition of proximal tubular Na+ reabsorption is, however, largely compensated by its increased reabsorption in more distal nephron segments, especially in the loop of Henle.

In Fanconi’s syndrome, caused by genetic or acquired (e.g., lead poisoning) factors, several Na+-coupled transport processes are impaired (→ A1–7), resulting in glucosuria, aminoaciduria, phosphaturia, proximal tubular acidosis, and hypokalemia (see below).

Increased proximal Na+ and water reabsorption concentrates the luminal uric acid and thus promotes uric acid reabsorption via luminal and basolateral anion exchangers and channels (→ A9). This causes hyperuricemia with deposition of poorly soluble uric acid in some joints (gout; → p. 250).

If an energy deficiency occurs (e.g., inadequate perfusion) Na+/K+-ATPase (→ ABC10) is impaired, electrolyte reabsorption is reduced
A. Transport Processes in Proximal Tubule

B. Transport Processes in Thick Ascending Loop of Henle

C. Transport Processes in Distal Nephron

Plate 5.3 Renal Transport Processes

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(salt-losing kidney), cellular swelling and cell death occurs.

The Ca\(^{2+}\) reabsorption is accomplished in the proximal tubules and loop of Henle, in part by paracellular transport (→ AB 11), by Ca\(^{2+}\) channels in the luminal membrane (→ AC 12), and by 3Na\(^{+}\)/Ca\(^{2+}\) exchangers in the peritubular membrane (→ AC 13). Increased intracellular Na\(^{+}\) concentration reduces the Na\(^{+}\) gradient for the 3Na\(^{+}\)/Ca\(^{2+}\) exchanger (→ A 13) and thus impairs Ca\(^{2+}\) reabsorption. Parathyroid hormone (PTH) stimulates Ca\(^{2+}\) reabsorption; conversely, hypoparathyroidism results in hypercalciuria. The paracellular shunt (→ B 11) is blocked by a high Ca\(^{2+}\) concentration (hypercalcemia). This impairs not only the reabsorption of Ca\(^{2+}\) but also of Mg\(^{2+}\) (loss of magnesium) and of Na\(^{+}\) (natriuresis, impaired urinary concentration; → p. 100). Hypercalciuria leads not only to Ca\(^{2+}\) deficiency, but also to calcium salts precipitating in the urine (→ p. 120).

Inhibition of Na\(^{+}\)-K\(^{+}\)-2 Cl\(^{-}\) cotransporter (→ B 14) by loop diuretics stops NaCl reabsorption in the loop of Henle and thus urinary concentration (→ p. 100). This results in massive natriuresis and diuresis. Distal tubules and collecting ducts are overwhelmed by Na\(^{+}\) and reabsorb Na\(^{+}\) in exchange for K\(^{+}\) (see below), leading to kaliuresis and hypokalemia. The Na\(^{+}\)-K\(^{+}\)-2 Cl\(^{-}\) cotransport needs K\(^{+}\) as substrate, which must recirculate via K\(^{+}\) channels (ROMK; → B 15). In K\(^{+}\) deficiency or hypokalemia the K\(^{+}\) channel is closed off and NaCl reabsorption in the loop of Henle is impaired. A genetic defect in the Na\(^{+}\)-K\(^{+}\)-2 Cl\(^{-}\) cotransporter, Cl\(^{-}\) or K\(^{+}\) channel are causes of Bartter’s syndrome which gives rise to impaired urinary concentration, natriuresis, hypokalemia (except in defects of ROMK), and lowered blood pressure, despite increased renin, angiotensin and aldosterone formation (→ p. 114). Because of the abnormal Na\(^{+}\) reabsorption, the kidney produces large amounts of prostaglandins that inhibit Na\(^{+}\)-reabsorption in more distal nephron segments and thus aggravate NaCl loss. Furthermore they cause life-threatening peripheral vasodilation.

Finally, the reabsorption of salt in the loop of Henle is reduced in hypercalcemia, for example, by blockage of the paracellular shunt (see above) as well as the activation of a Ca\(^{2+}\) receptor (→ B 16).

Sodium chloride is reabsorbed in the early distal tubules via a Na\(^{+}\)-Cl\(^{-}\) cotransporter (→ C 17). Thiazides cause renal loss of sodium and potassium by inhibiting the carrier (see above). They increase the gradient for the 3Na\(^{+}\)/Ca\(^{2+}\) exchanger by reducing the intracellular Na\(^{+}\) concentration and in this way promote the renal reabsorption of Ca\(^{2+}\) (see above and → D 1). A genetic defect of the transporter results in Gitelman’s syndrome, a mild variant of Bartter’s syndrome.

Na\(^{+}\) is reabsorbed in the late distal tubules and the collecting ducts via luminal Na\(^{+}\) channels (→ C 18) and the basolateral Na\(^{+}\)/K\(^{+}\)-ATPase. The influx of Na\(^{+}\) depolarizes the luminal cell membrane and thus promotes the secretion of K\(^{+}\) via luminal K\(^{+}\) channels. If Na\(^{+}\) reabsorption in the proximal tubules, loop of Henle, or early distal tubules is inhibited, more Na\(^{+}\) reaches the late distal parts of the nephron and it is reabsorbed there in exchange for K\(^{+}\). The result is renal loss of K\(^{+}\) (see above). Na\(^{+}\) channels and Na\(^{+}\)/K\(^{+}\)-ATPase are activated by aldosterone (→ D 1). Deficiency of aldosterone (hypoaldosteronism) or its reduced effectiveness (pseudohypoaldosteronism, e.g., due to a defective Na\(^{+}\) channel) results in the renal loss of Na\(^{+}\), decreased extracellular volume, and low blood pressure. Distal diuretics act by blocking the aldosterone receptors (aldosterone antagonists) or by directly inhibiting the Na\(^{+}\) channel. They cause mild natriuresis and renal K\(^{+}\) retention. Conversely, a hyperactive Na\(^{+}\) channel (Liddle’s syndrome) leads to Na\(^{+}\) retention and hypertension.

H\(^{+}\) secretion in the late distal tubules and in the collecting duct is achieved by H\(^{+}\)-ATPases (→ C 19) and H\(^{+}\)/K\(^{+}\)-ATPases (→ C 20). A defect results in distal-tubular acidosis (→ D 2, E 4). The affected person can produce only moderately acidic urine even when the plasma concentration of HCO\(_3\)\(^{-}\) is low. Furthermore, they suffer from CaHPO\(_4\) stones because phosphate is readily precipitated in alkaline urine (→ p. 120).

Water can be reabsorbed in the entire nephron, except the ascending loop of Henle. However, water reabsorption in the distal tubules and the collecting ducts requires ADH. A lack of ADH or decreased sensitivity of the nephron to ADH causes diabetes insipidus (→ p. 100).
D. Mechanisms of Renal $K^+$ Loss

- Proximal diuretics
- Loop diuretics
- Thiazides

Distal diuretics
Aldosterone
Flow rate↑

Lumen
Blood

E. Renal Tubular Acidoses

1. Normal acid excretion

2. Proximal tubular acidosis

3. Proximal tubular acidosis in reduced plasma bicarbonate

4. Distal tubular acidosis

HCO$_3^-$, or H$^+$/L GFR

mmol HCO$_3^-$, or H$^+$/L GFR
Abnormalities of Urinary Concentration

Depending on requirements, the kidney can normally excrete hypotonic (< 100 mosm/L) or hypertonic (> 1200 mosm/L) urine. Concentration and dilution of urine are in the first instance the result of processes in the thick ascending loop of Henle (pars ascendens) which transports NaCl (→ A, red arrow) to the interstitial space of the renal medulla (see also p. 96) without water (blue arrow) being able to follow. The tubular fluid becomes hypotonic (50–100 mosmol/L) by the time it passes the ascending part, while the interstitial space becomes hypertonic. The hyperosmolar interstitial space takes more water (blue arrow) than electrolytes (red arrow) from the descending part of the loop of Henle so that osmolality rises in the descending tubular fluid on its way to the apex of the loop.

The arrangement of the renal medullary vessels (vasa recta) in the loop prevents dilution of the medullary hyperosmolality.

Urea (violet arrow) only partly follows the reabsorbed water in the proximal and distal tubules and the loop of Henle, so that the luminal urea concentration increases up to the collecting duct. The medullary collecting duct is highly permeable to urea, which diffuses into the interstitial space. The high urea concentrations in the renal medulla draw water out of the descending part of the loop of Henle. Some of the urea diffuses into the tubular lumen and reaches the collecting duct via the loop of Henle and the distal tubule.

ADH stimulates the insertion of water channels (aquaporins) into the apical cell membrane in the distal tubule and collecting duct, and thus allows water reabsorption following the osmotic gradient. The tubular fluid in the distal tubule is at first hypotonic (see above), but toward the end of the distal tubule it attains the osmolality of the blood. More water is taken from the collecting duct in the renal medulla, until the osmolality of the luminal fluid in the collecting duct approaches that in the renal medulla.

In ADH deficiency (central diabetes insipidus) or in insensitivity of the distal nephron and the collecting duct for ADH (renal diabetes insipidus) the water permeability of the distal tubule and the collecting duct is low (→ A1).

Up to 20 L of hypotonic urine are excreted per day. The excretion of Na⁺ and urea can also be increased.

If reabsorption in the loop of Henle is inhibited, the hyperosmolality of the renal medulla dissipates. Therapeutic loop diuretics inhibit Na⁺-K⁺-2Cl⁻ cotransport. Hypercalcemia inhibits the reabsorption via a Ca²⁺ receptor at the tubule and by inhibiting paracellular reabsorption. Hypokalemia or defective K⁺ channels (ROMK, an inward rectifier K⁺ channel) inhibit the recirculation of K⁺ and thus indirectly Na⁺-K⁺-2Cl⁻ cotransport (→ p. 97 B).

Raised perfusion through the renal medulla washes out medullary hyperosmolality (→ A3). Mediators (e.g., kinins, prostaglandins) released during inflammation therefore lower medullary osmolality and thus reduce urinary concentration. Caffeine, too, acts as a dilator of the vasa recta. Raised blood pressure can also increase perfusion of the vasa recta and thus wash out the medulla (pressure diuresis).

The reabsorption of water can also be reduced if tubular fluid contains poorly absorbable or nonabsorbable substances. These substances are then concentrated by fluid reabsorption and hold back water (→ A4). Osmotic diuresis occurs. Secondarily, the impaired water reabsorption leads to reduced reabsorption of NaCl and urea. As a result, osmolality in the renal medulla is reduced and urinary concentration compromised. Osmotic diuresis is triggered therapeutically with mannitol, a poorly absorbed sugar. Furthermore, osmotic diuresis also occurs when increased amounts of glucose, bicarbonate, urea, and phosphate are excreted.

A protein-low diet impairs the concentrating ability of the kidney because of reduced contribution of urea to the concentrating mechanism (→ A5).

Impaired concentrating ability becomes apparent through nocturnal diuresis (nycturia), thirst, and large, unconcentrated volumes of urine.
A. Abnormalities of Urinary Concentration

- Inflammation
- Mediators
- Loop diuretics
- Hypercalcemia
- Hypokalemia
- Blood pressure
- Caffeine
- Vasodilation
- Perfusion
- Osmolarity
- Na⁺-K⁺-Cl⁻ cotransport
- NaCl and urea reabsorption
- Vasa recta
- Loop of Henle
- Loop diuretics
- Mannitol
- Excretion of: glucose, urea, bicarbonate, phosphate
- Diabetes insipidus central renal
- ADH insensitivity
- ADH deficiency
- Water permeability
- Protein deficiency
- Urea
- Polyuria, nycturia
- Osmotic diuresis
- Osmolarity
- Water reabsorption
- Diabetes insipidus central renal
- Excretion of: glucose, urea, bicarbonate, phosphate
- ADH insensitivity
- ADH deficiency
- Water permeability
- Protein deficiency
- Urea
- Polyuria, nycturia
- Osmolarity
- Water reabsorption
Abnormalities of Glomerular Function

The function of the glomeruli is to produce an adequate GFR, i.e., the volume of plasma water that is controlled by the renal epithelium. The selective permeability of this filter (→ p. 104) ensures the formation of a nearly protein-free filtrate. As all of the blood flowing through the kidney must pass through the glomerular vessels, the resistance of these vessels also determines RPF.

The GFR is determined by the effective filtration pressure (P_{eff}), the hydraulic conductivity (K_t), and the filtering surface (F): 

\[
\text{GFR} = K_t \cdot F \cdot P_{\text{eff}}
\]

The effective filtration pressure is made up of the hydrostatic (ΔP) and the oncotic (Δπ) pressure gradients across the filter (→ A): 

\[
P_{\text{eff}} = \Delta P - \Delta \pi
\]

Even if the filter is defective, π within the capsular space of the glomerulus can be ignored, i.e., Δπ practically equals the plasma oncotic pressure (π_{cap}). As a result of glomerular filtration, the protein concentration in plasma is increased and π_{cap} as a rule comes close to the hydrostatic pressure gradient toward the end of the glomerular capillary loops (filtration equilibrium).

Reduced hydraulic conductivity (→ A2) or a reduced filtration surface decreases the GFR. No filtration equilibrium can be achieved; as a result of the reduced increase in π_{cap}, P_{eff} ultimately rises. But this does not compensate for the reduced conductivity.

Constriction of the vas afferens (→ A3) when systemic blood pressure remains constant reduces the filtration pressure and thus the proportion of filtered plasma water (filtration fraction = GFR/RPF). At the same time the renal blood flow and the GFR fall because of the increased resistance.

Constriction of the vas efferens (→ A4) raises the effective filtration pressure and thus also GFR/RPF. Simultaneously it reduces glomerular perfusion and thus GFR at any given filtration fraction. The constriction of the vas efferens (e.g., on infusion of angiotensin II) or obstruction of venous flow (e.g., by renal vein thrombosis) can thus ultimately reduce GFR.

The glomeruli can be damaged by inflammatory disease (glomerulonephritis; → B). Among possible causes are soluble antigen–antibody complexes that become entangled in the glomeruli and, via complement activation, produce local inflammation (→ p. 48 ff.). This results in obstruction of the glomerular capillaries and destroys the filtering function (immune complex nephritis). Numerous drugs, allergens, and pathogens can act as antigens. Streptococci (group A, type 12) are very often responsible. Antibodies include IgG, IgM, and commonly IgA (IgA nephritis).

Masugi’s nephritis, caused by autoantibodies against the basement membrane, is much less common than immune complex nephritis. The local inflammation initially results in hyperemia, accumulation of neutrophils (exudative phase), and damage to the often markedly thickened basement membrane. It is common for endothelial, mesangial, or capillary epithelial cells to proliferate and ultimately for excess mesangial matrix to form (sclerosing).

The glomeruli may also be damaged without any local inflammation, for example, by deposition of amyloid in amyloidosis, by a high concentration of filtrable proteins in plasma (e.g., in multiple myeloma), by high pressure in the glomerular capillaries (e.g., in arterial hypertension, renal vein thrombosis, venous back pressure in right heart failure, or hyperfiltration in diabetic nephropathy) as well as by reduced perfusion (e.g., in atherosclerosis, arteriosclerosis).

In glomerulonephritis, resistance in the vasa afferentia and efferentia is increased and the RPF is reduced despite filtration pressure usually being high. The reduced hydraulic conductivity prevents filtration equilibrium being achieved and lowers GFR. The reduced renal perfusion stimulates the release of renin which, via angiotensin and aldosterone, raises blood pressure. In addition, the development of hypertension is aided by reduced excretion of NaCl and H₂O, brought about by the decrease in GFR (→ p. 114).

Selective permeability is lost by damage to the glomerular filter, thus leading to proteinuria and edema (→ p. 104).

Damage to the kidney can, for example, destroy erythropoietin-producing cells and thus result in the development of anemia.
A. Glomerular Filtration: Vascular Resistance and Hydraulic Conductivity

1. Normal Glomerulus
   - RPF
   - P
   - $P_{\text{eff}}$
   - Capsular space
   - GFR normal

2. Hydraulic conductivity
   - $\Delta P$
   - $\Delta \pi$

3. Resistance Vas afferens
   - $P_{\text{eff}}$
   - GFR

4. Resistance Vas efferens
   - $P_{\text{eff}}$
   - GFR

B. Glomerular Diseases

- Antigen-antibody complex ➔ Immune complex nephritis ➔ Autoantibodies
  - e.g., Multiple myeloma
  - Protein concentration in plasma ➔ Glomerular deposition of protein ➔ Glomerulonephritis ➔ Abnormalities of glomerular perfusion
  - e.g., Renal vein thrombosis, venous congestion ➔ Hydrostatic pressure ➔ Renal perfusion ➔ Abnormal permselectivity of the glomerular filter ➔ Death of erythropoietin-forming cells
  - Renin angiotensin ➔ GFR ➔ Hyperhydration ➔ Proteinuria, edema ➔ Anemia

Disorders of Glomerular Permselectivity, Nephrotic Syndrome

The glomerular filter (fenestrated endothelium, basement membrane, slit membrane between podocytes) is not equally permeable for all blood constituents (selective permeability or permselectivity). Molecules larger in diameter than the pores do not pass the filter at all. Molecules of clearly smaller diameter will in practice pass through, as will water, i.e., their concentration in the filtrate is approximately the same as that in plasma water. If these substances are not reabsorbed or secreted in the kidney, their clearance (C) is identical to the GFR, and the fractional excretion (C/GFR) is 1.0. If molecules are only slightly smaller in diameter than the diameter of the pores, only some of them can follow water through the pores, so that their concentration in the filtrate is lower than in plasma (→ A1).

However, permeability is determined not only by the size, but also by the charge of the molecule. Normally, negatively-charged molecules can pass through much less easily than neutral or positively-charged molecules (→ A1). This is due to negative fixed charges that make the passage of negatively-charged particles difficult.

In glomerulonephritis (→ p. 102) the integrity of the glomerular filter may be impaired, and plasma proteins and even erythrocytes can gain access to the capsular space (→ A2). This results in proteinuria and hematuria. Close observation of proteinuria indicates that it is especially the permeability for negatively-charged proteins that is increased. This behavior can be demonstrated most impressively by infusing differently charged polysaccharides, because polysaccharides—in contrast to proteins—are hardly reabsorbed by the tubules. Negatively-charged (−) dextrans are normally less well filtered than neutral (n) or cationic (+) dextrans. This selectivity is lost in glomerulonephritis and filtration of negatively-charged dextrans is massively increased (→ A2). One of the causes of this is a breakdown of negatively-charged proteoglycans, for example, by lysosomal enzymes from inflammatory cells that split glycosaminoglycan. As has been shown by electrophoresis, it is especially the relatively small, markedly negatively-charged albumins that pass across the membrane (→ A3). Even an intact glomerulus is permeable to a number of proteins that are then reabsorbed in the proximal tubules. The transport capacity is limited, though, and cannot cope with the excessive load of filtered protein at a defective glomerular filter. If tubular protein reabsorption is defective especially small proteins appear in the final urine (tubular proteinuria).

Renal loss of proteins leads to hypoproteinemia. Serum electrophoresis demonstrates that it is largely due to a loss of albumin (→ A4), while the concentration of larger proteins actually tends to increase. This is because the reduced oncotic pressure in the vascular system leads to increased filtration of plasma water in the periphery and thus to a concentration of the other blood constituents. Filtration in the peripheral capillaries is facilitated not only by the reduced oncotic pressure, but also by damage to the capillary wall that may also be subject to inflammatory changes. As a result of protein filtration in the periphery, protein concentration and oncotic pressure rise in the interstitial spaces, so that the filtration balance shifts in favor of the interstitial space (→ A5). If the removal of proteins via the lymphatics is inadequate, edemas form (→ A7).

If proteinuria, hypoproteinemia, and peripheral edema occur together, this is termed nephrotic syndrome. As the lipoproteins are not filtered even if the filter is damaged, but hypoproteinemia stimulates the formation of lipoproteins in the liver, hyperlipidemia results and thus also hypercholesterolemia (→ A6). It remains debatable whether a loss of glomerular lipoprotein lipase contributes to the effect.

Hypoproteinemia favours peripheral filtration, the loss of plasma water into the interstitial space leads to hypovolemia which triggers thirst, release of ADH and, via renin and angiotensin, of aldosterone (→ p. 122). Increased water intake and increased reabsorption of sodium chloride and water provide what is needed to maintain the edemas. As aldosterone promotes renal excretion of K+ and H+ (→ p. 98), hypokalemia and alkalosis develop.
A. Abnormalities of Glomerular Permselectivity and Nephrotic Syndrome

1. Normal Glomerular capillary
   - Glomerular filter
   - Capsular space

2. Abnormal permselectivity of the glomerular filter

3. Urine electrophoresis
   - Albumin

4. Serum electrophoresis
   - Normal
   - Immuno-globulins

5. Pressure
   - Filtration
   - Resorption
   - Length of capillary

6. Lipoprotein synthesis
   - Lipoprotein lipase deficiency
   - Hyperlipidemia

7. Edema
   - Hypovolemia
   - ADH ↑
   - Aldosterone ↑

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**Interstitial Nephritis**

The term interstitial nephritis is applied to inflammatory changes in the kidney if the inflammation does not originate in the glomeruli. Renal tissue is infiltrated by inflammatory cells (especially granulocytes) and the inflammation can lead to local destruction of renal tissue.

The most common form of interstitial nephritis is that caused by bacteria (pyelonephritis). Most often the infection originates in the urinary tract (bladder → ureter → kidney [ascending pyelonephritis]); less often in the blood (descending pyelonephritis) (→ A1). The renal medulla is practically always affected first, because its high acidity, tonicity, and ammonia concentration weaken the body’s defense mechanisms. Flushing out the renal medulla thus lowers the danger of infection. Infection is promoted by an obstruction to urinary flow (urinary tract stone [→ p. 120], pregnancy [→ p. 116], prostatic hypertrophy, tumor) and by reduced immune defenses (e.g., diabetes mellitus [→ p. 290]).

An interstitial nephritis can also cause the deposition of concrements (calcium salts, uric acid) in the renal medulla without any infection (→ A2). Uric acid deposits in the kidney are principally caused by an excessive dietary intake of purines, which are broken down in the body into uric acid, as well as by a massive increase of endogenous uric acid production, as occurs in the leukemias and in rare cases of enzyme defects of uric acid metabolism (→ p. 250). Calcium deposits are the consequence of hypercalciuria that occurs when intestinal absorption of calcium is increased (e.g., in hypervitaminosis D) as well as with increased mobilization of calcium from bone (e.g., by tumors, immobilization; → p. 132).

Lastly, interstitial nephritis can result from toxic (e.g., phenacetin) or allergic (e.g., penicillin) factors, from radiation or as a rejection reaction in a transplanted kidney. The renal medulla is especially prone to hypoxia because O₂ diffuses from the descending to the ascending limb of the vasa recta. In sickle cell anemia (→ p. 36) deoxygenation therefore leads to precipitation of hemoglobin, especially in the renal medulla, and thus to vascular occlusion.

Massive administration of prostaglandin synthesis inhibitors can damage the renal medulla by causing ischemia. In normal circumstances renal medullary perfusion at low perfusion pressure is maintained by the release of vasodilating prostaglandins. Inhibition of prostaglandin synthesis stops this protective mechanism, however.

In accordance with the site of the inflammatory processes, the first effects are caused by lesions in the segment of the nephron that lies within the renal medulla (loop of Henle and collecting duct). A relatively early occurrence is reduced urinary concentration, caused by damage to the ascending part, by flushing out of the medulla as a result of inflammatory hyperemia as well as by a lack of sensitivity of the damaged distal nephron to ADH. The increased urine volume causes nocturnal diuresis (nicturia). The decreased K⁺ secretion into the collecting duct can cause hyperkalemia, while reduced Na⁺ reabsorption can result in hypovolemia (→ A3). However, the reduced Na⁺ reabsorption in the loop of Henle can also result in an increased distal K⁺ secretion with accompanying hypokalemia, especially when more aldosterone is released as the result of hypovolemia (→ p. 266).

Renal acid excretion can be impaired, resulting in an alkaline urine being formed and also in systemic acidosis.

Various functions of the proximal tubules (reabsorption of glucose and amino acids, secretion of PAH) and the glomeruli (GFR) are affected only in advanced pyelonephritis.

Infection by urea-splitting pathogens leads to a breakdown of urea into ammonia in the urine. As ammonia binds hydrogen ions (→ A4), an alkaline urine will result. This promotes the precipitation of phosphate-containing concrements (→ p. 120) that in turn can cause obstruction to urinary flow and thus the development of ascending pyelonephritis, i.e., a vicious circle is established.
A. Interstitial Nephritis

1. Deposition of concrements: calcium salts, uric acid
2. Toxic damage, e.g. phenacetin
   - Allergic reaction, e.g. penicillin
   - Rejection reaction after transplantation
   - Inhibitors of prostaglandin synthesis
     - Ischemia
3. Lesions of distal nephron
4. Outflow obstruction
   - Precipitation of phosphate salts
   - Impaired urinary concentration
   - Hyperkalemia
   - Systemic acidosis
   - Alkaline urine

- Descending pathogens
- Ascending pathogens
- Immune defense

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Acute Renal Failure

Numerous and diverse disorders can lead to more or less sudden impairment of renal function (→ A1):

- **Obstruction of the urinary tract**, for example, by urinary stones (→ p. 120) can stop urinary excretion, even though the kidney remains intact—at least at first.

In **hemolysis** and in the destruction of muscle cells (**myolysis**) hemoglobin or myoglobin, respectively, is filtered through the glomeruli and precipitated in the acidic tubular lumen, especially because their tubular concentration is increased by fluid absorption. The resulting obstruction leads to urine formation being interrupted.

Renal function can also cease as a result of rapidly progressing renal diseases (e.g., **glomerulonephritis**; → p. 102) or **toxic damage** to the kidney.

**Loss of blood and fluid** impairs renal perfusion and glomerular filtration because in centralization of the circulation (→ p. 230) the kidney is treated like a peripheral organ, i.e., sympathetic activation produces renal vascular constriction via α-adrenoceptors. The result is acute ischemic renal failure.

Several **pathophysiological mechanisms** can prevent the recovery of GFR or restoration of normal excretion of substances filtered by the glomeruli, even after the state of shock has been overcome and blood pressure has been normalized (→ A1):

- **Constriction of the vasa afferentia**:
  - **Energy deficiency** impairs Na\(^+\)/K\(^+\)-ATPase; the resulting increase in intracellular concentration of Na\(^+\) also causes, via the 3Na\(^+\)/Ca\(^{2+}\) exchanger, a rise in intracellular Ca\(^{2+}\) concentration (→ p. 10,12) and thus vasoconstriction.
  - The ischemia promotes the release of renin both primarily and via an increased NaCl supply in the macula densa (reduced Na\(^+\) absorption in the ascending tubules) and thus the intrarenal formation of angiotensin II, which has a vasoconstrictor action.
  - If there is a lack of energy supply, **adenosine** is freed from ATP. It acts on the kidney—in contrast to the other organs—as a marked vasoconstrictor.

- **Obstruction of the glomerular filter** by fibrin and erythrocyte aggregates.
- **Seeping away of filtered fluid** in the damaged tubules.
- **Obstruction of the tubular lumen** by desquamated tubular cells, by crystals, or due to swelling of the tubular cells.
- **Intravascular stasis** (“sludge”) that cannot be flushed out of the network between renal medulla and cortex, even if the perfusion pressure rises.

In the first three days of acute renal failure no urine (anuria) or only a little volume of poorly concentrated urine (oliguria) is excreted as a rule (oliguric phase; → A2). However, urinary volume alone is a very poor indicator of the functional capacity of the kidney in acute renal failure, because the tubular transport processes are severely restricted and the reabsorption of filtered fluid is thus reduced. Despite normal-looking urine volume, renal excretion of all those substances that must normally be excreted in the urine may be markedly impaired. In this case determination of the plasma and urine creatinine concentration provides information on the true functional state of the kidneys.

Recovery after the oliguric phase will lead to a **polyuric phase** characterized by the gradual increase of the GFR while the reabsorption function of the epithelial nephron is still impaired (salt-losing kidney; → A3). If the renal tubules are damaged (e.g., by heavy metals), polyuric renal failure occurs as a primary response, i.e., large volumes of urine are excreted despite a markedly decreased GFR.

The **dangers** of acute renal failure lie in the inability of the kidney to regulate the water and electrolyte balance. The main threat in the oliguric phase is hyperhydration (especially with infusion of large volumes of fluid) and hyperkalemia (especially with the simultaneous release of intracellular K\(^+\), as in burns, contusions, hemolysis, etc.). In the polyuric phase the loss of Na\(^+\), water, HCO\(_3\)^{−}, and especially of K\(^+\) may be so large as to be life-threatening.
A. Acute Renal Failure

1. Glomerular inflammation, poisoning, etc.

2. Reduced renal perfusion, especially in shock

3. Fibrin deposition

4. Angiotensin

5. Adenosine

6. Obstruction of tubular lumen

7. Vasoconstriction

8. [Ca^{2+}] intracellular

9. Hypothetic mechanism (see text)

10. Ischemia

11. Acute phase

12. Reabsorption

13. Secondary phase

14. Recovery

15. Oliguria

16. Polyuria

17. Hyperhydration, hyperkalemia, ascending pyelonephritis

18. Dehydration, hypokalemia

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Chronic Renal Failure: Abnormal Functions

A number of renal diseases can ultimately lead to the destruction of renal tissue (→ p. 102 ff., 114). If the residual renal tissue is not in a position to adequately fulfill its tasks, the picture of renal failure evolves.

**Reduced renal excretion** is particularly significant. The decreased GFR leads to an inversely proportional rise in the plasma level of creatinine (→ A, top; see also p. 94). The plasma concentration of reabsorbed substances also rises, but less markedly, because renal tubular reabsorption is impaired in renal failure. The reabsorption of Na⁺ and water is inhibited in renal failure by a variety of factors, such as natriuretic hormone, PTH, and vanadate (→ p. 112). The reduced reabsorption of Na⁺ in the proximal tubules also directly or indirectly decreases the reabsorption of other substances, such as phosphate, uric acid, HCO₃⁻, Ca²⁺, urea, glucose, and amino acids. The reabsorption of phosphate is also inhibited by PTH.

Reduced NaCl reabsorption in the ascending limb compromises the concentrating mechanism (→ p. 100). The large supply of volume and NaCl from parts of the proximal nephron promotes the reabsorption of Na⁺ distally and aids in the secretion of K⁺ and H⁺ in the distal nephron and in the collecting duct. As a result, the plasma concentration of electrolytes can remain practically normal even if GFR is markedly reduced (compensated renal insufficiency). Disorders occur only once GFR has fallen to less than a quarter of the normal level. However, this compensation is carried out at the cost of the regulatory range, in that the damaged kidney is unable adequately to increase the excretion of water, Na⁺, K⁺, H⁺, phosphate, etc. (e.g., if oral intake is increased).

It is probably the disruption in renal water and electrolyte excretion that is responsible, at least partially, for the development of most of symptoms of chronic renal failure. Excess volume and the changed electrolyte concentrations lead to edemas, hypertension, osteomalacia, acidosis, pruritus, and arthritis, either directly or via the activation of hormones (→ p. 112). Also, abnormalities of the excitatory cells (polyneuropathy, confusion, coma, seizures, cerebral edemas), of gastrointestinal function (nausea, peptic ulcer, diarrhea), and of blood cells (hemolysis, abnormal leukocyte function, abnormal blood clotting) are due to this.

While uric acid can be precipitated at high concentrations, especially in the joints, and thus cause gout (→ p. 250), sufficiently high concentrations of uric acid are only rarely achieved in renal failure. The role of reduced elimination of so-called uremia toxins (e.g., acetone, 2,3-butyleneglycol, guanidinosuccinic acid, methylguanidine, indoles, phenols, aliphatic and aromatic amines, etc.) as well as of so-called middle molecules (lipids or peptides with a molecular weight of 300–2000 Da) in producing the symptoms of renal failure remains the subject of considerable debate. High concentrations of urea can destabilize proteins and bring about cell shrinkage. But its effect is partly canceled by the cellular uptake of stabilizing osmolytes (especially betaine, glycerophosphorylcholine).

The impaired renal production of erythropoietin leads to the development of renal anemia (→ p. 30 ff.), while the reduced formation of calcitriol contributes to abnormalities of mineral metabolism (→ p. 112). Depending on the cause and course of the disease, the intra-renal formation of renin and of prostaglandins can be raised (→ p. 114) or reduced (death of renin- or prostaglandin-producing cells). Increased formation of renin promotes, while its reduced formation inhibits, the development of hypertension, a frequent occurrence in renal failure (→ p. 112 ff). Prostaglandins, on the other hand, are more likely to cause vasodilation and a fall in blood pressure (→ p. 296). The loss of renal inactivation of hormones (→ p. 92) may slow down hormonal regulatory cycles. It is not clear, however, what the role of these changes is in the development of symptoms.

The reduced consumption of fatty acids by the kidney contributes to hyperlipidemia, while reduced gluconeogenesis favors the development of hypoglycemia.
A. Chronic Renal Failure

- Normal kidney
  - RPF
  - GFR

- Compensated renal failure
  - GFR
  - RPF

- Compensated renal failure
  - Creatinine
  - Urea
  - HPO₄²⁻, Mg²⁺, Uric acids
  - Na⁺, K⁺, Ca²⁺

- GFR ↓

- Anemia
  - Erythropoietin ↓
  - Renin
  - Ischemia

- Hypertension

- Retention of:
  - VnO₄
  - NaCl
  - H₂O
  - ‘middle molecules’
  - Uremia toxins
  - Uric acids
  - Urea

- Break-down of free fatty acids

- NH₃ production ↓

- Acidosis
  - H⁺
  - K⁺
  - Phosphate

- Pruritus, arthritis, gout

- Neuropathy, gastroenteropathy, susceptibility to infection, coagulopathies

- Hyperlipidemia

- Demineralization

- Calcitriol ↓

- Plasma-Ca²⁺ ↓

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Chronic Renal Failure: Abnormal Regulation

Reduced renal elimination of water and electrolytes is particularly important in the development of symptoms of renal failure (see also p. 110). The extracellular volume expands if there is an excess of NaCl and water (→ A), and hypervolemia as well as edemas develop (→ p.122); pulmonary edema being the most dangerous complication (→ p. 80). If it is predominantly water which is in excess, the osmotically driven entry of water increases the intracellular volume (→ A) and there is a danger of cerebral edema (→ p. 358).

The hypervolemia results in the release of atrial natriuretic factor (ANF) and probably also of ouabain. The latter inhibits Na⁺/K⁺-ATPase (→ A1). Vanadate (VNO₄⁻), which is largely excreted by the kidney, has a similar effect. Its clearance is about the same as GFR and its plasma level is markedly raised in renal failure.

Inhibition of Na⁺/K⁺-ATPase causes reduced Na⁺ reabsorption in the kidney. Additionally, the intracellular K⁺ concentration falls in cells from diverse tissues and in the cells depolarize. The intracellular concentration of Na⁺ rises. This impairs 3Na⁺/Ca²⁺ exchange (→ A2), and thus the intracellular concentration of Ca²⁺ also increases. The consequences of depolarization are abnormal neuromuscular excitability, cellular accumulation of Cl⁻, and cell swelling (→ A; see also p. 10). The increased Ca²⁺ concentration causes vasoconstriction as well as increased release of hormones (e.g., gastrin, insulin) and increased hormonal effects (e.g., epinephrine).

Abnormalities of mineral metabolism also contribute greatly to the symptoms of renal failure (→ B). If the GFR is reduced to less than 20% of normal rate, less phosphate is filtered than is absorbed through the gut. Even if the entire amount of filtered phosphate is eliminated, i.e., there is no reabsorption, renal elimination cannot keep up with intestinal absorption, and the plasma concentration of phosphate rises. When the solubility is exceeded, phosphate combines with Ca²⁺ to form poorly soluble calcium phosphate. The precipitated calcium phosphate is deposited in the joints and skin (causing joint pains or pruritus, respectively).

When Ca²⁺ forms a complex with phosphate, the concentration of Ca²⁺ is lowered. The hypocalcemia stimulates the release of PTH from the parathyroid gland, mobilizing calcium phosphate from bone (→ B). The result is demineralization of bone (osteomalacia). Normally PTH makes it possible, by simultaneous inhibition of renal reabsorption of phosphate, for the plasma concentration of phosphate to fall so that, despite mobilization of calcium phosphate from bone, the solubility product in plasma is not exceeded and Ca²⁺ concentration can increase. In renal insufficiency, however, renal excretion cannot be enhanced, plasma phosphate concentration increases, CaHPO₄ is precipitated, and plasma Ca²⁺ concentration remains low. The stimulus for PTH release therefore continues. Under this persisting secretory stimulus the parathyroid glands hypertrophy and, in a vicious circle, release ever larger amounts of PTH.

As the receptors for PTH are, in addition to those in the kidney and bones, in many other organs (nervous system, stomach, blood cells, gonads) it is assumed that PTH plays a role in the development of abnormalities in these organs. In fact, removal of the parathyroid glands is thought to significantly improve numerous symptoms of renal failure.

The formation of calcitriol is reduced in renal failure, which also plays a part in causing the abnormalities of mineral metabolism. Normally this hormone stimulates the absorption of calcium and phosphate in the gut (→ B). Although calcitriol deficiency reduces the intestinal absorption of phosphate, it aggravates the hypocalcemia. There are receptors for calcitriol in various organs. Calcitriol substitution does not necessarily improve the symptoms and endangers the patient with renal failure by stimulating the intestinal absorption of phosphate.
A. Disorders of Salt and Water Balance in Renal Failure

Cell metabolism
hormone release,
nervous system

Vasoconstriction
Hypertension

Cell swelling

K⁺  
Cl⁻  
Na⁺  
Ca²⁺

VnO₄

H₂O

Ca²⁺

HPO₄²⁻

Ca²⁺

Calcitriol

Gut

Calcium phosphate

Parathyroid

Joint pains

Pruritus

Abnormalities

Stomach
Nervous system
Blood cells
Gonads

B. Effects of Renal Failure on Mineral Balance

Calcium phosphate

Calcium phosphate

Abnormalities

Stomach
Nervous system
Blood cells
Gonads
Renal Hypertension

Most renal diseases can cause hypertension; about 7% of all forms of hypertension can be traced back to renal disease. In addition, the kidneys play a significant role in the genesis and course of hypertensive disease, even when there is no primary renal disease (→ p. 208 ff.).

Renal ischemia is an important cause of hypertension brought about by renal disease. Reduction of renal perfusion pressure also leads to hypertension in animal experiments (Goldblatt kidney). This happens regardless of the site where renal blood flow is decreased, whether intrarenally in the course of renal disease (e.g., glomerulonephritis [→ p. 102], pyelonephritis [→ p. 106]), in the renal artery (renal artery stenosis), or in the aorta above the origin of the renal arteries (aortic coarctation) (→ A1).

Reduced perfusion of the kidney results in hypertension via stimulation of the renin–angiotensin mechanism (→ A2), in which renin is released in the juxtaglomerular apparatus, for example, by renal ischemia, and splits off angiotensin I from angiotensinogen, a plasma protein originating in the liver. Angiotensin I is then changed into angiotensin II through the mediation of a converting enzyme that is present in many tissues. Angiotensin II has a strong vasoconstrictor action which causes a rise in blood pressure. At the same time angiotensin II stimulates the release of aldosterone and ADH, which bring about the retention of NaCl and of water through the activation of Na\(^{+}\) channels and water channels, respectively (→ A3).

The plasma concentration of the angiotensinogen formed in the liver does not saturate renin, i.e., an increase in angiotensinogen concentration can raise the blood pressure further. Thus, overexpression of angiotensinogen favors the development of hypertension as does overexpression of renin.

Hypertension is caused by the retention of sodium and water even without the renin–angiotensin mechanism. A primary increase in aldosterone release (hyperaldosteronism; → p. 266) leads to hypertension just as an overactive Na\(^{+}\) channel does (Liddle’s syndrome; → p. 98) and—in those who are “salt-sensitive”—an excessive supply of Na\(^{+}\). It is possible that hypervolemia promotes the release of ouabain, which increases vascular smooth muscle tone through the inhibition of Na\(^{+}\)/K\(^{+}\)-ATPase and the subsequent increase in intracellular Na\(^{+}\) concentration, reversal of the 3Na\(^{+}\)/Ca\(^{2+}\) exchanger, and a rise in cytosolic Ca\(^{2+}\) concentration (→ p. 112). This hypothesis has not, however, been definitively proved. Nevertheless, hypervolemia regularly results in hypertension (→ p. 208 ff.).

Other diseases can also bring about hypertension without the above-mentioned primary causes being involved. Thus, for example, a renin-producing renal tumor or a polycystic kidney can (in an unknown manner) lead to hyperreninism and thus hypertension without ischemia.

Lack of renal production of vasodilating prostaglandins (→ p. 296) probably plays a subordinate role in the development of renal hypertension.

The effects of hypertension are, primarily, damage to heart and vessels (→ A, bottom). Every form of hypertension leads to damage to the kidney. Longer lasting hypertension damages the renal arterioles (→ p. 208 ff.) and the glomeruli (nephrosclerosis) and in due course leads to renal ischemia. Thus, primary extrarenal hypertension can develop into renal hypertension through the development of nephrosclerosis. All this results in a vicious circle in which the renal ischemia and hypertension mutually reinforce one another. A kidney with renal arterial stenosis or both kidneys in aortic coarctation are unaffected by this vicious circle, because there is a normal or even reduced blood pressure distal to the stenosis, preventing arteriolar damage. A special case arises when the development of hypertension due to renal artery stenosis damages the contralateral, originally healthy, kidney. After removal of the stenosis, the hypertension due to enhanced renin production of the contralateral kidney may persist.
A. Renal Hypertension

1. Kidney disease, e.g. glomerulonephritis

2. Renin
   - Angiotensinogen
   - Angiotensin I
   - Angiotensin II
   - Aldosterone
   - ADH
   - Blood
   - Lumen
   - Vasoconstriction
   - Ouabain
   - Hypertension
   - Cardiac output (CO)
   - Hypervolemia

3. Water and salt excretion decreases

   - Nephrosclerosis
   - Increased afterload on heart
   - Vascular damage

- Coarctation of the aorta
- Renal artery stenosis
- Ischemia
- Renal artery stenosis
Kidney Disease in Pregnancy

In a normal pregnancy (→A) the placenta forms vasodilating prostaglandins (especially PGE₂) and possibly other substances that reduce the reactivity of vessels to vasoconstrictor stimuli. As a result, the peripheral vascular resistance (R) is decreased and blood pressure falls. In the kidney, too, the vascular resistance, the RPF, and the GFR rise markedly.

Na⁺ reabsorption in the proximal tubules does not keep in step with a high GFR. In addition, estrogens inhibit the K⁺ channel in the proximal tubules (IsK). The resulting depolarization retains HCO₃⁻ in the cell, and the intracellular acidosis inhibits the Na⁺/H⁺ exchanger (→ p.97 A). The depolarization also inhibits the electrogenic transport processes for glucose, amino acids, etc. Due to the reduced reabsorption of Na⁺ and fluid, uric acid is less concentrated within the lumen and thus also less of it is reabsorbed. Among the consequences of reduced proximal tubular reabsorption are a fall in the renal threshold for glucose (tendency toward glycosuria) and for bicarbonate (fall in plasma bicarbonate concentration).

It is possible that the release of renin is stimulated by the increased supply of NaCl to the macula densa. The plasma level of renin and thus also of angiotensin II and aldosterone are raised. Aldosterone increases the distal reabsorption of Na⁺. All in all, NaCl and water are retained in pregnancy, despite a rise in GFR, and extracellular and plasma volumes increase. However, because of the low reactivity of peripheral vessels to vasoconstrictor stimuli, no hypertension develops, despite the high angiotensin level and hypervolemia.

Edema, proteinuria, and hypertension (EPH) occur in ca. 5% of all pregnant women (preeclampsia, toxemia of pregnancy, or EPH-gestosis). The symptoms point to renal damage, hence the term nephropathy of pregnancy (→B). The pathogenesis of toxemia of pregnancy with EPH is still not adequately known.

Release of thrombokinase in the placenta may be a pathophysiologically relevant factor. Stimulation of blood clotting (→ B 1) causes fibrin to be deposited, for example, in the glomeruli, leading to thickening of the basement membrane and injury to the endothelial cells. Damage to the glomeruli could explain the proteinuria. Corresponding damage to the peripheral vessels leads to the development of edemas at the expense of the plasma volume, which is reduced.

The placenta of patients with preeclampsia also has a reduced ability to form vasodilating prostaglandins (and other vasodilators?) (→ B 2). The sensitivity of the vessels to vasoconstrictor influences (e.g., angiotensin II) is therefore markedly increased. This leads, on the one hand, to peripheral vasoconstriction and hypertension and, on the other hand, to an increase in the resistance of renal vessels (→ B 3); RPF and GFR are reduced. As a consequence of volume deficiency an increased amount of Na⁺ is reabsorbed in the proximal tubules, luminal flow is reduced, the contact time with the reabsorbing epithelium is prolonged, and reabsorption of uric acid is thus raised. The plasma level of uric acid is increased, providing a valuable diagnostic indication.

It is not quite clear whether or not the plasma concentration of renin and angiotensin II is increased in preeclampsia. Stimulation of renin secretion in the kidney could be explained by the reduction in renal perfusion. In any case, the vasoconstrictor action of angiotensin II is greatly increased in preeclampsia by the raised vascular reactivity (see above). In addition to an increase in peripheral resistance, the raised vascular reactivity also leads to the development of local vascular spasms. These are thought to occur in various organs (including the brain), where in a few cases they can cause convulsions and coma (eclampsia). Occasionally, vascular narrowing can be seen in the ocular fundi even a few days before the onset of eclampsia.
A. Normal Pregnancy

Prostaglandins (esp. E₂) → Vasodilation

Blood pressure ↓

Blood volume ↑

GFR ↑

Na⁺, Uric acid, glucose

RPF ↑

Na⁺ and H₂O retention

B. Nephropathy of Pregnancy

Prostaglandins (esp. E₂) → Thrombokinase

Blood clotting → Fibrin

Blood volume ↓

Edema

H₂O

Abnormal permselectivity

Proteinuria

Na⁺ and H₂O retention

Uric acid

GFR ↓

Proteins

Blood pressure ↓

Ischemia, CNS

Hypertension

Renin

Angiotensin

Aldosterone
Hepatorenal Syndrome

Renal ischemia and ultimately oliguric renal failure, a disease combination called hepatorenal syndrome, occurs relatively frequently in patients with cirrhosis of the liver. Several factors contribute to the development of this syndrome, but it has not as yet been agreed which of the factors are most significant or whether there are others which are important, too.

In liver cirrhosis, congestion in the portal venous system due to narrowing of the vascular bed within the liver (→ p. 170) occurs initially. The hydrostatic pressure in the capillaries rises and excessive amounts of fluid are filtered into the abdominal cavity (ascites, → p. 170). Because of the high protein permeability of the liver sinusoid, plasma proteins are also lost into the extracellular space. In addition, fewer plasma proteins are produced in the liver parenchyma. The resulting hypoproteinemia results in the increased filtration of plasma water and thus in the development of peripheral edemas. The formation of ascites and peripheral edemas occurs at the expense of the circulating plasma volume. The result is hypovolemia.

In the further course of the disease peripheral vasodilation occurs. Vasodilating mediators (e.g., substance P) produced in the gut and endotoxins released by bacteria are normally detoxified in the liver. In liver cirrhosis the loss of liver parenchyma and the increased amount of blood passing from the portal circulation directly into the systemic circulation, short-circuiting the liver (→ p.170), brings those substances into the systemic circulation unhindered. The mediators have a direct vasodilator effect, while the endotoxins exert a vasodilator effect by stimulating the expression of nitric oxide synthase (iNOS). This may lead to a fall in blood pressure, causing massive sympathetic stimulation. This, together with the hypovolemia, results in diminished renal perfusion and thus a fall in GFR. The reduced renal blood flow promotes the release of renin and thus the formation of angiotensin II, ADH, and aldosterone (→ p. 266). ADH and aldosterone increase the tubular reabsorption of water and sodium chloride (loss of potassium; → p. 124), and the kidney excretes small volumes of highly concentrated urine (oliguria).

Incomplete hepatic inactivation of mediators that have a direct vasoconstrictor effect on the kidney (e.g., leukotrienes) also contributes to renal vasoconstriction.

Renal ischemia normally stimulates the release of vasodilating prostaglandins that prevent further reduction in renal perfusion (→ p. 296). If there is insufficient formation of prostaglandins (e.g., due to administration of prostaglandin synthesis inhibitors), this protective mechanism is abolished and the development of renal failure accelerated. A decreased ability to synthesize prostaglandins (lack of precursors?) has in fact been found in patients with the hepatorenal syndrome.

Renal vasoconstriction can possibly also be elicited by hepatic encephalopathy (→ p. 174). The reduced metabolic activity of the liver leads to a change in amino acid concentration and a rise in NH₄⁺ concentration in blood and brain. This causes swelling of the glial cells and a profound disturbance of transmitter metabolism in the brain that, via activation of the sympathetic nervous system, causes renal vascular constriction.

Due to the impaired synthesizing activity of the liver, less kininogen is formed, and therefore too few vasodilating kinins (e.g., bradykinin), facilitating renal vasoconstriction.

Lastly, an abnormal fat metabolism may contribute to kidney damage in liver failure. Among other consequences, the liver forms less lecithin-cholesterol acyltransferase (LCAT), an enzyme that esterifies cholesterol with fatty acids (→ p. 246) and plays an important part in breaking down or transforming lipoproteins. In familial LCAT deficiency (due to an enzyme defect) renal failure regularly occurs, probably through lipid deposition in the kidney.
A. Hepatorenal Syndrome

- Disorders of metabolism
  - Gut
  - Blood
  - Endotoxins
  - Leukotrienes
  - Substance P
  - Leukotrienes

- Abnormal inactivation
  - NO synthase
  - Ammonia

- Portal vein congestion
  - Hypoproteinemia
  - Capillary pressure

- Hypovolemia
  - Oncotic pressure

- Asites
  - Peripheral edemas

- Abnormal amino acid balance

- Decreased protein synthesis

- Liver cirrhosis

- Activation of sympathetic nerves
  - CO
  - Vasoconstriction

- Drop in blood pressure

- Prostaglandin synthesis inhibitor

- Prostaglandin

- Oliguria

- Renal perfusion
  - GFR

- Disorders of metabolism
  - Decreased protein synthesis
  - Oncotic pressure

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Urolithiasis

Concrement-forming substances (→ A1) can reach concentrations in the urine that lie above their solubility threshold. In the so-called metastable range the formation of crystals may not occur at all, or only slowly, despite supersaturation of the solution. However, when the concentrations rise beyond the metastable range, crystallization occurs. Dissolving already formed crystals is possible only by reducing the concentration to below the metastable range.

The most frequently found components in kidney stones are calcium oxalate (ca. 70%), calcium phosphate or magnesium-ammonium phosphate (ca. 30%), uric acid or urate (ca. 30%) as well as xanthine or cystine (<5%). Several substances may be contained in one stone, because crystals that have already formed act as nuclei for crystallization and facilitate the deposition of other metastably dissolved substances (hence the total is > 100%).

Certain substances that form complexes, such as citrate, pyrophosphate, and (acid) phosphate, can bind Ca²⁺ and, by reducing the Ca²⁺ concentration, are able to prevent calcium phosphate and calcium oxalate from precipitating.

Causes of stone formation. The raised concentration of stone-forming substances can be the result of prerenal, renal, and postrenal factors:

Prerenal causes produce the increased filtration and excretion of stone-producing substances via a raised plasma concentration (→ p.94). Thus, prerenal hypercalciuria and phosphaturia are the result of raised intestinal absorption or mobilization from bone, for example, if there is an excess of PTH or calcitriol (→ A2). Hyperoxalemia can be brought about by a metabolic defect in amino acid breakdown or by increased intestinal absorption (→ A3). Hyperuricemia occurs as a result of an excessive supply, increased new synthesis, or increased breakdown of purines (→ A3). Xanthine stones may occur when the formation of purines is greatly increased and the breakdown of xanthines to uric acid is inhibited. However, xanthine is much more soluble than uric acid and xanthine stones are therefore much less common.

Abnormal renal reabsorption is a frequent cause of increased renal excretion in hypercalciuria and an invariable cause in cystinuria (→ p.96). The Ca²⁺ concentration in blood is then maintained by the intestinal absorption and mobilization of bone minerals, while the cystine concentration is maintained by a reduced breakdown.

Release of ADH (in volume depletion, stress, etc.; → p.260) leads to a raised concentration of stone-forming substances via enhanced urine concentration (→ A4).

The solubility of some substances depends on the pH of urine. Phosphates are easily dissolved in an acidic urine, but poorly in an alkaline one. Phosphate stones are therefore, as a rule, only found in alkaline urine. Conversely, uric acid (urate) is more soluble when dissociated than undissociated, and uric acid stones are formed more readily in acidic urine. If the formation of NH₃ is reduced, the urine has to be more acidic for acid to be eliminated, and this promotes the formation of urate stones.

A significant factor is also how long crystals that have already formed actually remain in the supersaturated urine. The length of time depends on the diuresis and the flow conditions in the lower urinary tract that can, for example, lead to crystals getting caught (postrenal cause).

The effect of urolithiasis is that it blocks the lower urinary tract (→ A5). In addition, stretching of the ureteric muscles elicits very painful contractions (renal colic). Obstruction to flow leads to ureteral dilation and hydronephrosis with cessation of excretion. Even after removal of a stone, damage to the kidney may persist. The urinary obstruction also promotes growth of pathogens (urinary tract infection; pyelonephritis; → p.106). Urea-splitting pathogens form NH₃ from urea, thus alkalining the urine. This in turn, in a vicious circle, favors the formation of phosphate stones. Even without bacterial colonization, intrarenal deposition of uric acid (gouty kidney) or of calcium salts (nephrocalcinosis) can result in inflammation and destruction of renal tissue.
A. Urolithiasis

1. Reduced reabsorption

2. Absorption

3. Disordered metabolism

4. Hypovolemia

5. Metastable solution

- PTH
- Calcitriol
- Ca²⁺
- HPO₄²⁻
- Oxalate
- Xanthine
- Uric acid
- CaHPO₄
- MgNH₄PO₄
- ADH
- H₂O
- Urine concentration

- Cystin
- Xanthine
- Uric acid
- NH₄⁺
- Ca²⁺
- H⁺

- pH
- Citrate etc.

- Stagnant urine
- Precipitation
- Stone formation

- Renal damage
- Colics
- Infection
- Kidney stones
Disorders of Water and Salt Balance

By decreasing osmolality (receptors in the liver and brain) and via hypervolemia (stretch receptors in the right atrium) an excess of water normally inhibits ADH release and thus triggers diuresis (→ p. 100). The blood pressure, raised by the hypervolemia, inhibits the renin–angiotensin–aldosterone system. At the same time the release of ANF and possibly also of ouabain is stimulated. The result is natriuresis which, after some delay, brings about the correction of the plasma volume and osmolality. Excess NaCl increases ADH release via hyperosmolality and thus leads to antidiuresis and also an adjustment of osmolality.

An excess of water and NaCl (→ A) occurs, for example, when fluid with greater osmolality than that of urine is ingested (e.g., shipwrecked people drinking sea-water). The renal excretion of water and NaCl is also reduced in impaired renal function (GFR ↓). Uncontrolled infusion of isotonic NaCl solution can then lead to an excess of NaCl and water, while infusion of isotonic glucose solution results in an excess of water that remains in the body after glucose has been metabolized. Even when kidney function is intact, there will be an excess of water or NaCl if the release of mineralocorticoids or ADH is inappropriately increased (e.g., by hormone-producing tumors, → p. 260, 266). If the filtration balance in the peripheral vasculature is tipped, edemas occur at the expense of plasma volume (→ p. 234). This results in a decreased plasma volume, which stops the release of natriuretic factors (Atrial natriuretic factor, ouabain) and stimulates that of ADH, renin, angiotensin, and aldosterone. The renal retention of NaCl then leads to the correction of plasma volume, and thus to an increase in extracellular volume.

A lack of water and NaCl (→ B) can be the result of external fluid loss as is the case, for example, with excessive sweating (fever, heat), in diarrhea, blood loss, burns or salt-losing kidney (→ p. 108). Renal water loss can occur in ADH deficiency (central diabetes insipidus; → p. 260) and in lack of responsiveness of the kidney to ADH (renal diabetes insipidus; → p. 100). Even when the external balance is kept, dangerous “internal losses” can occur, such as a shift of plasma volume into the intestinal lumen (in ileus; → p. 156), into the abdominal cavity (ascites; → p. 170) or in the periphery (edema; → p. 234).

An excess of water (hyperhydration) necessarily leads to the enlargement of one body compartment (→ C). If there is NaCl excess at the same time (isotonic or hypertonic hyperhydration), the extracellular space is increased. In hypertonic hyperhydration the extracellular space is increased, partly by osmotic withdrawal of water from the cells. If the NaCl content is normal or reduced (hypotonic hyperhydration), it is mainly the intracellular space that is enlarged.

In lack of water (dehydration) the extracellular space is reduced, especially when there is a simultaneous lack of NaCl (isotonic or hypotonic dehydration). In isolated lack of water the intracellular space is reduced (hypertonic dehydration), while it is increased in isolated lack of NaCl (hypotonic dehydration).

Any reduction in extracellular space is especially dangerous because of the decrease in plasma volume (hypovolemia). Signs of this are reduced central venous pressure, tachycardia, and a tendency to faint. If there is a drop in blood pressure, renal function is impaired and the release of ADH and aldosterone leads to oliguria (danger of urolithiasis). Conversely, an enlargement of extracellular volume leads to a rise in blood pressure when a part of the volume remains in the intravascular space (→ p. 114). On the other hand, the dilution of intravascular proteins promotes filtration in the peripheral capillaries and edema formation (→ p. 234) and, in the worst case, pulmonary edema (→ p. 80).

If the intracellular volume is enlarged, there is a particular danger that cerebral edemas will develop (→ p. 358). Reduction in the intracellular volume also leads mainly to disorders of the central nervous system that can progress to loss of consciousness and even death.
A. Causes of Hyperhydration

Hyperhydration

- **GFR**: Decreased
- **ADH**: Increased
- **Aldosterone**: Increased
- **Excretion**: Decreased

- **Hypertonic hyperhydration**
- **Isotonic hyperhydration**
- **Hypotonic hyperhydration**

- **Edemas**
- **Hypovolemia**

B. Causes of Dehydration

Dehydration

- **ADH**: Decreased
- **Aldosterone**: Decreased
- **Excretion**: Increased

- **Hypertonic dehydration**
- **Isotonic dehydration**
- **Hypotonic dehydration**

- **Diarrhea, intestinal fistula**
- **Blood loss**
- **Sweating, burns**

C. Most Important Effects of Hyperhydration and Dehydration

- **Hyperhydration**
  - **NaCl**: Increased
  - **H2O**: Increased
  - **ECS**: Increased
  - **ICS**: Increased
  - **Cerebral edema**

- **Dehydration**
  - **H2O**: Decreased
  - **NaCl**: Decreased
  - **ECS**: Decreased
  - **ICS**: Decreased
  - **CNS disorders**

- **Urolithiasis**

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Abnormalities of Potassium Balance

An abnormal potassium level is the result of a disorder of K⁺ balance or of its distribution between the intracellular and extracellular space. An abnormal potassium balance occurs, for example, if potassium supply is inadequate (→ A1). As intravenous infusion of K⁺ initially passes into a compartment, namely plasma, that has a relatively low potassium content; too rapid K⁺ administration can lead to a dangerous level of hyperkalemia even if there is a K⁺ deficiency. The secretion of K⁺ in exchange for Na⁺ in the distal tubules and collecting duct is the decisive step in the renal elimination of K⁺ (→ A2; see also p. 96 ff.). Renal loss of K⁺ occurs, for example, in hyperaldosteronism (→ p. 266) or if there is an increased availability of Na⁺ in the distal tubules (→ p. 98 D). Conversely, renal K⁺ elimination is decreased if: 1) Na⁺ reabsorption is impaired in the distal tubules, as in hypoaldosteronism; 2) diuretics acting on the connecting tubule and collecting duct have been administered; or 3) there is a decreased supply of Na⁺ (e.g., in renal failure). In alkalosis fewer H⁺ ions are secreted in the connecting tubule and collecting duct and more K⁺ is lost, while conversely acidosis decreases K⁺ secretion in the distal nephron. K⁺ may also be lost via the gut (→ A3). If there is an increased supply of Na⁺ or in hyperaldosteronism, an increased amount of Na⁺ is similarly absorbed in the colon in exchange for K⁺.

Even minor shifts of K⁺ between intracellular and extracellular fluid lead to massive changes in plasma K⁺ concentration, because the K⁺ content in cells is more than 30 times that in the extracellular space. Cellular loss of K⁺ and hyperkalemia occur, for example, in case of cellular energy deficiency (→ A4), during severe physical work (K⁺ loss via the muscles), cell death (e.g., in hemolysis, myolysis), and in transfusion of blood which has been stored for some time (loss of K⁺ from erythrocytes). Furthermore, hemolysis at the time of blood-taking can increase the K⁺ concentration in the plasma and be mistaken for hyperkalemia.

In (extracellular) alkalosis the cells release H⁺ in exchange for Na⁺ (Na⁺/H⁺ exchangers) and pump the Na⁺ out again in exchange for K⁺ (Na⁺/K⁺-ATPase) (→ A5). This K⁺ uptake by the cells causes hypokalemia. Conversely, acidosis leads to hyperkalemia. Glucose stimulates the release of insulin that, by activating Na⁺/H⁺ exchangers, Na⁺–K⁺–2 Cl⁻ cotransporters and Na⁺/K⁺-ATPase, stimulates the uptake of K⁺ by the cells. In insulin deficiency or hypoglycemia (when fasting), the cells lose K⁺. The administration of insulin in diabetic hyperglycemia (→ p. 286 ff.) or food intake by a starving person may lead to dangerous hypokalemia because the cells will be taking up K⁺.

Catecholamines promote the uptake of K⁺ by the cells via β-receptors and the cellular release of K⁺ from the cells via α-receptors.

The effects of changed plasma K⁺ concentration are in part mediated by changes in the membrane potential. Hypokalemia hyperpolarizes, while hyperkalemia depolarizes the K⁺ equilibrium potential, and thus the membrane potential of selective cells. In this way hypokalemia reduces the excitability of nerve cells (hyporeflexia), skeletal muscles (adynamia), and smooth muscles (gut, bladder, etc.) (→ A6). Conversely, hyperkalemia can increase the excitability of the nervous system (hyperreflexia), smooth muscles (→ A7), and skeletal muscles (→ p. 306).

In contrast, a decrease in K⁺ concentration reduces the conductance of the K⁺ channels, thus decreasing the hyperpolarizing effect of K⁺ on the membrane potential. This promotes the heterotopic automaticity of the heart that may even trigger ventricular fibrillation (→ p. 188 ff.). The reduction of K⁺ conductance is also responsible for delayed repolarization of the Purkinje fibers. Hypokalemia often produces a prominent U wave in the electrocardiogram (ECG) (→ A6). Conversely, hyperkalemia increases the K⁺ conductance, the action potential is shortened, and correspondingly also the ST segment in the ECG (→ A7).

Lack of potassium promotes the cellular retention of H⁺ and its secretion in the distal tubules. This results in an alkalosis (→ p. 86). Conversely, K⁺ excess leads to acidosis (→ p. 88). Hypokalemia also causes polyuria (→ p. 100) and can ultimately lead to irreversible tubular cell damage. Lastly, the release of a number of hormones is abnormal in K⁺ deficiency (especially insulin [→ p. 286] and aldosterone [→ p. 266]).
A. Deranged Potassium Metabolism

1. Insulin and energy deficiency
   - Aldosterone
   - Hypoaldosteronism, distal diuretics

2. Reduced renal elimination
   - GFR
   - Release of cellular potassium
   - Muscle work

3. Renal loss of potassium
   - Intestinal loss
   - Deficient supply

4. Heart:
   - Delayed repolarization (shortened ST segment)
   - Neuromuscular excitability
   - Acidosis
   - Hormone release

5. Alkalosis
   - Renal loss of potassium
   - Insulin
   - Diuretics, salt-losing nephritis
   - Epinephrine (β)

6. Heart:
   - Delayed repolarization
   - Heterotopic automatism
   - Neuromuscular excitability
   - Acidosis
   - Hormone release

7. Hypokalemia
   - K⁺ equilibrium potential
   - K⁺ conductance
   - Hyperkalemia
   - K⁺ equilibrium potential
   - K⁺ conductance

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Abnormalities of Magnesium Balance

Half of the body’s magnesium is bound in bone, almost one half is intracellular. Mg²⁺ concentration in extracellular fluid is relatively low (= 1 mmol/L). Mg²⁺ is essential for the activity of numerous enzymes. In many functions it acts antagonistically to Ca²⁺, which it can displace from its binding to proteins. In this way Mg²⁺ can inhibit the release of transmitters in synapses of the nervous system and can thus inhibit synaptic transmission. It is as true for Mg²⁺ as it has been shown for K⁺ that the plasma concentration measured in a blood sample is an unreliable indicator of its real concentration.

Magnesium deficiency occurs when there is an inadequate supply or a loss via the gut (malabsorption; → A1; see also p. 152 ff.) or the kidneys. In the kidneys magnesium is mainly reabsorbed in the ascending part of the loop of Henle (→ p. 96). Its reabsorption takes place paracellularly through the tight junctions, driven by the transepithelial potential that is indirectly created by NaCl reabsorption (→ A2). The permeability of the tight junctions is reduced in hypercalcemia and alkalosis. This results, for example, in magnesuria. In a rare genetic disease, the protein allowing for paracellular transport (paracellin) is defective. The most prominent disorder of those patients is magnesuria. Furthermore, Ca²⁺ inhibits, via a Ca²⁺ receptor, Na⁺-K⁺-2 Cl⁻ cotransport, causing a decrease in the transepithelial potential and thus of Mg²⁺ reabsorption. A genetic defect of the Na⁺-K⁺-2 Cl⁻ cotransporter, of the Cl⁻ channel or of the luminal K⁺ channel (Bartter’s syndrome) similarly leads to magnesuria.

NaCl reabsorption and thus the transepithelial potential in the ascending limb are increased by ADH. ADH release ceases in alcoholism, and the reabsorption of NaCl and Mg²⁺ falls.

The reabsorption of Mg²⁺ is also reduced in salt-losing nephropathy, in osmotic diuresis (e.g., glycosuria in diabetes mellitus), and due to the effect of loop diuretics. Renal loss of Mg²⁺ also occurs in hyperaldosteronism, probably via volume expansion, which causes reduced Na⁺ and Mg²⁺ reabsorption in the proximal tubules and the ascending limb (→ A2).

Even when the Mg²⁺ balance is in equilibrium shifts of Mg²⁺ between the intracellular and extracellular spaces can change the plasma concentration of Mg²⁺. As insulin stimulates the cellular uptake of both K⁺ (→ p. 124) and Mg²⁺ (→ A3, A7), loss of Mg²⁺ may occur in diabetes mellitus or prolonged fasting. Substitution of insulin or resumption of food intake may then bring about hypomagnesemia.

A decrease in ionized Mg²⁺ may occur in acute pancreatitis (→ A4). Activated lipases from the damaged pancreas split triglycerides (TGs) in the fat tissue, and the liberated fatty acids (FAs) together with Mg²⁺ form insoluble complexes (Mg[FA]₂).

The effects of Mg²⁺ deficiency are an increased neuromuscular excitability, hyperreflexia, and cramps (→ A5). These cramps sometimes resemble those after damage to the basal ganglia (→ p. 312 ff.). Cardiovascular signs can be tachycardia and arrhythmias, even ventricular fibrillation, and a rise in blood pressure. These symptoms are accentuated (if not in fact caused by) hypercalcemia that may occur as a result of a decreased release of PTH (Mg²⁺ stimulates the release of PTH). Usually Mg²⁺ deficiency coexists with K⁺ deficiency (common causes; → p. 124) so that the symptoms of hypokalemia are accentuated.

Mg²⁺ excess is caused by renal failure (→ A6). If the glomerular filtration rate is reduced (GFR↓), Mg²⁺ excretion can at first be maintained by a reduction in reabsorption. Only if GFR drops below ca. 30 mL/min can a decrease of filtration no longer be compensated by the tubules. Hypermagnesemia (without excess Mg²⁺) can also occur in diabetes mellitus (→ A7). Lastly, excessive supply of Mg²⁺ (Mg²⁺-containing infusions, parenteral feeding, or therapeutic Mg²⁺ administration to reduce neuromuscular excitability) can cause hypermagnesemia.

The effects of Mg²⁺ excess are impaired neuromuscular excitability (hyporeflexia) that may even lead to respiratory arrest, disorders of cardiac action potential generation and propagation, vomiting, and constipation (→ A8).
A. Deranged Magnesium Metabolism

1. Deficient supply
2. Pars ascendens
3. Malabsorption
4. Insulin
5. Magnesium uptake into cells
6. Excess supply
7. Uptake into cells
8. Hypermagnesemia

- Cardiac arrhythmias
- Neuromuscular excitability
- Hyporeflexia
- Respiratory arrest
- Constipation
- Vomiting

- Renal retention
- Diabetes mellitus
- Insulin

- Tachycardia
- Blood pressure
- Neuromuscular excitability
- Hyperreflexia
- Cramps

- PTH
- Calcium

- Hypomagnesemia

- Insulin
- Magnesium
- FA
- TG
- Lipases
- Pancreatitis

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Abnormalities of Calcium Balance

Ca\(^{2+}\), as “intracellular transmitter”, mediates electromechanical coupling. It stimulates the release of neurotransmitters (synaptic transmitters) and hormones, the secretory activity of exocrine glands and of a number of enzymes (e.g., glycogenolysis, phospholipase A, adenyllycyclase, phosphodiesterases). Ca\(^{2+}\) activates some K\(^+\) channels, for example, in the heart, where Ca\(^{2+}\)-sensitive K\(^+\) channels take part in the process of repolarization. Extracellular Ca\(^{2+}\) stabilizes Na\(^+\) channels, reduces the permeability of the basement membranes and the tight junctions, and plays a role in blood clotting.

The regulation of the extracellular Ca\(^{2+}\) concentration is, in the first instance, the task of PTH. It is normally released in hypocalcemia and its action increases the plasma concentration of Ca\(^{2+}\) (\(\rightarrow A\), A2). PTH stimulates the mobilization of calcium phosphate from bone, decreases the plasma concentration of phosphate by inhibiting its renal reabsorption, and stimulates the formation of calcitriol, which promotes the enteric absorption of Ca\(^{2+}\) and phosphate, and thus aids in the mineralization of the bones.

Hypocalcemia (\(\rightarrow A\)) can be the result of reduced PTH release (hypoparathyroidism) or effect (pseudohypoparathyroidism). In addition, vitamin D deficiency can lead to hypocalcemia via a diminished formation of calcitriol. In renal failure phosphate elimination by the kidney is reduced, the plasma phosphate level rises, and calcium phosphate is deposited in the body (\(\rightarrow p.110\)). One of the consequences is hypocalcemia. Mg\(^{2+}\) deficiency also leads to hypocalcemia, especially if there is no stimulation of PTH release.

Even when the total Ca\(^{2+}\) concentration in blood is normal, the concentration of the effective ionized Ca\(^{2+}\) may be reduced because of increased formation of complexes with proteins (in alkalosis), bicarbonate (in metabolic alkalosis), phosphate (in renal failure, see above), and fatty acids (in acute pancreatitis; \(\rightarrow p.126, 158\)) (\(\rightarrow A\)).

Hypercalcemia (\(\rightarrow A\)) occurs in hyperparathyroidism and vitamin D excess. Malignant tumors with bone metastases lead to an increased mobilization of calcium phosphate from bone and thus to hypercalcemia. Occasionally malignant tumors will, even in the absence of skeletal metastases, produce bone-mobilizing hormones such as osteoclast-activating factor (OAF). Lastly, minerals in bone will be mobilized on acute immobilization associated with atrophy of inactivity. Increased enteric Ca\(^{2+}\) absorption is brought about by an excessive supply of Ca\(^{2+}\) and alkaline substances (milk-alkali syndrome).

The clinically most significant effect of hypocalcemia is an increased excitability of muscles and nerves with the occurrence of involuntary muscle spasms (tetany) and paresthesias (\(\rightarrow A4\)). The increased excitability is probably due to the lowered threshold of Na\(^+\) channels in hypocalcemia. In severe cases epileptic seizures may occur (\(\rightarrow p.338\)). Hypocalcemia triggers a lengthening of the action potential in the heart because of the delayed activation of the K\(^+\) channels, resulting in prolongation of the ST segment and QT interval in the ECG.

The effects of hypercalcemia (the condition is often asymptomatic) may include gastrointestinal symptoms (peptic ulcers due to stimulation of gastrin release and inhibition of pancreatic HCO\(_3^{-}\)-secretion by the Ca\(^{2+}\) receptor, nausea, vomiting, constipation), polyuria (inhibition of renal reabsorption due to closure of tight junctions and activation of the Ca\(^{2+}\) receptor), increased thirst with polydipsia, and psychogenic disorders (\(\rightarrow A5\)). If present for long, nephrolithiasis may result. If total plasma Ca\(^{2+}\) concentration is above 3.5 mmol/L (so-called hypercalcemia syndrome), coma, cardiac arrhythmias, and renal failure (mainly due to Ca\(^{2+}\) deposition in renal tissue) occur. An important indication of the presence of hypercalcemia syndrome is precipitation of calcium phosphate in the locally alkaline cornea (through loss of CO\(_2\); cataract; “keratitis”). In the ECG the ST segment is shortened in line with accelerated activation of the repolarizing K\(^+\) channels. Of great clinical significance in hypercalcemia is the increased sensitivity of the heart to digitalis, as this effect is normally mediated via an increased cytosolic Ca\(^{2+}\) concentration (\(\rightarrow p.182\)).
A. Deranged Calcium Metabolism

**Hypercalcemia**
- Heart:
  - Shortening of action potentials
  - Increased digitalis sensitivity
- Nephrocalcinosis, keratitis
- Psychiatric disorders
- Polyuria, magnesiuria, constipation, indigestion, nausea

**Hypocalcemia**
- Heart:
  - Prolonging of action potentials
  - Tetany, paresthesias
- Calcium retention, renal 
  - 
- Lack of mobilization
- Renal Ca\(^{2+}\) loss, renal HPO\(_4\)\(^{2-}\) retention

**25-OH-D\(_3\)**
- Alkali
- Inactivity
- Tumor cells
- Interleukin
- PTH
- Renal retention
- \(\text{Ca}^{2+}\)
- Calcitriol
- \(\text{Na}^+\)
- \(\text{K}^+\)
- Prot
- FS
- HPO\(_4\)\(^{2-}\)
- H\(^+\)
- Alkalosis

**D\(_3\) excess**
- \(\text{D}_3\) deficiency

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Abnormalities of Phosphate Balance

Phosphate is a constituent of a wide variety of compounds, for example, nucleotides (ATP, cAMP, cGMP, etc.), nucleic acids, creatine phosphate, intermediary substrates of carbohydrate metabolism (e.g., glucose phosphate), and phospholipids. Phosphate activates or inactivates many enzymes and is an essential buffer in cells and in urine. It also plays a significant role in the mineralization of bone.

PTH and calcitriol are essential for the regulation of phosphate balance. When kidney function is normal, PTH reduces the plasma phosphate level by inhibiting renal reabsorption, but at the same time it promotes the mobilization of phosphate in bone. Calcitriol raises the plasma phosphate level by stimulating its enteric absorption and renal reabsorption.

Abnormal phosphate metabolism can be caused by an uneven external balance or by changes in distribution within the body (intracellular and extracellular spaces; bone). The external balance is determined by the relationship between enteric absorption and renal excretion.

Phosphate deficiency can be the result of reduced enteric absorption, for example, the result of inadequate supply in food (common in alcoholics), due to malabsorption, vitamin D deficiency, or chronic intake of phosphate-binding aluminum hydroxide (→ A1). Renal loss of phosphate occurs in hyperparathyroidism, vitamin D deficiency, certain transport defects in the proximal tubules (phosphate diabetes, Fanconi’s syndrome; → p.96), and, to a lesser extent, in salt-losing nephritis, in expansion of the extracellular space, during diuretic treatment, and under the influence of glucocorticoids.

Phosphate excess can be caused by a large oral intake of phosphate as well as by vitamin D intoxication (→ A2). The renal elimination of phosphate is impaired in reduced filtration (renal failure) or if renal tubular reabsorption is raised (hypoparathyroidism).

The phosphate concentration is markedly higher in the cells than in the extracellular space (see also potassium; → p.124). For this reason shifts between intracellular and extracellular space play an important role in determining the plasma phosphate level. Uptake of phosphate by the cells occurs when phosphate is incorporated into the body’s metabolism, for example, the formation of glucose phosphate from free glucose. A dramatically increased uptake occurs after food intake by starving people and alcoholics, after insulin administration in diabetic coma, and in severe alkalosis (→ A3). This results in, at times marked, hypophosphatemia. Conversely, phosphate is released from cells in acidosis, diabetic coma, and cell damage (→ A4).

Lastly, an excess of phosphate can occur as a result of its mobilization from bone (e.g., by tumor, skeletal immobilization, hyperparathyroidism), unless its renal elimination is stimulated at the same time. In renal failure, skeletal demineralization, stimulated by hyperparathyroidism, contributes to the development of hyperphosphatemia (→ p.132).

The clinical effects of hypophosphatemia depend on the duration and extent of the abnormality. If the serum phosphate level is below 0.3 mmol/L, myopathy (muscular weakness, myolysis), heart failure, hemolysis, and nervous system dysfunction (convulsions, coma) will occur. The abnormalities are explained mainly by a reduced energy metabolism in the cells (ATP). The decrease of 2,3-bisphosphoglycerate (2,3-BPG) in erythrocytes leads to a decreased oxygen release to the tissues. Skeletal demineralization occurs in prolonged hypophosphatemia (osteomalacia; → p.132).

Effects of hyperphosphatemia include precipitation of calcium phosphate with the development of soft-tissue calcifications in tissues of low metabolic turnover (e.g., mucus bursae, joints, skin). Corresponding symptoms are itching (pruritus), joint pain (arthritis), etc. The plasma Ca2+ concentration falls and the release of PTH is stimulated. In renal failure a vicious circle develops (→ p.110ff.).
A. Deranged Phosphate Metabolism

1. Hypophosphatämie
   - Vitamin D₃ deficiency
   - Al(OH)₃
   - Inadequate supply, malabsorption
   - Renal loss
   - Cellular uptake ↑

2. Hyperphosphatemia
   - Glucose
   - Glucose phosphate
   - ATP etc.
   - Glucose phosphate
   - H⁺
   - 2,3-BPG
   - PTH
   - Vitamin D₃ supply
   - Calcitriol↑

3. Glucose phosphate
   - Ca²⁺
   - CaHPO₄ precipitation

4. Osteomalacia
   - Muscle weakness, myolysis, heart failure, hemolysis, seizures, coma
   - O₂ affinity of hemoglobin ↑

5. Osteomalacia
   - [Ca²⁺][HPO₄²⁻]↓
   - ATP etc.↓
   - 2,3-BPG

6. Urolithiasis
   - Arthritis
   - Pruritus
   - Ca²⁺↓

7. Increased supply and intestinal absorption
   - Renal retention
   - GFR↓ (30 mL/min)
   - Immobilization
   - Tumor cells
   - Bone demineralization
   - Interleukin
   - Cellular loss

8. Vitamin D₃ deficiency
   - Insulin deficiency
   - Acidosis

9. Insufficient supply, alkalinosis
   - Renal retention
   - Inadequate supply, malabsorption
   - Alkalosis

10. PTH
   - Insulin↑
   - Alkalosis

11. Bone demineralization
   - Pruritus
   - Arthritis

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Pathophysiology of Bone

Bone consists of connective tissue or bone matrix (sulfate-containing proteoglycans, glycoproteins and hydroxyproline-containing collagen fibers) and the bone minerals (alkaline salts of \( \text{Ca}^{2+} \), phosphate, \( \text{Na}^+ \), \( \text{CO}_3^{2-} \), \( \text{Mg}^{2+} \), \( \text{K}^+ \), and \( \text{F}^- \)).

**Construction and mineralization.** Formation of the bone matrix is promoted, among others, by insulin and inhibited by glucocorticoids.

Bone mineralization is inhibited by pyrophosphate (two esterified phosphoric acids). It is probably initiated through splitting of pyrophosphate by *alkaline phosphatase*. The plasma concentration of this enzyme, produced by osteoblasts, is a measure of osteoblast activity. The mineralization is fostered by increase of \( \text{Ca}^{2+} \) and phosphate plasma concentration—an effect of calcitriol. The formation of *calcitriol* (1,25-[OH]_2-D_3) occurs in several steps (→ A1): under the influence of ultraviolet light vitamin D_3 is formed in the skin from 7-dehydrocholesterol. Vitamin D_3 is converted in the liver to 25-OH-D_3 under the influence of estrogens, and in the kidney to 1,25-(OH)_2-D_3 under the influence of PTH. The building up of bone and mineralization are additionally stimulated by mechanical use of the bone.

The breaking down of the bone matrix leads to the increased renal excretion of hydroxyproline (→ A2), while demineralization leads to increased renal excretion of \( \text{Ca}^{2+} \) and phosphate (urothiasis; → A3).

The breakdown of bone is, among other factors, due to lacking mechanical stress (immobilization). Localized breakdown of bone can be caused by osteoclast activating factor (OAF), which in tumors results in demineralization of bone.

The most important abnormalities of bone are osteopenia (or osteoporosis) and osteomalacia (or rickets in children). Osteopenia is defined as reduction of bone mass below the norm for age, race, and sex, caused by prolonged imbalance between buildup and breakdown of bone. Osteoporosis is defined as the clinical state resulting from reduced bone mass (→ A4). Causes include excess glucocorticoids, lack of estrogen (postmenopausal), insulin deficiency (diabetes mellitus), and inactivity (rigid cast, tetraplegia, microgravity).

However, most often the cause remains unknown (primary osteoporosis).

**Effects of osteoporosis** include skeletal pain even at rest, intervertebral disc prolapse, lower arm or femoral neck fractures. Hypercalcemia may be present in extreme cases. Depending on its cause, the osteoporosis may be localized (e.g., under a rigid cast) or generalized (e.g., due to excess glucocorticoids).

In osteomalacia and rickets the mineralization of the bone matrix (osteoid) or of the growth plate is disturbed (→ A5). Before longitudinal growth is concluded and before epiphyseal fusion has occurred, the abnormality mostly leads to rickets (widening of the growth plates and distorted growth). After longitudinal growth has ceased the decreased mineralization of the newly formed osteoid (formed in the course of normal bone remodeling), leads to osteomalacia. Both rickets and osteomalacia can be caused by a reduced formation of calcitriol, for example, in lack of ultraviolet light and of vitamin D, by estrogen deficiency (postmenopausal), or by renal failure (→ p. 110ff.). Even without calcitriol deficiency, hypophosphatemia (phosphate diabetes, Fanconi’s syndrome; → p. 96, 110ff.) or chronic renal tubular acidosis can result in osteomalacia. Osteomalacia can occur in dialyzed patients who suffer from aluminum intoxication. Lastly, a rickets-like or osteomalacia-like clinical syndrome occurs in the rare, genetic deficiency of alkaline phosphatase (hypophosphatasia).

The effects of rickets are retarded growth, bow-legs or knock-knees, vertebral column deformities, prominence of the costochondral junctions (rachitic rosary) as well as thin and soft cranial, particularly occipital, bones (cranio-tabes). Osteomalacia leads to bone pain (pain on movement), translucent bands of demineralization in bone (pseudofractures or Looser’s zones), and muscular weakness (\( \text{Ca}^{2+} \) deficiency).
A. Bone Diseases

1. Estrogen deficiency — Dehydrocholesterol ↓ — UV light ↓ — Vit. D₃ — Diet

2. 1,25-(OH)₂-D₃ (Calcitriol)

3. Renal failure

4. Glucocorticoids ↑

5. Osteomalacia

Bone pain, spine deformation, fractures, muscle weakness

Osteoporosis

Skeletal pain, vertebral prolapse, fractures of ulnar, radius or neck of femur

Function of the Gastrointestinal Tract

To cover the material and energy demands of the organism food must be swallowed, processed and broken down (digestion) as well as taken up (absorption) by the intestine. Solid foods are chewed by the teeth, each bite being mixed with saliva from the salivary glands. Saliva contains mucin, a lubricant, and antibodies as well as α-amylase to digest polysaccharides. It is the task of the esophagus to rapidly transport the food from the throat to the stomach. The lower esophageal sphincter briefly opens, but otherwise prevents reflux of the potentially harmful gastric juice. The proximal stomach primarily serves to store food taken up during a meal. Its muscle tone determines the supply to the distal stomach, where the food is processed (broken up further and emulsified). Proteins are denatured and broken down by the gastric acid and pepsins, and lipases begin fat digestion. The distal stomach also has the task of apportioning chyme. In addition, the stomach secretes the intrinsic factor that is essential for the absorption of cobalamin (vitamin B₁₂).

The breakdown of food particles is completed in the small intestine by means of enzymes from the pancreas and the mucosa of the small intestine. The HCO₃⁻ ions of the pancreatic juice are needed to neutralize the acidic chyme. Fat digestion in addition requires bile salts supplied in bile. The products of digestion (monosaccharides, amino acids, dipeptides, monoglycerides, and free fatty acids) as well as water, minerals, and vitamins are absorbed in the small intestine.

Together with the bile secreted by the liver, excretory products (e.g., bilirubin) reach the stool. The liver has numerous additional metabolic functions: it is the obligatory intermediate station for almost all substances absorbed from the small intestine, and it is able to detoxify numerous foreign substances and metabolic end-products and to bring about their excretion.

The large intestine is the last station for water and ion absorption. It is colonized by bacteria with physiological functions. The large intestine, especially the caecum and rectum, are also storage places for the feces, so that defecation is necessary relatively rarely, despite frequent food intake.

The two plexuses in the wall of the esophagus, stomach, and intestine serve to control motility and secretion, with superregional reflexes and modulating influences of the central nervous system transmitted via the autonomic nervous system and visceral–afferent nerve tracts. In addition, the gastrointestinal tract secretes numerous peptide hormones and transmitters that participate in controlling and regulating the gastrointestinal tract and its accessory glands.

There are many nonspecific and specific mechanisms which defend against pathogenic organisms on the inner surface (ca. 100 m²) of the gastrointestinal tract. Beginning at the mouth, components in saliva, such as mucins, immunoglobulin A (IgA), and lysozyme, inhibit microorganisms invading. Hydrochloric acid and pepsins have a bactericidal effect, and Peyer’s patches in the gastrointestinal tract are their own immunocompetent lymph tissue. Special M cells (“membranous cells”) of the mucosa provide luminal antigens with access to Peyer’s patches, which can respond with release of IgA (oral immunization or, as an abnormal process, allergization). IgA is combined in the intestinal epithelium with the secretory component which protects the secreted IgA against digestive enzymes. Macrophages in the intestinal wall and in the sinusoids of the liver (Kupffer cells) form a further barrier against invading pathogenic organisms.
A. Function of Organs of the Gastrointestinal Tract

**Mouth**
- Tasting,
- chewing,
- forming food bolus

**Saliva**
- Lubrication,
- rinsing,
- digesting

**Esophagus**
- Transport

**Liver**
- Bile (excretion, fat digestion),
- metabolism,
- detoxication

**Gallbladder**
- Storage of bile

**Pancreas (exokrine)**
- Digestive enzymes,
- $\text{HCO}_3^-$ as $\text{H}^+$ buffer

**Proximal stomach**
- Storage

**Distal stomach**
- Preparation,
- digestion,
- apportioning

**Small intestine**
- Digestion,
- absorption

**Cecum**
- Storage

**Colon**
- Absorption

**Rectum**
- Storage,
- excretion
Esophagus

The musculature in the upper third of the esophageal wall is partly made up of striated muscle, partly of smooth muscle. On swallowing (deglutition) the upper esophageal sphincter opens reflexly and a (primary) peristaltic reflex wave moves the bolus of food into the esophagus. Here the dilation by the bolus initiates further (secondary) peristaltic waves that continue until the bolus has reached the stomach. The lower esophageal sphincter is opened by a vagovagal reflex at the beginning of the swallowing action. This receptive relaxation reflex is mediated by the inhibitory noncholinergic nonadrenergic (NCNA) neurones of the myenteric plexus (\(\rightarrow A\)).

Esophageal motility, for example, the progression of the peristaltic wave, is usually tested by pressure measurements in the various segments of the esophagus (\(\rightarrow A1,2\)). The resting pressure within the lower esophageal sphincter is ca. 20–25 mmHg. During receptive relaxation the pressure falls to the few mmHg that prevail in the proximal stomach (\(\rightarrow A3\)), indicating opening of the sphincter.

The lower esophageal sphincter is usually closed, just like its upper counterpart. This barrier against reflux of the harmful gastric juice (pepsin and HCl) is strengthened when the sphincter pressure is raised (\(\rightarrow B\)), for example, by the action of acetylcholine liberated from the ganglion cells of the myenteric plexus, or by adrenergic agonists, by hormones, such as gastrin (reflux protection during digestive gastric motility), motilin (reflux protection during interdigestive motility), somatostatin, and substance P, by paracrine action (histamine, PGF\(_{2\alpha}\)), or by protein-rich food, or by high intra-abdominal pressure (contraction of abdominal muscles, obesity, ascites). This pressure would tear open the sphincter but for the fact that part of the 3–4 cm long lower esophageal sphincter lies within the abdominal space. As a consequence, the sphincter pressure is increased (from outside) in proportion to the increase in intra-abdominal pressure. Furthermore, parts of the diaphragm surround the lower esophageal sphincter (left and right crux) in a scissor-like manner, so that the sphincter is automatically clamped when the diaphragm contracts. An intact phrenico-esophageal ligament (\(\rightarrow E1\)) and a relatively acute angle of His between the end of the esophagus and the stomach are also important in providing reflux protection during swallowing.

Factors that lower sphincter pressure will promote reflux. Among these are vasoactive intestinal polypeptide (VIP) and ATP, the transmitters of the inhibitory NCNA neurones as well as dopamine and \(\beta\)-adrenergic agonists, hormones such as secretin, cholecystokinin (CCK), progesterone, and glucose-dependent insulintropic peptide (GIP = formerly: gastric inhibitory polypeptide), paracrine substances (NO, PGI\(_2\), PGE\(_2\)), a progestosterone effect during pregnancy, food with a high fat content, and many others.

Sporadic reflex of gastric juice is an everyday physiological event, either from unexpected pressure on a full stomach, or during swallowing (opening of sphincter for a few seconds; \(\rightarrow B5\), right), or during transient openings of the sphincter (\(\rightarrow B5\), left) that last up to half a minute and are triggered by marked dilation of the stomach wall and not by the act of swallowing. These transient sphincter openings are probably part of the expulsion reflex through which swallowed air and CO\(_2\) can be expelled from the stomach. The fact that significant reflux occurs as a consequence can be concluded from the marked drop in pH in the distal esophagus (\(\rightarrow B4\)).

Three mechanisms are responsible for protecting the esophageal mucosa after reflux:

\(\blacktriangledown\) Volume clearance, i.e., the rapid replacement of reflux volume into the stomach by the esophageal peristalsis reflex. Reflux volume of 15 mL, except for a small residual amount, normally remains in the esophagus for only five to 10 seconds (\(\rightarrow B1\)).

\(\blacktriangledown\) pH clearance. Residual gastric juice, left behind by the volume clearance, has an unchanged, low pH. It only rises, step by step (\(\rightarrow B2\)), with each act of swallowing (\(\rightarrow B3\)), i.e., the swallowed saliva buffers the residual
A. Motility of Esophagus

Pharynx
Upper sphincter
Striated muscles
Smooth muscles

Vagus n.
Cholinergic fibers excite: shortening
NCNA fibers inhibit: opening

Neuronal control of sphincter

B. Pressure, Volume, and pH Clearance of Distal Esophagus

Acetylcholine, α-adrenergic agonists, hormones, protein-rich food, histamine, high intra-abdominal pressure, PGF$_{2α}$, etc.

Increased pressure in esophageal sphincter

Inhibits reflux

VIP, β-adrenergic agonists, hormones, dopamine, NO, PGI$_2$, PGE$_2$, chocolate, acid gastric juice, fat, smoking, etc.

Decreased pressure in esophageal sphincter

Promotes reflux

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reflux volume. pH clearance is dependent on the amount and buffering capacity of saliva.

The wall of the esophagus contains epithelium with barrier properties. Of its 25–
30 cell layers (→ E, right) it is particularly the stratum corneum (ca. 10 layers) located
at the luminal aspect that is especially dense. This largely prevents the invasion of the
harmful components of gastric juice (H⁺ ions, pepsin, and sometimes bile salts). Additionally, as in the gastric mucosa (→ p.144), H⁺ ions that have penetrated into the cells are very efficiently removed to the outside (Na⁺/H⁺ exchange carrier), and also a small number of HCO₃⁻ ions are secreted.

The most important functional disorders of the esophagus are caused by abnormal
esophageal contraction (hypermotility or hypomotility, disordered coordination) or failure
of the protective mechanisms to cope with reflux (gastroesophageal reflux disease).

Hypermotility may be caused by a thickened muscular layer, an increased sensitivity of
the muscle toward excitatory transmitters (acetylcholine), or hormones (e.g., gastrin),
or a reduced sensitivity toward inhibitory transmitters (e.g., VIP). Hypermotility may also
be due to increased neuronal activity of cholinergic neurones or diminished activity
of inhibitory NCNA neurones. The latter is true of achalasia (→ C). This is caused by a
reduction in the number of intramural NCNA neurones as well as diminished reactivity of
these neurones to preganglionically liberated acetylcholine. As a result of this disorder,
patients with achalasia have a greatly elevated resting pressure in the lower esopha-
geal sphincter, receptive relaxation sets in late and, most importantly, is too weak, so
that during the reflex phase the pressure in the sphincter is markedly higher than that
in the stomach (→ C, bottom). As a result, swallowed food collects in the esophagus,
causing a pressure rise throughout and under certain circumstances leading to an enor-
mous dilation of the esophagus (→ C). Furthermore, propagation of the peristaltic
wave ceases (see also A1,2 and C, right). Thus, the symptoms of achalasia are dyspha-
gia (trouble swallowing), regurgitation of food (not vomiting), retrosternal pain, and

weight loss. Serious complications of achalasia are esophagitis and pneumonia, caused by
aspiration of esophageal contents (containing bacteria).

Hypomotility of the esophagus is caused by factors that are the opposite of those
described above. In scleroderm (→ D), an au-
toimmune disease, hypomotility in its early
stages is due to neuronal defects that later
result in atrophy of the smooth muscles of
the esophagus, so that peristalsis in the distal
portion ultimately ceases altogether. Con-
trary to achalasia, the lower sphincter pres-
sure is reduced, so that gastroesophageal re-
flux disease develops.

Gastroesophageal reflux disease (→ E). Re-
flux of gastric juice into the esophagus is to
some extent a physiological phenomenon
(see above); heart burn indicates reflux
esophagitis. This can be caused by:

- factors that diminish the pressure in the
  lower esophageal sphincter (→ B,D);
- increased frequency of transient sphincter
  opening (swallowing air, drinks containing
  CO₂);
- decreased volume clearance (abnormal
distal esophageal peristalsis);
- slowed pH clearance, for example, due to
decreased salivary flow (sleep, chronic
saliva deficiency [xerostomia]), or de-
creased buffering capacity of the saliva
(smoking cigarettes);
- hiatus hernia, in which the abdominal
  part of the esophagus is displaced into
  the thorax, so that an important mecha-
nism of sphincter closure, increased in-
tra-abdominal pressure, is absent;
- direct irritation and damage to the esopha-
geal mucosa, for example, by citrus fruits,
tomato-based foods, hot spices, high-
proof alcohol, and nonsteroid anti-inflam-
myatory drugs (NSAIDs; → p.142).

The result of chronic esophageal reflux is
epithelial metaplasia (→ p.4) in the distal
esophagus that, as a precancerous condition,
can develop into cancer.
C. Achalasia

- Excitation of the NCNA neurons
- Sphincter pressure too high
- Weight loss
- Trouble swallowing
- Pain

Swallowing

Distal esophagus

Lower sphincter

Stomach

Sphincter pressure too low

Diaphragm

Esophagogastric border

E. Gastroesophageal Reflux Disease

- Transient sphincter opening (air, CO₂)
- Saliva production (in sleep, xerostomia)
- Buffering capacity of saliva (e.g. through smoking)

Sphincter pressure

Abnormal peristalsis

Volume clearance

pH clearance

Hiatus hernia

Defective mucosal protective mechanism (e.g. alcohol)

Reflux esophagitis

Epithelial metaplasia

Carcinoma

Phrenico-esophageal ligament

Diaphragm

Esophagogastric border

D. Scleroderma

- Neuronal defects
- Muscle atrophy
- no peristalsis in smooth muscles
- Hypomotility

Swallowing

Sphincter pressure too low

Gastroesophageal reflux disease

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Nausea and Vomiting

Vomiting, with its precursor warning signs of nausea and retching, is mainly a protective reflex, but also an important symptom. Chronic vomiting causes severe disorders.

The vomiting center, located in the medulla oblongata (→ A, top), is reached, among others, via chemoreceptors of the area postrema on the bottom of the 4th ventricle (chemoreceptor trigger zone [CTZ]), where the blood–brain barrier is less tight. CTZ is activated by dopamine agonists such as apomorphine (therapeutic emetic), by numerous drugs or toxins, for example, digitalis glycosides, nicotine, staphylococcal enterotoxins as well as hypoxia, uremia, and diabetes mellitus. The CTZ cells also contain receptors for neurotransmitters (e.g., epinephrine, serotonin, GABA, substance P), allowing neurons access to the CTZ.

However, the vomiting center can also be activated without mediation by the CTZ, such as during unphysiological stimulation of the organs of balance (kinesia [motion sickness]). In addition, diseases of the inner ear (vestibule), such as Ménière’s disease, cause nausea and vomiting.

The vomiting center is activated from the gastrointestinal tract via vagal afferents:
- on overstretching of the stomach or damage to the gastric mucosa, for example, by alcohol;
- by delayed gastric emptying, brought about by autonomic nervous efferents (also from the vomiting center itself), by food which is difficult to digest as well as by blockage of the gastric exit (pyloric stenosis, tumor), or of the intestine (atresia, Hirschsprung’s disease, ileus) (→ p. 156);
- by overdistension and inflammation of the peritoneum, biliary tract, pancreas, and intestine.

Finally, visceral afferents from the heart may also cause nausea and vomiting, for example, in coronary ischemia. Nausea and vomiting are common during the first trimester of pregnancy (vomitus matutinus). Exceptional disturbances (see below) due to the vomiting may occur (hyperemesis gravidarum). Psychogenic vomiting occurs mostly in (non-pregnant) young women, brought about by sexual conflicts, problems in the home environment, loss of parental attention, etc. Vomiting can be precipitated deliberately by putting a finger into the throat (afferent nerves from touch sensors in the pharynx). It may occasionally provide relief, but frequent vomiting by patients with bulimia (→ p. 26) may lead to serious consequences (see below).

Finally, exposure to radiation (e.g., in the treatment of malignancy) and raised intracranial pressure (intracranial bleeding, tumors) are important clinical factors in precipitating nausea and vomiting.

The consequences of chronic vomiting (→ A, bottom) are brought about by diminished food intake (malnutrition) and by loss of gastric juice, together with the loss of swallowed saliva, drinks, and sometimes also of small-intestinal secretions. The result is hypovolemia. Release of ADH, initiated by the vomiting center, favors retention of water; the excessive loss of NaCl and relatively small loss of H2O leads to hyponatremia which is exacerbated by increased excretion of NaHCO3. The latter is a response to a non-respiratory alkalosis. This results from the parietal cells of the stomach passing one HCO3− ion for each H+ ion secreted into the lumen. While the H+ ions (10–100 mmol/L gastric juice) are lost with the vomit, and therefore do not use up any HCO3− to buffer them in the duodenum, HCO3− accumulates in the organism. The alkalosis is made worse by hypokalemia; K+ is lost both with the vomit (food, saliva, and gastric juice) and the urine. The hypovolemia leads to hyperaldosteronism, during which K+ excretion increases in the course of increased absorption of Na+ (→ p. 98 and 122 ff).

The act of vomiting and the vomit cause further damage, namely gastric rupture, tears in the esophageal wall (Mallory–Weiss syndrome), dental caries (due to acid), inflammation of the oral mucosa, and aspiration pneumonia are the most important potential consequences.
A. Causes and Consequences of Vomiting

- Apomorphine, nicotine, digitalis, uremia, bacterial toxins, hypoxia, etc.
- Chemoreceptor trigger zone (area postrema)
- Medulla oblongata
- ‘Vomiting center’ (reticular formation)
- ADH (see below)
- Warning signs:
  - Outbreak of sweat
  - Flow of saliva
  - Wide pupils
  - Nausea
  - Pallor
  - Retching
- Loss of gastric juice
- Food uptake ↓
- Chronic
  - Loss of K⁺
  - Loss of Na⁺
  - Loss of H⁺
  - Hypovolemia
  - Renin
  - Angiotensin II
  - Aldosterone
  - ADH (s.o.)
  - H₂O excretion ↓
  - [Na⁺] in plasma ↓
  - NaHCO₃ excretion ↑
  - K⁺ excretion ↑
  - Hypokalemia
  - Hyponatremia
  - Nonresp. alkalosis
  - Malnutrition
- Distension
- Inflammation
- Intestinal obstruction
- ‘Heavy’ meal
- Gastric rupture
- Mallory-Weiss syndrome
- Esophageal rupture
- Motion sickness, vestibular disease
- Exposure to radiation
- Psychogenic
- Pregnancy
- ADH
- Inflammation and overtension of peritoneum, bile passages, pancreas, intestine, etc.
- Food uptake ↓
- Loss of Na⁺
- Loss of K⁺
- Loss of H⁺
- Hypovolemia
- Renin
- Angiotensin II
- Aldosterone
- ADH (s.o.)
- H₂O excretion ↓
- [Na⁺] in plasma ↓
- NaHCO₃ excretion ↑
- K⁺ excretion ↑
- Hypokalemia
- Hyponatremia
- Nonresp. alkalosis
- Malnutrition
- Outbreak of sweat
- Flow of saliva
- Wide pupils
- Nausea
- Pallor
- Retching
- Gastric rupture
- Mallory-Weiss syndrome
- Esophageal rupture
- Motion sickness, vestibular disease
- Exposure to radiation
- Psychogenic
- Pregnancy
- ADH
- Inflammation and overtension of peritoneum, bile passages, pancreas, intestine, etc.
Gastritis

Simplifying the situation somewhat, one can differentiate three main types of gastritis: - erosive and hemorrhagic gastritis - nonerosive, chronic active gastritis - atrophic (fundal gland) gastritis (As complete inflammatory reaction is often absent in many cases of gastritis, the term gastropathy is now often used).

Erosive and hemorrhagic gastritis (→ A1) can have many causes, for example: - intake of nonsteroidal anti-inflammatory drugs (NSAIDs), whose local and systemic mucosa-damaging effect is described in greater detail on p. 146; - ischemia (e.g., vasculitis or while running a marathon); - stress (multi-organ failure, burns, surgery, central nervous system trauma), in which the gastritis is probably in part caused by ischemia; - alcohol abuse, corrosive chemicals; - trauma (gastroscope, swallowed foreign body, retching, vomiting, etc.); - radiation trauma. This type of gastritis can quickly produce an acute ulcer (e.g., through stress or NSAIDs; → p.146), with the risk of massive gastric bleeding or perforation of the stomach wall (→ A1).

Nonerosive, chronic active gastritis (type B; → A2) is usually restricted to the antrum. It has become increasingly clear in the last decade that its determining cause is a bacterial colonization of the antrum with Helicobacter pylori, which can be effectively treated with antibiotics (see also ulcer; → p.144 ff). Helicobacter colonization not only diminishes mucosal protection, but can also stimulate antral gastrin liberation and thus gastric juice secretion in the fundus, a constellation that favors the development of chronic ulcer.

A fourth type, reactive gastritis, (→ A4) occurs in the surroundings of erosive gastritis (see above), of ulcers or of operative wounds. The latter may partly be caused after operations on the antrum or pylorus by enterogastric reflux (reflux gastritis), resulting in pancreatic and intestinal enzymes and bile salts attacking the gastric mucosa. On the other hand, the alkaline milieu of the intestinal juice counteracts gastrin release and is also a hostile medium for Helicobacter pylori. (For similar reasons, Helicobacter colonization is diminished in atrophic gastritis.)

Atrophic (fundal gland) gastritis (type A; → A3), most often limited to the fundus, has completely different causes. In this condition the gastric juice and plasma usually contain autoantibodies (mainly immunoglobulin G, infiltrates of plasma cells, and B lymphocytes) against parts and products of parietal cells (→ A, upper right), such as microsomal lipoproteins, gastrin receptors, carboxyhydrase, H⁺/K⁺-ATPase, and intrinsic factor (IF). As a result, the parietal cells atrophy with the effect that acid and IF secretion falls markedly (achlorhydria). IF antibodies also block the binding of cobalamines to IF or the uptake of IF–cobalamine complexes by cells in the ileum, ultimately resulting in cobalamine deficiency with pernicious anemia (→ blood, p. 34). In atrophic gastritis more gastrin is liberated in response to this, and the gastrin-forming cells hypertrophy. Hyperplasia of the enterochromaffin-like (ECL) cells occurs, probably as a consequence of the high level of gastrin. These cells carry gastrin receptors and are responsible for producing histamine in the gastric wall. This ECL cell hyperplasia can sometimes progress to a carcinoma. However, the main danger in atrophic gastritis is extensive metaplasia of the mucosa which, as a precancerous condition, may lead to carcinoma of the stomach.

Except for Helicobacter pylori, gastritis is only rarely caused by a specific microorganism such as Mycobacterium tuberculosis, cytomegalovirus, or herpes virus, or by fungi (e.g., Candida albicans). However, these gastritides are not uncommon in immunocompromised patients (AIDS, immunosuppression with organ transplantation, etc.).
Plate 6.5 Gastritis

1. Erosive and hemorrhagic gastritis

2. Chronic active antral gastritis (Type B)
   - Gastrin↑
   - Acid secretion normal or increased

3. Atrophic fundal gland gastritis (Type A)
   - Pepsinogen↓
   - Acid secretion↓
   - IF secretion↓
   - Gastrin↑
   - Cobalamin absorption↓

4. Reactive gastritis
   - Epithelial metaplasia
   - ECL-cell hyperplasia
   - G-cell hyperplasia

- NSAIDs, alcohol
- Multi-organ failure, burns
- Trauma
- Ischemia
- Helicobacter pylori infection

- Autoantibodies
- Carbonic anhydrase
- Parietal cell
- H^+ / K^+ - ATPase
- Lumen
- IF

- NSAIDs, alcohol
- Multi-organ failure, burns
- Trauma
- Ischemia
- Helicobacter pylori infection

- Reactive gastritis
- Epithelial metaplasia
- ECL-cell hyperplasia
- G-cell hyperplasia

- Carcinoid
- Pernicious anemia

- Bleeding
- Perforation

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Ulcer

The H⁺ ions in gastric juice are secreted by the parietal cells that contain H⁺/K⁺-ATPase in their luminal membrane, while the chief cells enrich the glandular secretion with pepsinogen (→ A). The high concentration of H⁺ (pH 1.0–2.0) denatures the food proteins and activates pepsinogens into pepsins which are endopeptidases and split certain peptide bindings in food proteins.

The regulation of gastric secretion (→ A1) is achieved through neural, endocrine, paracrine, and autocrine mechanisms. Stimulation is provided by acetylcholine, the post-ganglionic transmitter of vagal parasympathetic fibers (muscarinic M₁ receptors and via neurons stimulating gastrin release by gastrin-releasing peptide [GRP]), gastrin (endocrine) originating from the G cells of the antrum, and histamine (paracrine, H₂ receptor), secreted by the ECL cells and mast cells of the gastric wall. Inhibitors are secretin (endocrine) from the small intestine, somatostatin (SIH; paracrine) as well as prostaglandins (especially E₂ and L₂), transforming growth factor α (TGF-α) and adenosine (all paracines and autocrines). The inhibition of gastric secretion by a high concentration of H⁺ ions in the gastric lumen is also an important regulatory mechanism (negative feedback; → A1, left).

Protection of the gastric and duodenal mucosa. Because the acid–pepsin mixture of gastric secretion denatures and digests protein, the protein-containing wall of the stomach and duodenum has to be protected from the harmful action of gastric juice. The following mechanisms are involved in this (→ A2):

a A gel-like mucus film, 0.1–0.5 mm thick, protects the surface of the gastric epithelium. The mucus is secreted by epithelial cells (and depolymerized by the pepsins so that it can then be dissolved).

b The epithelium secretes HCO₃⁻ ions that are enriched not only in the liquid layer directly over the epithelium, but also diffuse into the mucus film, where they buffer H⁺ ions that have penetrated from the gastric lumen. Prostaglandins are important stimulants of this HCO₃⁻ secretion.

c In addition, the epithelium itself (apical cell membrane, tight junctions) has barrier properties that largely prevent the penetration of H⁺ ions or can very effectively remove those H⁺ ions that have already penetrated (Na⁺/H⁺ exchange carrier only basolaterally). These properties are regulated, among others, by the epidermal growth factor (EGF) contained in saliva and bound to receptors of the apical epithelial membrane. Glutathione-dependent, antioxidative mechanisms are also part of this cytoprotection.

d Finally, good mucosal blood flow serves as the last “line of defense” that, among other actions, quickly removes H⁺ ions and provides a supply of HCO₃⁻ and substrates of energy metabolism.

Epithelial repair and wound healing. The following mechanisms repair epithelial defects that occur despite the protective factors listed above (→ B, bottom left):

The epithelial cells adjoining the defect are flattened and close the gap through sideward migration (→ p. 4) along the basal membrane. This restitution takes about 30 minutes.

Closing the gap by cell growth takes longer (proliferation; → p. 4). EGF, TGF-α, insulin-like growth factor (IGF-1), gastrin-releasing peptide (GRP), and gastrin stimulate this process. When the epithelium is damaged, especially those cell types proliferate rapidly that secrete an EGF-like growth factor.

If ultimately the basement membrane is also destroyed, acute wound healing processes are initiated: attraction of leukocytes and macrophages; phagocytosis of necrotic cell residua; revascularization (angiogenesis); regeneration of extracellular matrix as well as, after repair of the basement membrane, epithelial closure by restitution and cell division.

The danger of epithelial erosion and subsequent ulcer formation exists whenever the protective and reparative mechanisms are weakened and/or the chemical attack by the acid–pepsin mixture is too strong and persists for too long (→ A3 and B, top). Gastric and duodenal ulcers may thus have quite different causes.
A. Gastric Juice Secretion, Mucosal Protection and Risk of Ulcer

1 Formation of gastric juice

Vagus n.
H⁺ Pepsin

Gastrin
Protein digestion

Tubular gland

Acetycholine Gastrin Histamine
M₁ receptors H₂ receptors
Parietal cell Chief cell

Secretin SIH PG₄ PG₁₂ Adenosine TGFα

2 Mucosal protection

a Mucus film
Pepsin H⁺

b HCO₃⁻ secretion
pH1 pH3 pH7
Buffering: 
HCO₃⁻ + H⁺ → CO₂ + H₂O

H⁺

Prostaglandins
EGF (in saliva)

Blood supply

Mucosa Submucosa Circular smooth muscle Longitudinal muscle Ulcer

3 Danger of ulcer

Helicobacter pylori
Secretion of gastric juice ↑↑
HCO₃⁻ secretion ↓
Cell formation ↓
Blood perfusion ↓
Infection with Helicobacter pylori (H. pylori) is the most common cause of ulcer. As a consequence, administration of antibiotics has been shown to be the most efficacious treatment in most ulcer patients not receiving nonsteroidal anti-inflammatory drugs (NSAIDs; see below). H. pylori probably survives the acidic environment of the mucus layer because it possesses a special urease. The bacterium uses this to produce CO₂ and NH₃, and HCO₃⁻ and NH₄⁺, respectively, and can thus itself buffer H⁺ ions in the surroundings. H. pylori is transmitted from person to person, causing inflammation of the gastric mucosa (gastritis, especially in the antrum; → p.142). A gastric or duodenal ulcer is ten times more likely to develop in such cases than if a person does not suffer from gastritis of this kind. The primary cause of such an ulcer is a disorder in the epithelium’s barrier function, brought about by the infection (→ B).

It is likely that, together with this ulcer formation due to the infection, there is also an increased chemical attack, as by oxygen radicals that are formed by the bacteria themselves, as well as by the leukocytes and macrophages taking part in the immune response, or by pepsins, because H. pylori stimulates pepsinogen secretion.

The fact that infection of the gastric antrum also frequently leads to duodenal ulcer is probably related to gastrin secretion being increased by the infection. As a result, acid and pepsinogen liberation is raised and the duodenal epithelium is exposed to an increased chemical attack. This causes metaplasia of the epithelium, which in turn favors the embedding of H. pylori, leading to duodenitis and increased metaplasia, etc.

A further common cause of ulcer is the intake of NSAIDs, for example, indomethacin, diclofenac, aspirin (especially in high doses). Their anti-inflammatory and analgesic action is based mainly on their inhibitory effect on cyclo-oxygenase, thus blocking prostaglandin synthesis (from arachidonic acid). An undesirable effect of NSAIDs is that they systemically block prostaglandin synthesis also in gastric and duodenal epithelia. This decreases HCO₃⁻ secretion, on the one hand (weakened mucosal protection; → B, top left), and stops inhibition of acid secretion, on the other (→ A1). In addition, these drugs damage the mucosa locally by nonionic diffusion into the mucosal cells (pH of gastric juice < pKᵦ of the NSAIDs). During intake of NSAIDs an acute ulcer may thus develop after days or weeks, the inhibitory action of these drugs on platelet aggregation raising the danger of bleeding from the ulcer.

Acute ulcers also occur if there is very severe stress on the organism (stress ulcer), as after major surgery, extensive burns, and multi-organ failure (“shock”). The main cause here is probably impaired blood flow through the mucosa correlated with high plasma concentrations of cortisol.

Often psychogenic factors favor ulcer development. Strong emotional stress without an outward “safety valve” (high cortisol levels) and/or disturbed ability to cope with “normal” stress, for example, in one’s job, are the usual causes. Psychogenically raised secretion of gastric acid and pepsinogen, as well as stress-related bad habits (heavy smoking, antiheadache tablets [NSAIDs], high-proof alcohol) often play a part.

Smoking is a risk factor for ulcer development. A whole series of moderately effective single factors seem to add up here (→ B). Alcohol in large quantities or in high concentration damages the mucosa, while moderate drinking of wine and beer increases gastric secretion through their nonalcoholic components.

Rare causes of ulcer are tumors that autonomically secrete gastrin (gastrinoma, Zollinger–Ellison syndrome), systemic mastocytosis, or basophilia with a high plasma histamine concentration.

Apart from antibiotics (see above) and (rarely necessary) surgical intervention, the treatment of ulcer consists of lowering acid and pepsinogen secretion by blocking H₂ and M₁ receptors (→ A1) and/or of H⁺/K⁺-ATPase. Treatment with antacids acts partly by buffering the pH in the lumen, but also has further, as yet not fully understood, effects on the mucosa.
B. Ulcer Formation

- Stress (shock, burns, operation)
- Indomethacin, diclofenac, acetylsalicylic acid, etc.
- Helicobacter pylori infection
- Smoking
- Prostaglandin synthesis
- Bile salts, pancreatic enzymes
- O₂ radicals
- Gastritis
- Psychogenic components
- Smoking
- Gastrinoma, etc.
- Barrier function disturbed
- Chemical aggression
- H⁺ secretion
- Pepsinogen secretion
- Blood perfusion
- O₂ radicals
- Smoking
- Mucosal protection
- Epithelial damage
- Rapid restitution through migration
- Covering defect through cell division
- Wound
- Granulation, angiogenesis, restitution of basal membrane
- Wound healing
- Ulcer
- Radiograph: Treichel J. Doppelkontrastuntersuchung des Magens, 2nd ed. Stuttgart: Thieme; 1990

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Disorders After Stomach Surgery

Gastric tumors are treated surgically by removing the stomach (gastrectomy [GE]) and replacing it with jejunal loops, or by gastric resection (Billroth I or II, or Roux). Treatment-resistant gastric ulcers have also been treated with selective vagotomy (VT). Non-selective VT is often unavoidable in tumor operations or when bleeding occurs. These procedures may result in undesirable functional disorders (→ A):

Surgical reduction of gastric volume and disordered accommodation and receptive relaxation reflexes after VT increase gastric wall tension when ingesting a normal meal; this leads to feeling full, nausea, and vomiting as well as premature satiety. A serious consequence is too rapid gastric emptying. This is due to: 1) an absent accommodation reflex that raises the pressure gradient from stomach to small intestine; 2) the “apportioning” antrum and pylorus are absent; and 3) gastric emptying into the small intestine is no longer inhibited. The latter is especially true in VT (no vagovagal reflex) and in gastric resection after Billroth II or Roux, in which chyme circumvents the duodenal chemoreceptors.

Consequences of too rapid gastric emptying are (→ A, bottom):

- **Too high a chyme volume** per unit time distends the intestinal wall and, via hormones and neurotransmitters, brings about nausea, vomiting, cramps, and pain as well as vasomotor reactions with cutaneous vascular dilation (flush), tachycardia, palpitations, and abnormal orthostatic regulation. This early dumping syndrome (occurring 30–60 min after food intake) is also in part due to:

- **Hypertonicity** of chyme that is emptied too quickly. Via osmotically obliged water secretion into the intestinal lumen, this chyme also: 1) increases intestinal distension; 2) results in diarrhea; and 3) leads to further cardiovascular reactions that are initiated by the resulting hypovolemia.

- Furthermore, the secreted water dilutes the enzymes and bile salts in the intestinal lumen. This dilution can be critical, for example, for the liberation of heme-iron from hemo-
moglobin in food or for absorption of fat including the fat-soluble vitamin D (see below).

- High concentrations of carbohydrate and especially sugar (e.g., marmelade) in chyme also cause symptoms because the rapid absorption of glucose causes a high hyperglycemia peak that 90–180 minutes after food intake followed by reactive hypoglycemia due to the release of insulin (confusion, loss of consciousness), the so-called late dumping syndrome.

- Rapid gastric emptying also exceeds the digestive capacity of the upper small intestine. Moreover, VT results in a halving of pancreatic secretion, and in Billroth II the upper duodenum does not receive the flow of chyme, so that there is no physiological stimulus for secretin and CCK secretions. As a result, the distal small intestine takes part in the digestion and absorption of nutrients. Its chemoreceptors are intensively involved in initiating reflexes and hormonal signals that bring about the feeling of premature satiety (see above), so that these patients eat too little and lose weight. Deficient chyme preparation is partly responsible for the distal shift of digestion and absorption. After distal gastric resection, the pieces of food leaving the stomach are too large (>2 mm). As one third of iron in food comes from hemoglobin (in meat), incomplete digestion of oversized food particles diminishes the availability of heme-iron.

Billroth II (but not Roux-Y) gastrectomy can lead to the blind loop syndrome (→ p. 34 and 152).

Reduced H⁺ secretion in the stomach decreases the liberation of iron in food and the absorption of Fe(II). Loss of the sources of iron will ultimately lead to iron-deficiency anaemia (→ p. 38).

Additionally, when the number and activity of the parietal cells is diminished, the secretion of intrinsic factor is also reduced. If it falls below 10% of ist normal value, cobalamin absorption is affected so that (long-term) cobalamin deficiency can arise and the anemia is further aggravated (→ p. 34). Osteomalacia will ultimately result from Ca²⁺ and vitamin D deficiency (→ p.132).
A. Disorders After Stomach Surgery

1. **Disorders After Stomach Surgery**

2. **Gastric resection**
   - Billroth II operation
   - Vagotomy (VT)

3. **Gastric volume**
   - Wall distension
   - Glucose absorption
   - Intestinal distension

4. **Accommodation reflex**
   - Vomiting, pain
   - Flushing, tachycardia

5. **Emptying**
   - Hypoglycemia
   - Vasomotor reactions
   - Diarrhea

6. **Preparation of chyme**
   - Hypo-volemia
   - Dilution of enzymes and bile salts

7. **Pancreatic secretion**
   - Fat absorption
   - Fe absorption
   - Fe salts

8. **Gastric secretion**
   - Heme-Fe availability
   - IF deficiency
   - Fe deficiency

9. **Digestion**
   - Premature satiety
   - Food intake
   - Vitamin D deficiency
   - Cobalamine deficiency

10. **Sugar**
    - Weight loss
    - Osteomalacia
    - Anemia

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Diarrhea

The term diarrhea is used if stool has lost its normal firm consistency. This is usually associated with an increase in its weight (in males > 235; in females > 175 g/d) and its frequency (> 2 per day). Diarrhea can have various causes:

- **Osmotic diarrhea** results from the intake of a large number of substances that are poorly absorbable even normally, or in malabsorption (→ p. 152 ff.). Among the first group are sorbitol (in “sugar-free” medications and sweets or certain fruits), fructose (in lemonades, diverse fruits, honey), magnesium salts (antacids, laxatives) as well as poorly absorbed anions such as sulfate, phosphate, or citrate.

Nonabsorbed substances are osmotically active in the small intestine and therefore “suck” water into the lumen. (H₂O secretion; → B, left). Table A illustrates this in a simulated experiment. Intake of, for example, 150 mmol of a nonabsorbable substance (in this example, polyethylene glycol, PEG) in 250 mL water (PEG concentration = [PEG] = 600 mmol/L) starts osmotic water secretion in the duodenum so that the volume is increased to 750 mL ([PEG] falls to 200 mmol/L). The osmolality has adjusted to that of plasma (290 mosm/L, 90 mosm/L now being contributed by Na⁺, K⁺ and the accompanying anions (ion secretion into the lumen because of the high chemical gradients). The volume in the middle of the small intestine has risen to 1000 mL. [PEG] has fallen to 150 mmol/L, and the entering ions contribute 140 mosm/L. Because of the high active absorption, especially of Na⁺ (plus anions −) in ileum and colon (denser epithelium than in the jejunum), the osmolality contributed by the ions falls to 90 and 40 mosm/L, respectively. The main cation in stool is K⁺ (marked Na⁺ absorption in ileum and colon). The result is that given 150 mmol PEG in 250 mL H₂O, the volume of diarrhea will be 600 mL. Without ion absorption in the ileum and colon (e.g., after resection, disease), the volume of diarrhea could even rise to 1000 mL (PEG is, e.g., given to cleanse the gut before a colonoscopy).

In malabsorption of carbohydrates (→ B, right and p. 152 ff.) the reduced Na⁺ absorption in the upper small intestine (diminished Na⁺ symport with glucose and galactose) leads to reduced water absorption. The osmotic activity of the nonabsorbed carbohydrates additionally results in water secretion. However, bacteria in the large intestine can metabolize up to 80 g/d (divided over four meals) of nonabsorbed carbohydrates into organic acids useful for providing energy that together with water are absorbed in the colon (→ B). It is only the large amounts of marked gas produced (flatulence) that provide evidence of carbohydrate malabsorption. However, if > 80 g/d (i.e., > ¼ of normal carbohydrate supply) is not absorbed or the intestinal bacteria are decimated by antibiotics, diarrhea occurs.

- **Secretory diarrhea** (in the narrow sense) occurs when Cl⁻ secretion of the small intestinal mucosa is activated (→ C). Within the mucosal cells Cl⁻ is secondarily actively enriched by a basolateral Na⁺-K⁺-2Cl⁻ symport carrier and is secreted via luminal Cl⁻ channels. These open more frequently when the intracellular concentration of cAMP rises. cAMP is formed in greater amounts in the presence of, for example, certain laxatives and bacterial toxins (Clostridium difficile, Vibrio cholerae). Cholera toxin causes massive diarrhea (up to 1000 mL/h) that can rapidly become life-threatening because of the loss of water, K⁺, and HCO₃⁻ (hypovolemic shock, hypokalemia, nonrespiratory acidosis).

Overproduction of VIP (vasoactive intestinal peptide) by pancreatic islet cell tumors also causes high cAMP levels in intestinal mucosa cells leading to copious, life threatening diarrhea: pancreatic “cholera” or watery diarrhea syndrome.

There are several reasons why diarrhea occurs after resection of the ileum and of part of the colon (→ D). Bile salts, normally absorbed in the ileum, cause accelerated passage through the colon (reduced water absorption). In addition, the nonabsorbed bile salts are dehydroxylated by the bacteria in the colon. The resulting bile salt metabolites stimulate the secretion of NaCl and H₂O in the colon. Finally, there is also a lack of active absorption of Na⁺ in the resected intestinal segments.
A. Osmotic Diarrhea

Uptake of 150 mmol of a nonabsorbable, osmotically active substance (PEG) in 250 mL H₂O

<table>
<thead>
<tr>
<th>H₂O (mL)</th>
<th>PEG (mmol)</th>
<th>[PEG] (mmol/L)</th>
<th>[Na⁺]+[K⁺] (mmol/L)</th>
<th>[Anions] (mmol/L)</th>
<th>Osmol. (mosm/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>150</td>
<td>600</td>
<td>-0</td>
<td>-0</td>
<td>600</td>
</tr>
<tr>
<td>750</td>
<td>150</td>
<td>200</td>
<td>45</td>
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<tr>
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<td>150</td>
<td>150</td>
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<tr>
<td>750</td>
<td>150</td>
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<td>45</td>
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<td>290</td>
</tr>
<tr>
<td>600</td>
<td>150</td>
<td>250</td>
<td>20</td>
<td>20</td>
<td>290</td>
</tr>
</tbody>
</table>

B. Malabsorption of Carbohydrates

Poorly absorbed carbohydrates (e.g., sorbitol, fructose), Disorder of carbohydrate digestion and absorption (e.g., disaccharidase deficiency, carrier defects)

Disorder of carbohydrate digestion and absorption (e.g., disaccharidase deficiency, carrier defects)

C. Raised Cl⁻ Secretion

Hormones and neurotransmitters (e.g., VIP), Laxatives, Toxins (cholera, clostridium difficile)

D. Partial Intestinal Resection

Resection of ileum and parts of colon, Bile salt reabsorption

Colon bacteria, Bile salt metabolites, Accelerated passage through colon

Water absorption, NaCl and H₂O secretion, Diarrhea

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Maldigestion and Malabsorption

A defect in the processing and enzymatic splitting within the gastrointestinal tract is called maldigestion; a disorder of absorption is called malabsorption. As both of them are closely intertwined, they are grouped together here as malabsorption (in the wider sense).

Malabsorption may affect the three energy carriers of food, i.e., fats, proteins, and carbohydrates, as well as vitamins, iron, calcium, magnesium, and trace elements, for example, zinc (→ C). Malabsorption of the enterohepatically circulating bile salts is also clinically significant (→ D). The respective site of absorption (→ A) of these substances is determined by: 1) the number and duration of preceding steps of processing and splitting; and 2) the provision in the intestinal segments of specific mechanisms of absorption.

Thus, monosaccharides such as glucose and galactose can be absorbed at the beginning of the duodenum; disaccharides must first be split by the enzymes of the brush border; polysaccharides (just like proteins and fats) must first come into contact with pancreatic juice, with the result that they may not be absorbed until they reach the jejunum (→ A) Rapid emptying of the stomach can mean that the place of absorption is moved distally (→ p.148), i.e. intestinal segments which lie further downstream can take over absorption that, in the long term, can lead to a change in the mucosa. The ileum, for example, may take on jejunum-like properties. This is not possible with substances for which only the terminal ileum possesses specific absorption mechanisms (cobalmine, bile salts).

Normal digestion and absorption consists of the following serial steps (→ B):
1. Mechanical processing of food (chewing, distal gastric peristalsis);
2. Luminal digestion (gastric, intestinal, and pancreatic juices; bile);
3. Mucosal digestion by enzymes of the brush border;
4. Absorption by the mucosal epithelium;
5. Processing in the mucosal cell;

6. Transportation into blood and lymph, through which the absorbed substances reach the liver and the systemic circulation, respectively.

The causes of malabsorption can affect all these steps (→ C, D):

- After gastric resection and/or vagotomy (see also p.148), the stimulation of enteral hormone secretion (CCK, e.g.) is reduced and the synchronization of chyme apportioning with pancreatic secretion, gallbladder emptying, and choleresis is disturbed. Furthermore, passage through the small intestine is accelerated and the pH in the duodenal lumen is too acidic, so that the digestive process may be greatly disturbed (enzyme inactivation, bile salt precipitation). A gastrinoma (Zollinger–Ellison syndrome) can cause malabsorption for the same reason.

- Pancreatic diseases, for example, chronic pancreatitis (→ p.160), carcinoma of the pancreas, cystic fibrosis (→ p.162), or resection of the pancreas may lead to malabsorption due to a lack of important enzymes (lipase, colipase, trypsin, chymotrypsin, amylase, etc.) as well as of HCO₃⁻ which is necessary for buffering acidic chyme.

- Atrophic gastritis with achlorhydria (→ p.142) will firstly diminish gastric digestion and secondly favor colonization of the small intestine with bacteria. This may also be caused by stasis in the small intestine due to diverticulosis or a small-intestine shunt (blind loop syndrome, → p.148). The bacteria deconjugate bile salts (→ D) and split the binding between cobalamine and intrinsic factor. The resulting cobalamine malabsorption leads to cobalamine deficiency, as does a reduced intake (strictly vegetarian diet; it is true also for breastfed infants of such mothers, because their milk also lacks cobalmine), intrinsic factor deficiency (achlorhydria; see also p.142), lack of enzymatic liberation of cobalamine from its binding with other proteins (high gastric pH, trypsin deficiency), or resection of the terminal ileum, the site of absorption of the cobalmine–intrinsic factor complex.
A. Sites of Absorption of Potentially Malabsorbed Substances

- **Proximal duodenum:** monosaccharides
- **Inflow of bile and pancreatic juice**
- **Distal duodenum:** disaccharides, fat-soluble vitamins, Fe, Ca^{2+}
- **Jejunum:** Proteins (as amino acids), starch (as glucose), water-soluble vitamins
- **Ileum:** fats
- **Terminal ileum:** bile salts, cobalamines

B. Steps in Digestion the Failure of which Leads to Malabsorption

- Processing
  - Luminal digestion
  - Mucosal digestion
- Absorption
  - Mucosal processing
  - Removal

C. Causes and Consequences of Malabsorption (see also D.)

- **Chronic pancreatitis, pancreas carcinoma**
- **Gastrectomy, gastric resection, vagotomy**
- **Gastrinoma**
- **Achlorhydria**
- **Bacteria in small intestine**
- **Disaccharidase deficiency (e.g. lactase)**
- **Specific carrier defect (Hartnup, cystinuria)**
- **Global defects (e.g. resection, sprue, Crohn’s)**
- **Lymphangiectasia**
- **Ischemia, vasculitis**

<table>
<thead>
<tr>
<th>Malabsorption of</th>
<th>Proteins</th>
<th>Carbohydrates</th>
<th>Zinc</th>
<th>Iron</th>
<th>Cobalamine Folate</th>
<th>Ca^{2+}, Mg^{2+}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema</td>
<td>Weight loss</td>
<td>Flatulence</td>
<td>Taste</td>
<td>Anemia, glossitis, etc.</td>
<td>Tetany</td>
<td>Paresthesias</td>
</tr>
<tr>
<td></td>
<td>Muscle wasting</td>
<td>Watery diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bacterial splitting of carbohydrates in colon</td>
<td>Wound-healing</td>
<td>Acro-dermatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
Lack of brush-border disaccharidase causes malabsorption of the corresponding disaccharide. A lack of lactase, which splits lactose into glucose and galactose, is common. Lactase deficiency, which goes hand in hand with intolerance to milk and lactose-containing foods, is rarely congenital, but often develops after weaning. There are marked ethnic differences.

Defects of specific mucosal carriers cause specific malabsorption. In Hartnup disease, for example, there is a specific carrier defect for certain neutral amino acids; in cystinquira for cationic (basic) amino acids and cystine. (The uptake of the affected amino acids as dipeptides is undisturbed, because the mucosa has its own carrier for dipeptides).

Global defects of mucosal digestion and absorption occur in diffuse mucosal diseases, such as celiac disease, tropical sprue, Crohn’s disease, Whipple’s disease, AIDS, infections (e.g., with Salmonella), radiation enteritis, and after resection of large portions of the small intestine.

In addition to alcohol (pancreatic insufficiency, chronic liver disease), a number of drugs cause malabsorption: colchicine (inhibits division of crypt cells and disaccharidases), neomycin and similar antibiotics (inhibit division of crypt cells and disaccharidases; precipitate bile salts and micellar fatty acids), methotrexate (inhibits folic acid absorption), cholestyramine (binds bile salts), certain laxatives, biguanides, etc.

Especially in fat absorption, processing within the mucosal cells (formation of chylomicrons) is an important partial step whose disturbance in abetalipoproteinemia (→ p. 247) results in fat malabsorption (→ D). Another cause is lymphatic blockage (lymphangiectasia, lymphoma, etc.).

Finally, malabsorption naturally occurs if blood flow through the intestine is disturbed (ischemia, e.g., in vasculitis).

The consequences of malabsorption are dependent on the kind of malabsorbed substance:

- Malabsorption of proteins (→ C) can lead to muscular atrophy and weight loss, while any resulting hypoproteinemia will result in edema (see also p. 235).

- Malabsorption of carbohydrates in the small intestine (→ C) means that some of them are metabolized to short-chain fatty acids and to gases (CO₂, H₂) resulting in distension and flatulence. If more than 80 g/d of carbohydrates fail to be absorbed, osmosis-induced watery diarrhea occurs (→ p. 150).

- Malabsorption of fats (→ D) is characterized by fatty stools (steatorrhea) and leads to weight loss from a lack of these high-calorie components of food. Malabsorption of the fat-soluble vitamins A, D, E, and K occurs especially if fat malabsorption is caused by a lack of bile salts or by other reasons of abnormal formation of micelles (→ D). This is because these vitamins can only reach the absorbing mucosa in an uninterrupted lipophilic milieu for which micelles are essential. If vitamin K deficiency occurs, the glutamyl residues of prothrombin and other blood clotting factors cannot be γ-carboxylated in the liver, and thus bleeding may occur. Vitamin D deficiency causes rickets in children and osteomalacia in adults. In vitamin A deficiency hyperkeratosis and night blindness develop.

- Malabsorption of the water-soluble vitamin cobalamine (B₁₂) (for causes, see above) and folate (e.g., in global malabsorption or methotrexate administration) leads to macrocytic anemia (→ p. 34), termed pernicious anemia if there is a cobalamin deficiency, to glossitis and aphthous ulcers as well as neurological defects (nerve degeneration) if there is a cobalamin deficiency.

- Iron malabsorption (see also p. 38) leads to hypochromic anemia.
D. Malabsorption of Fat

- Achlorhydria
- Intestinal stasis
- Bacterial colonization of small intestine
- Liver damage
- Cholestasis, biliary tract occlusion
- Ileum resection

- Desynchronization of chyme emptying and bile secretion, pancreatic secretion
- Bile salt deconjugation
- Bile salt synthesis
- Bile salt precipitation
- Bile salt resorption

- Lipase deficiency
- Bile salt deficiency

- Fat malabsorption
  - Abnormal micellar formation
  - Maldigestion of fat
  - Fat removal
  - Steatorrhea
  - Vitamin K deficiency
  - Vitamin D deficiency
  - Bleeding
  - Osteomalacia
  - Weight loss

- Gastrinoma (Zollinger-Ellison)
- Billroth II
- Billroth I
- Gastric resection
- Pancreas stimulation
- Pancreatic HCO$_3^-$ secretion
- Diffuse small intestinal disease
- Abetalipoproteinemia
- Obstruction of lymphatic vessels
- Ischemia
- Chronic pancreatitis, pancreatic carcinoma, pancreatic resection, cystic fibrosis, etc.

- Pancreatic HCO$_3^-$ secretion
  - Duodenal pH
  - Lipase inactivation
  - Pancreas stimulation

- Ileum resection
- Liver damage

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Constipation and (Pseudo-)Obstruction

The symptom of constipation may signify different things in individual cases, depending on what is considered to be “normal”: too little, too hard or rare a stool, difficult defecation, or the sensation of incomplete emptying. Constipation is often harmless, but it can be a sign of numerous diseases.

The causes of constipation are:

\* **Low-fiber diet**, as intestinal motility depends on the volume of intestinal contents. The larger the volume the greater the motility.

\* **Reflex** and/or **psychogenic disorders**. These include: 1) **anal fissure** that is painful and reflexly raises the tone of the anal sphincter, thus increasing the pain, and so on; 2) so-called **anismus** (outlet obstruction), i.e., contraction (rather than the normal relaxation) of the pelvic floor when the rectum is stretched. Such a “false” reflex is commonly found in women who were abused as children, but also in patients with Parkinson’s disease; 3) **paralytic ileus** (acute pseudo-obstruction) that may be caused reflexly by operations (particularly in the abdomen), trauma, or peritonitis, and may persist in the colon for several days.

\* **Functional disorders of transport**, whether of neurogenic, myogenic, reflex (see above), medicinal (e.g., opiates), or ischemic cause (e.g., trauma or arteriosclerosis of the mesenteric arteries). Functional intestinal obstruction is called **pseudo-obstruction**.

\* **Neurogenic causes**. Congenital absence of ganglion cells near the anus (aganglionosis in *Hirschsprung’s disease*), resulting in persisting spasm of the affected segment due to failure of receptive relaxation (→ A, bottom right) and absence of anorectal inhibitory reflexes (internal anal sphincter fails to open when rectum fills). In *Chagas’ disease* the causative organism (*Trypanosoma cruci*) de-nerve the intestinal ganglia, thus producing dilation of the colon (megacolon; see below). In addition, **systemic nervous diseases** (Parkinson’s disease, diabetic polyneuropathy, viral neuritis, tabes dorsalis, multiple sclerosis) or **nerve and spinal cord lesions** that, among other effects, interrupt intestinal distance reflexes, can cause pseudo-obstruction.

\* **Myogenic causes**. Muscular dystrophies, scleroderma (see also Plate 6.3), dermatomyositis, and systemic lupus erythematosus.

\* **Mechanical obstruction** in the intestinal lumen (e.g., foreign bodies, roundworms [Ascaris], gallstones), in the intestinal wall (e.g., tumor, diverticulum, stenosis, stricture, hematoma, infection) or from outside (e.g., pregnancy, adhesion, hernia, volvulus, tumor, cyst). The result is mechanical intestinal occlusion (**obstruction**).

Finally, in some patients constipation (alternating with diarrhea) may occur without any of the above causes being identified. Emotional or physical stress is often the precipitating factor in what is called **irritable colon**.

**Effects of obstruction and pseudo-obstruction**. Complete occlusion leads to a proximal accumulation of gases and fluid and dilates the intestine, which initially contracts **painfully** every few minutes. Especially if the proximal small intestine is affected, the advancing **dilation** impairs **blood flow**, causes **vomiting** and results in dehydration (**hypovolemia**). This can progress rapidly because increased amounts of fluid can be secreted in the intestine. As well as dilation, bacteria ascending from the large to the small intestine also cause this; their endotoxins result in the liberation of **VIP**, **PGI**₂, and **PGF**₂. Inflammation caused by bacteria along with edema formation in the intestinal wall and peritonitis as well as possibly resulting **ischemia** (see above) can quickly become life-threatening. If the (pseudo-)obstruction is located far toward the anus, **megacolon** may develop (→ A). It may occur acutely in case of fulminating colitis, volvulus, or without recognizable cause (Ogilvie syndrome). Distinction between this and paralytic ileus (see above) is largely made from the patient’s history.
A. Causes and Consequences of Constipation and (Pseudo-)Obstruction

- Psychogenic reflex disorder e.g. anism
- Surgery, trauma, peritonitis, etc.
- Mechanical obstruction: luminal, mural, external (foreign body, tumor, hernia, adhesion, stricture, etc.)
- Acute reflex
- Neurogenic or myogenic disorder of transport
- Paralytic ileus
- Paralysis
- Abnormal dilatation
- Drugs (opiates, phenothiadiazines, etc.)
- Food low in bulk
- Intestinal volume
- Intestinal motility
- Rectal distension
- Contraction (instead of dilation) of the pelvic floor
- Spasm
- Mechanical obstruction: luminal, mural, external (foreign body, tumor, hernia, adhesion, stricture, etc.)
- Surgery, trauma, peritonitis, etc.
- Ischemia
- Inflammation
- Wall edema
- Ascension of bacteria
- Endotoxins
- VIP, prostaglandins
- Absorption, secretion
- Vomiting
- Hypovolemia
- Pain
- Megacolon (here: Hirschsprung’s disease)
- Paralytic ileus

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Acute Pancreatitis

Most pancreatic enzymes are activated by enteropeptidase only when they reach the intestinal lumen. The activation of trypsinogen to trypsin is a key feature in this, because trypsin activates other enzymes. If it is activated in the acinar cells, the pancreatic trypsin inhibitor–protein is responsible for trypsin not being effective there. However, if this protective mechanism does not keep up with the trypsin activation, or trypsin becomes active in the lumen of the pancreatic duct, self-digestion of the pancreas occurs, i.e., acute pancreatitis.

Even though there is a history of high alcohol consumption and gallstones in 80% of cases, the pathogenetic mechanism is not quite clear. The following possibilities are being discussed as playing a part, either in combination or separately depending on the case:

- **Increased pressure in the pancreatic duct** (flow resistance and/or flow too high) can play a part in the development of acute pancreatitis (→ A1). Occlusion of the duct after the merging of the bile duct (e.g., by a gallstone; → A2) also leads to reflux of bile into the pancreas, where it damages the duct epithelium and accelerates fat digestion.

- While it is unclear, in relation to the above points, how trypsin is activated, if duodeno-pancreatic reflux occurs (e.g., when the duodenum is obstructed distally), the enzymes activated in the duodenum pass back into the pancreas (→ A3).

- Alcohol, acetylsalicylic acid, histamine, etc. increase the permeability of the pancreatic duct epithelium, so that larger molecules can pass through it. Enzymes secreted by the acinar cells thus diffuse into periductal interstitial tissue and damage it (→ A4). In addition, alcohol in the duct system seems to precipitate proteins, causing a rise in upstream pressure (→ A4).

- Research on animal models with acute pancreatitis indicates that under some circumstances pancreatic enzymes may also be activated intracellularly. The process of sorting out lysosomal enzymes and H⁺-ATPase, on the one hand, and the pancreatic proenzymes to be secreted, on the other, as normally occurs in the Golgi apparatus, seems to be disturbed (→ A5). Thus, the proenzymes together with the lysosomal proteases will be incorporated into the same vesicles, so that trypsin will be activated there. Trace amounts are enough for this, because trypsin can activate itself autocatalytically.

  **Trypsin activates other enzymes** (phospholipase A₂, elastase, etc.), **clotting factors** (prothrombin to thrombin), **tissue hormones** (bradykinin and kallidin are activated via kallikrein), and **cytotoxic proteins** (complement system). In the pancreas (→ A6; P in the computed tomogram) there is at first generalized cell swelling (pancreatic edema; → A7, P + E). Activated elastase, in particular, causes vessel arrosion with bleeding (hemorrhagic pancreatitis) and ischemic zones in the organ. These ischemic areas are further enlarged by the formation of thrombi brought about by thrombin activation, the result being necrosis. The endocrine islet cells are also destroyed, causing insulin deficiency and thus hyperglycemia. Fat necrosis develops around the pancreas with accompanying soap formation, a process that uses up Ca²⁺ (Ca²⁺ sequestration) and also causes hypocalcemia (see below). Mg²⁺ ions in the plasma binding to the liberated fatty acids cause hypomagnesemia (→ p. 126). All this damage can spread to neighboring retroperitoneal organs, i.e., spleen, mesentery, omentum, duodenum, etc.

As the activated enzymes appear in plasma, where their presence is of diagnostic significance, hypoalbuminemia develops with resulting hypocalcemia, as well as systemic vasodilation and plasma exudation (triggered by bradykinin and kallidin), ultimately ending in circulatory shock. Phospholipase A₂ and free fatty acids (due to increased lipolysis) in plasma destroy the surfactant on the alveolar epithelium, causing arterial hypoxia. Finally, the kidneys will also be damaged (danger of anuria).
A. Causes and Consequences of Acute Pancreatitis

1. Gallstones

2. Bile reflux

3. Enzyme diffusion, protein precipitation

4. Enzyme plug

5. Autocatalysis

6. Acute pancreatitis

7. Extracellular and/or intracellular trypsin activation

Activation of:

- Phospholipase A$_2$
- Elastase
- Complement
- Prothrombin
- Kallikrein
- Systemic damage

- Bile
- Fat necrosis
- Islet necrosis
- Cell toxicity
- Thrombin
- Bradykinin, kallidin
- Hypocalcemia
- Hyperglycemia
- Pancreatic gangrene
- Pain
- Shock
- Hypoxia
- Anuria

Hypocalcemia

Hyperglycemia

Pancreatic gangrene

Pain

Shock

Hypoxia

Anuria

**Chronic Pancreatitis**

Chronic pancreatitis is an inflammatory process that destroys the exocrine and endocrine tissues and leads to fibrosis of the organ. There are several forms of chronic pancreatitis:

- **Chronic calcifying pancreatitis** (→ A, left) is the most common form (70–80% of cases), caused by chronic alcohol abuse (> 80 g/d over many years) and is characterized by irregularly distributed tissue lesions with intraductal protein plugs and stones as well as atrophy and stenosis of the ductal system. Three mechanisms play a role in its pathogenesis:
  1. While normally, in parallel with the stimulation of the acini (enzyme-rich secretions), there is greater secretion in the ducts (HCO$_3^-$, water), it is reduced in chronic pancreatitis. As a result, protein concentration in the pancreatic juice is increased, especially when acinar secretion is stimulated. This leads to protein precipitation in the ductal lumens and **protein plugs and deposits** are thus formed.
  2. Calcium salts are deposited on the precipitated protein, resulting in the **formation of stones** in the lumen of small ducts, and concentric calcium deposits on the walls of the larger ducts. The cause of all this may be that two components of pancreatic juice are diminished in chronic pancreatitis, namely those that normally prevent the precipitation of calcium salts from pancreatic juice. One of these components is citrate, which binds calcium complexly, the other is the 14 kDa protein, **lithostatin** (= pancreatic stone protein [PSP]), which holds calcium salts in solution during (physiological) hypersaturation.
  3. Similar to acute pancreatitis (→ p. 158), intraductal **activation of trypsin** occurs. This not only contributes to the autodigestion of pancreatic tissue, but also activates other aggressive enzymes, such as elastase and phospholipase A$_2$, in the ductal system and, in some circumstances, also interstitially. It is thought that the cause of the premature enzyme activation is that impaired drainage has increased intraductal pressure, resulting in epithelial lesions, together with raised proenzyme content (while the concentration of trypsin inhibitor–protein remains unchanged; → p. 158).

- The rarer **chronic–obstructive pancreatitis** (→ A, right) is caused by occlusion of the main excretory duct(s) by tumors, scar stricture, or stenosis of the papilla, among others. There is no calcification, but the ductal system is markedly **dilated** upstream of the stenosis (→ A; endoscopic retrograde pancreatography [ERP], in which contrast media are injected for radiological visualization). If the obstruction is removed in time, this form of chronic pancreatitis (in contrast to the calcifying form) is reversible.

Other forms of chronic pancreatitis include the **idiopathic**, nonalcoholic form in malnourished juveniles in the tropics, and the form seen in **hypercalcemia** due to hyperparathyroidism.

**Acute exacerbation** of chronic pancreatitis is usually difficult to distinguish from acute pancreatitis, especially when there is a history of high alcoholic intake. In both cases the premature activation of pancreatic enzymes is a prominent feature (see above and p. 158). It can lead, via pancreatic edema, to pancreatic hemorrhage and necrosis as well as to acute pseudocysts, abscess, and/or impairment of neighboring organs such as duodenum, antrum, choledochal duct, and colon.

The **results** of chronic pancreatitis are tissue atrophy, ductal stenosis, and periductal fibrosis with scarring. This gradually leads to **loss of parenchyma**, which will cause exocrine and later also endocrine **pancreatic insufficiency**. Intermittent or continuous pain, **malabsorption** (→ p. 152 ff.), diarrhea (→ p. 150), and **weight loss** as well as **diabetes mellitus** (→ p. 286 ff.) and **damage to neighboring organs** (pancreatic ascites, portal and splenic vein thrombosis, obstructive jaundice, etc.) are associated with this.
A. Causes and Consequences of Chronic Pancreatitis

Alcohol abuse

Tumor, stricture, papillary stenosis

Occlusion of main pancreas duct

Pancreatitis

1. Causes and Consequences of Chronic Pancreatitis

Alcohol abuse

Pancreas

Occlusion of main pancreas duct

Pancreatic juice:
- Secretion of HCO$_3^-$ and fluid
- Citrate concentration
- Lithostatin concentration
- Proenzyme concentration
- Calcium salt precipitation
- Protein plug

Calcium deposition

Epithelial lesions

Enzyme activation

Chronic inflammation and fibrosis of exocrine and endocrine pancreas, damage to neighboring organs

Tissue atrophy
Ductal stenosis
Periductal fibrosis
Pain
Malabsorption
Weight loss
Diabetes mellitus
Pancreatic ascites
Thrombosis of portal and splenic veins
Obstructive jaundice
Diarrhea
Pseudocysts


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Cystic Fibrosis

Cystic fibrosis (CF) is a genetic syndrome in which the epithelial secretion, for example, in the lungs, pancreas, liver, genital tract, intestine, nasal mucosa, and sweat glands are affected. Among Caucasians CF is the most frequent lethal (after a mean of 40 years) gene defect (1 per 2,500 births).

The defect is autosomal recessive and affects the epithelial transport protein CFTR (cystic fibrosis transmembrane conductance regulator). CFTR in healthy people consists of 1480 amino acids that form 12 transmembrane domains, two nucleotide-binding domains (NBD1, NBD2), and a regulator domain. At the latter, CFTR is regulated by a cAMP-dependent protein kinase A (\(\rightarrow A1\); CFTR is shown opened up frontally). CFTR is probably a chloride channel that opens when the intracellular cAMP concentration is raised and, in addition, ATP is bound to NBD1 (and split?). Furthermore, intact but not defective CFTR inhibits certain Na\(^+\) channels (type ENaC). The fact that more of them open in CF results in increased absorption of Na\(^+\)and water, for example, at the bronchial epithelium, from the mucus secreted into the lumen, so that the latter is thickened (see below).

Patients with cystic fibrosis have various mutations of CFTR, but the serious forms are most frequently caused by two defects on the NBD1 (\(\rightarrow A3\)): either the amino acid 508, phenylalanine (= F; mutation ΔF508), is missing, or glycine (= G) in position 551 is replaced by aspartate (= D) (mutation G551D).

CFTR is incorporated into the apical (luminal) cell membrane of many epithelial cells. CFTR has an important function in the excretory ducts of the pancreas, in that it is involved in secretion of a liquid rich in NaHCO\(_3\). HCO\(_3^-\) is exchanged for Cl\(^-\) in these cells via an antiporter (\(\rightarrow A4\)). The opening of CFTR—for example, by secretin, which increases intracellular cAMP concentration—causes the Cl\(^-\) that has entered the cell to be recycled, so that chloride is again available for the secretion of HCO\(_3^-\), followed by Na\(^+\) and water. If the concentration of cAMP decreases, CFTR is closed and secretion dries up.

In patients with CF, CFTR does not open up even when cAMP concentration is high. As a result, especially when acinar secretion is stimulated, the small pancreatic ducts contain a protein-rich, viscous secretion that occludes the transporting ducts and thus leads to chronic pancreatitis with its consequences (e.g., malabsorption due to lack of pancreatic enzymes and HCO\(_3^-\) in the duodenum; \(\rightarrow p.160\)).

Among other effects, abnormal CFTR affects the intestinal epithelium so that neonatal meconium becomes viscous and sticky and thus cannot, as usual, pass out of the ileum after birth (meconium ileus).

As in the pancreas, the bile ducts may become obstructed and neonatal jaundice may thus be prolonged. The CFTR defect in the male genital organs may cause infertility (obstruction of the vas deferens); in the female genital organs it causes decreased fertility. The consequences of abnormal secretion in the nasal mucosa are polyps and chronic inflammation of the nasal sinuses. In the sweat glands the defect increases sweat secretion that during fever or high ambient temperature can lead to hypovolemia and even circulatory shock. In addition, electrolyte concentration is increased in sweat and the concentration of Na\(^+\) is higher than that of Cl\(^-\) (the reverse of normal), a fact that is used in the diagnosis of CF (sweat test).

Morbidity and life-threatening complications of CF are mainly due to its effects on the bronchial epithelium. Its superficial mucus is normally thinned by fluid secretion. The CFTR defect causes (in addition to increased mucus secretion) the reabsorption instead of secretion of fluid. This results in a highly viscous and protein-rich layer of mucus that not only hinders breathing, but also forms a fertile soil for infections, especially with Pseudomonas aeruginosa and Staphylococcus aureus. Chronic bronchitis, pneumonia, bronchiectasis, and secondary cardiovascular disorders are the result.
A. Causes and Consequences of Cystic Fibrosis

Autosomal recessive gene defect on chromosome 7

Mutation ΔF508 or Mutation G551D

Cystic fibrosis
Fluid secretion abnormal in:
- Pancreas,
- Gonads,
- Liver, intestine,
- Gallbladder,
- Sweat glands,
- Bronchi, etc.

Bronchial secretion too thick

Chronic pancreatitis

Malabsorption

Meconium ileus

Infection

Bronchiectasis, pneumonia, etc.

Gallstone Disease (Cholelithiasis)

In about 75% of patients, gallstones consist of cholesterol (more women than men are affected in this way), the rest are so-called pigment stones that contain unconjugated bilirubin in the main. What the two types of stone components have in common is that they are poorly soluble in water.

Cholesterol (Ch) is normally not precipitated in bile, because it contains sufficient conjugated bile salts (BS) and phosphatidylcholine (Pch = lecithin) for it to be in a micellar solution (→ A4, green area). If the concentration ratio [Ch]/[BS + Pch] increases, Ch will remain, within a small range, in a “supersaturated” micellar solution (→ A4, orange area). This apparent supersaturation is probably based on the liver also secreting cholesterol in a highly concentrated form within the “nucleus” of a unilamellar vesicle in the gallbladder (→ A2) in such a way that Pch makes up the solution-aiding “peel” of this vesicle, 50–100 nm in diameter. If the relative cholesterol content increases further, multimicellar vesicles are formed (up to 1000 nm). They are less stable and give up cholesterol that is then precipitated in the aqueous environment in the form of cholesterol crystals (→ A2: → A4, red area). These crystals are the precursors of gallstones.

Important causes of an increased [Ch]/[BS + Pch] ratio are:

- Increased cholesterol secretion (→ A2). This will occur because there is either an increased cholesterol synthesis (raised activity of 3-hydroxy-3-methylglutaryl [HMG]-CoA-cholesterol reductase), or an inhibition of cholesterol esterification, for example, by progesterone during pregnancy (inhibition of acetyl-CoA-cholesterol-acetyl transferase [ACAT]).
- Reduced bile salt secretion (→ A1). This is due to either a decrease in the bile salt pool, as in Crohn’s disease or after gut resection, or a prolonged sequestration of bile salts in the gallbladder, as in fasting (possibly even if only overnight) or parenteral nutrition. The latter decreases the enterohepatic circulation of bile salts so that their secretion into the bile is reduced. As cholesterol secretion is not linearly related to bile salt secretion (→ B, right), the [Ch]/[BS + Pch] ratio increases when bile salt secretion is low. This ratio rises further under the influence of estrogens, because they cause an increase in the concentration ratio of cholate to chenodeoxycholate (activation of 12α-hydroxylase; → B, left), so that more cholesterol is secreted per mol bile salts (→ B; compare the two curves).
- A reduced secretion of phosphatidylcholine as a cause of cholesterol stones has been found in Chilean women who live almost exclusively on vegetables.

Pigment stones (→ C) consist to a large extent (ca. 50%) of calcium bilirubinate, which gives them their black or brown color. The black stones additionally contain calcium carbonate and phosphate, while the brown stones also contain stearate, palmitate, and cholesterol. A raised amount of unconjugated bilirubin in the bile, which “dissolves” only in micelles, is the main cause of pigment stone formation; normally bile contains only 1–2%. The causes of an increased concentration of unconjugated bilirubin are (→ C):

- Increased liberation of hemoglobin, for example, in hemolytic anaemia, in which there is so much bilirubin that the glucuronidase-mediated process of conjugation in the liver does not meet demand (→ p. 169);
- Reduced conjugating capacity in the liver, for example, in liver cirrhosis (→ p. 172);
- Nonenzymatic deconjugation of (especially monoglucuronated) bilirubin in bile;
- Enzymatic deconjugation (β-glucosidase) by bacteria.

The latter is almost always the cause of brown pigment stones. The bacteria also enzymatically deconjugate the bile salts (decreased micellar formation with cholesterol precipitation) and additionally liberate, by means of its phospholipase A2, palmitate and stearate (from phosphatidylcholine) which precipitate as calcium salts. Black stones, mainly formed by the first three of the above mechanisms, contain in addition to other compounds, calcium carbonate and phosphate, these latter presumed to be formed by the gallbladder’s decreased capacity to acidify.
A. Cholelithiasis: Abnormal Cholesterol to Bile Salt Ratio

1. Liver

   - Enterohepatic circulation

   - Gallbladder

   - Duodenum

   - Ileum

2. Fasting (over night!), parenteral diet

   - Crohn’s disease, intestinal resection

   - Unbalanced diet

   - Bile salt loss

   - Phosphatidylcholine

   - Cholesterol

3. Bile salts

   - Phosphatidylcholine

   - Cholesterol

   - New synthesis

   - HO

   - Cholesterol salts

   - VLDL

4. Dissociation: cholesterol crystals

   - Supersaturation

   - Crystal formation

   - Cholesterol stones

   - Supersaturated

   - Cholesterol secretion

   - Enterohepatic circulation

   - Liver

   - Gallbladder

   - Ileum

   - Duodenum

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B. Cholesterol/Bile Salts: Dependence on Bile Salt Type and Bile Salt Secretion Rate

The gallbladder, in which the specific bile components (Ch, BS, Pch) are concentrated many times over by withdrawal of water, also plays an important part (→D) in the formation of gallstones (cholelithiasis after cholecystectomy is rare). Disorders of gallbladder emptying can be among the causes, either due to insufficient CCK being liberated (lack of free fatty acid [FFA] release in the lumen in pancreatic insufficiency), so that the main stimulus for gallbladder contraction is weakened, or because after nonselective vagotomy the second most important contraction signal, acetylcholine, is absent. Gallbladder contraction is also weakened in pregnancy. This means that not only occasional or absent emptying (see above) but also incomplete emptying increases the duration for which bile remains in the gallbladder. As a result, there is enough time for the precipitated crystals to form large concrements. A raised mucus secretion (stimulated by prostaglandins) can thus lead to an increased number of nuclei of crystallization.

Possible consequences of cholelithiasis are (→E):

- **Colic.** When the cystic duct or the common bile duct is transiently blocked by a stone, pressure rises in the bile ducts and increased peristaltic movement in the region of the blockage causes severe visceral pain in the epigastric area, possibly with radiation into the back, as well as vomiting (→p.140).

- **In acute cholecystitis** fever and leukocytosis are added to the symptoms listed above. Important causes are trauma to the gallbladder epithelium caused by stones. Prostaglandins are liberated from the gallbladder epithelium in addition to phospholipase A₂. The latter splits phosphatidylcholine to lysolecithin (i.e., removal of the fatty acid at C2), which in turn brings about acute cholecystitis. In some circumstances it may lead to gallbladder perforation.

- **Bacterial cholangitis** usually occurs when bile flow is stopped because of cholelithiasis. A rise in pressure with dilution of the bile ducts is the result, and posthepatic cholestasis and biliary pancreatitis may also develop.

- In relatively rare cases **gallbladder cancer** develops on the basis of gallstone disease.
C. Causes of Pigment Stone Formation

- Hemolytic anemia
- Liver cirrhosis
- Bilirubin glucuronide
- Non-enzymatic
- β-glucosidase
- Micellar formation

Unconjugated bilirubin → Calcium bilirubinate → Calcium palmitate and -stearate → Calcium carbonate and -phosphate → Pigment stones

D. Role of Gall Bladder in Cholelithiasis

- Vagotomy
- Pregnancy
- CCK deficiency, vagotomy, pregnancy
- Bile: Cholesterol/Bile salt
  (cf fig. A), bile concentration

Gallbladder emptying (not often enough, incomplete) → Fasting → Cholesterol crystals → Mucus secretion

E. Consequences of Cholelithiasis

- Spasm
- Acute cholecystitis
- Cholangitis, obstructive jaundice, pancreatitis
- Ulceration, perforation
- Carcinoma
- Colic

(partly after Netter)
Jaundice (Icterus)

Bilirubin, largely originating from hemoglobin breakdown (ca. 230 mg/d), is taken up by the liver cells and coupled by glucuronyl transferase to form bilirubin-mono- and bilirubin-diglucuronide. This water-soluble conjugated (direct reacting) bilirubin is secreted into the bile canaliculi and 85% is excreted in the stool. The remaining 15% is degraduced and absorbed in the intestine for enterohepatic recirculation.

The normal plasma concentration of bilirubin is maximally 17 µmol/L (1 mg/dL). If it rises to more than 30 µmol/L, the sclera become yellow; if the concentration rises further, the skin turns yellow as well (jaundice [icterus]). Several forms can be distinguished:

- **Prehepatic jaundice** is the result of increased bilirubin production, for example, in hemolysis (hemolytic anemia, toxins), inadequate erythropoiesis (e.g., megaloblastic anemia), massive transfusion (transfused erythrocytes are short-lived), or absorption of large hematomas. In all these conditions unconjugated (indirect reacting) bilirubin in plasma is increased.

- **Intrahepatic jaundice** is caused by a specific defect of bilirubin uptake in the liver cells (Gilbert syndrome Meulengracht), conjugation (neonatal jaundice, Crigler–Najjar syndrome), or secretion of bilirubin in the bile canaliculi (Dubin–Johnson syndrome, Rotor syndrome).

In the first two defects it is mainly the unconjugated plasma bilirubin that is increased; in the secretion type it is the conjugated bilirubin that is increased. All three steps may be affected in liver diseases and disorders, for example, in viral hepatitis, alcohol abuse, drug side effects (e.g., isoniazid, phenytoin, halothane), liver congestion (e.g., right heart failure), sepsis (endotoxins), or poisoning (e.g., the Amanita phalloides mushroom).

- In posthepatic jaundice the extrahepatic bile ducts are blocked, in particular by gallstones (→ p. 164 ff.), tumors (e.g., carcinoma of the head of the pancreas), or in cholangitis or pancreatitis (→ p. 158). In these conditions it is particularly conjugated bilirubin that is increased.

Cholestasis

Cholestasis (→ A, B), i.e., blockage of bile flow, is due to either intrahepatic disorders, for example, cystic fibrosis (→ p. 162), granulomatosis, drug side effects (e.g., allopurinol, sulfonylamides), high estrogen concentration (pregnancy, contraceptive pill), graft versus host–reaction after transplantation, or, secondarily, extrahepatic bile duct occlusion (see above).

In cholestasis the bile canaliculi are enlarged, the fluidity of the canalicular cell membrane is decreased (cholesterol embedding, bile salt effect), their brush border is deformed (or totally absent) and the function of the cytoskeleton, including canalicular motility, is disrupted. In addition, one of the two ATP-driven bile salt carriers, which are meant for the canalicular membrane, is falsely incorporated in the basolateral membrane in cholestasis. In turn, retained bile salts increase the permeability of the tight junctions and reduce mitochondrial ATP synthesis. However, it is difficult to define which of these abnormalities is the cause and which the consequence of cholestasis. Some drugs (e.g., cyclosporin A) have a cholestatic action by inhibiting the bile salt carrier, and estradiol, because it inhibits Na⁺-K⁺-ATPase and reduces membrane fluidity.

Most of the consequences of cholestasis (→ B) are a result of retention of bile components: bilirubin leads to jaundice (in neonates there is a danger of kernicterus), cholesterol to cholesterol deposition in skin folds and tendons, as well as in the cell membranes of liver, kidneys, and erythrocytes (echinocytes, ankathocytes). The disturbing pruritus (itching) is thought to be caused by retained endorphins and/or bile salts. The absence of bile in the intestine results in fatty stools and malabsorption (→ p. 152 ff.). Finally, infection of accumulated bile leads to cholangitis, which has its own cholestatic effect.
A. Types of Jaundice

- Blood
- Hemoglobin etc. → Bilirubin

- Specific syndromes (Gilbert, Crigler-Najjar, Dubin-Johnson, Rotor)
- Acute and chronic liver damage
- Drug side effects
- Estrogens, cystic fibrosis, etc.

Blood

Hemolysis etc.

Production

Uptake

Conjugation

Secretion

Outflow

Conjugated bilirubin

Liver

Gall stones, tumors, etc.

Extrahepatic outflow

Jaundice:

Pre-hepatic

Intrahepatic

Post-hepatic

B. Mechanisms and Consequences of Cholestasis

Bile salts, bilirubin, cholesterol
Enzymes, copper, endorphins

Bilirubin

Endorphins (?)

Bile salts (?)

Cholesterol (hepatic breakdown ↓, enteral synthesis ↑)

Blood

Liver cell

Mitochondria

ATP

ATP synthesis impaired

Carrier insertion on wrong side

Fluidity of cell membrane

Retention of bile components

Deformation of brush border

Dilation

Bile salt deficiency in intestine

Cholestasis

Icterus

Pruritus

Cholangitis

Fat stools, vitamin A, E and K deficiency

Cholesterol deposition
Portal Hypertension

Venous blood from stomach, intestines, spleen, pancreas, and gallbladder passes via the portal vein to the liver where, in the sinusoids after mixture with oxygen-rich blood of the hepatic artery, it comes into close contact with the hepatocytes (→ A1). About 15% of cardiac output flows through the liver, yet its resistance to flow is so low that the normal portal vein pressure is only 4–8 mmHg.

If the cross-sectional area of the liver's vascular bed is restricted, portal vein pressure rises and portal hypertension develops. Its causes can be an increased resistance in the following vascular areas, although strict separation into three forms of intrahepatic obstructions is not always present or possible:

- **Prehepatic**: portal vein thrombosis (→ A2);
- **Posthepatic**: right heart failure, constrictive pericarditis, etc. (→ A2 and p. 228);
- **Intrahepatic** (→ A1):
  - *presinusoidal*: chronic hepatitis, primary biliary cirrhosis, granuloma in schistosomiasis, tuberculosis, leukemia, etc.
  - *sinusoidal*: acute hepatitis, *damage from alcohol* (fatty liver, *cirrhosis*), toxins, amyloidosis, etc.
  - *postsinusoidal*: venous occlusive disease of the venules and small veins; Budd-Chiari syndrome (obstruction of the large hepatic veins).

*Enlargement of the hepatocytes* (fat deposition, cell swelling, hyperplasia) and increased production of extracellular matrix (→ p. 172) both contribute to sinusoidal obstruction. As the extracellular matrix also impairs the exchange of substances and gases between sinusoids and hepatocytes, cell swelling is further increased. *Amyloid deposits* can have a similar obstructive effect. Finally, in acute hepatitis and acute liver necrosis the sinusoidal space can also be obstructed by *cell debris*.

**Consequences of portal hypertension**. Wherever the site of obstruction, an increased portal vein pressure will lead to disorders in the preceding organs (*malabsorption*, splenomegaly with anemia and thrombocytopenia) as well as to blood flowing from abdominal organs via vascular channels that bypass the liver. These *portal bypass circuits* (→ A3) use collateral vessels that are normally thin-walled but are now greatly dilated (*formation of varices*; “haemorrhoids” of the rectal venous plexus; *caput medusae* at the paraumbilical veins). The enlarged *esophageal veins* are particularly in danger of rupturing. This fact, especially together with *thrombocytopenia* (see above) and a deficiency in clotting factors (reduced synthesis in a damaged liver), can lead to massive bleeding that can be acutely life-threatening.

The vasodilators liberated in portal hypertension (glucagon, VIP, substance P, prostacyclins, NO, etc.) also lead to a *fall in systemic blood pressure*. This will cause a compensatory rise in cardiac output, resulting in hyperperfusion of the abdominal organs and the collateral (bypass) circuits.

**Liver function** is usually unimpaired in prehepatic and presinusoidal obstruction, because blood supply is assured through a compensatory increase in flow from the hepatic artery. Still, in sinusoidal, postsinusoidal, and posthepatic obstruction liver damage is usually the cause and then in part also the result of the obstruction. As a consequence, drainage of protein-rich hepatic lymph is impaired and the increased portal pressure, sometimes in synergy with a reduction in the plasma’s osmotic pressure due to liver damage (*hypoalbuminemia*), pushes a protein-rich fluid into the abdominal cavity, i.e., *ascites* develops. This causes secondary hyperaldosteronism (→ p. 174) that results in an increase in extracellular volume.

As blood from the intestine bypasses the liver, toxic substances (NH₃, biogenic amines, short-chain fatty acids, etc.) that are normally extracted from portal blood by the liver cells reach the central nervous system, among other organs, so that portal systemic (“hepatic”) *encephalopathy* develops (→ p. 174).
A. Causes and Consequences of Portal Hypertension

- Fibrosis, cirrhosis
- Alcohol, fatty liver
- Acute hepatitis, amyloidosis
- Granulomas
- Right heart failure, constrictive pericarditis
- Portal vein thrombosis
- Intrahepatic obstructions:
  - postsinusoidal
  - presinusoidal
- Sinusoidal, postsinusoidal, and posthepatic obstruction
- Normal pressure: 4–8 mmHg
- Liver damage
  - Hypalbuminemia
  - Ascites
- Malabsorption
  - Splenomegaly
  - Vasodilation
  - Blood pressure
- Portal hypertension
  - Portal collateral circulation
  - Varices
  - Portal vein
  - Esoph. vv.
  - Int. iliac v.
  - Rectal venous plexus
- Right heart failure, constrictive pericarditis
- Portal vein thrombosis

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Fibrosis and Cirrhosis of the Liver

Liver cirrhosis is a disease in which necrosis, inflammation, fibrosis, nodular regeneration, and formation of vascular anastomoses develop more or less simultaneously. It is usually caused by the long-term action of noxious factors, especially alcohol abuse, which is the cause in 50% of cases worldwide. While the probability of cirrhosis developing after a cumulative uptake of 13 kg ethanol/kg body weight is only about 20%, it rises to over 90% after 40 kg. The substance that is most responsible for the development of fibrosis, and thus cirrhosis, is the ethanol metabolite acetaldehyde. Cirrhosis can also be the final stage of viral hepatitis (20–40% of cirrhosis cases in Europe). In acute fulminating disease it may develop in a matter of weeks; in chronic recurrent disease after months or years. It can also occur after an obstruction to blood outflow (congestive liver; → p.170) or after other liver damage, for example, as final stage of a storage disease (hemochromatosis, Wilson's disease; → p.252) or genetically determined enzyme deficiency.

Factors involved in liver-cell damage are:
- ATP deficiency due to abnormal cellular energy metabolism;
- increased formation of highly reactive oxygen metabolites (O$_2^–$, ·OH, H$_2$O$_2$, H$_2$O$_2$) with concomitant deficiency of antioxidants (e.g., glutathione) and/or damage of protective enzymes (glutathione peroxidase, superoxide dismutase).

The O$_2$ metabolites react with, for example, unsaturated fatty acids in phospholipids (lipid peroxidation). This contributes to damage of plasma membranes and cell organelles (lysosomes, endoplasmic reticulum). As a result, cytosolic Ca$^{2+}$ concentration rises, activating proteases and other enzymes so that the cells are ultimately irreversibly damaged.

Fibrosis of the liver develops in several steps (→ A). When damaged hepatocytes die, lysosomal enzymes, among others, leak out and release cytokines from the extracellular matrix. These cytokines and the debris of the dead cells activate the Kupffer cells in the liver sinusoids (→ A, center) and attract inflammatory cells (granulocytes, lymphocytes, and monocytes). Diverse growth factors and cytokines are then liberated from the Kupffer cells and the recruited inflammatory cells. These growth factors and cytokines now
- transform the fat-storing Ito cells of the liver into myofibroblasts
- transform the imigrated monocytes into active macrophages
- trigger the proliferation of fibroblasts

The chemotactic action of transforming growth factor β (TGF-β) and monocyte chemotactic protein 1 (MCP-1), whose release from the Ito cells (stimulated by tumor necrosis factor α [TNF-α], platelet-derived growth factor [PDGF], and interleukins) strengthens these processes, as do a number of other signaling substances. As a result of these numerous interactions (the details of which are not yet entirely understood), the production of the extracellular matrix is increased by myofibroblasts and fibroblasts, i.e., leading to an increased deposition of colagens (Types I, III, and IV), proteoglycans (decorin, biglycan, lumican, aggrecan), and glycoproteins (fibronectin, laminin, tenascin, undulin) in the Dissé space. Fibrosis of the latter impairs the exchange of substances between sinusoid blood and hepatocytes, and increases the flow resistance in the sinusoids (→ p.170).

The excess amount of matrix can be broken down (by metalloproteases, in the first instance), and the hepatocytes may regenerate. If the necroses are limited to the centers of the liver lobules (→ A, top left), full restitution of the liver’s structure is possible. However, if the necroses have broken through the peripheral parenchyma of the liver lobules, connective tissue septa are formed (→ A, bottom). As a result, full functional regeneration is no longer possible and nodules are formed (cirrhosis). The consequence of this is cholestasis (→ p.168), portal hypertension (→ p.170), and metabolic liver failure (→ p.174).
A. Fibrosis and Cirrhosis of the Liver

Noxious factors (alcohol, viral hepatitis, etc.) → Necrosis → Enzyme leak → Cell debris

Hepatocyte → Matrix → Cytokines and other matrix components

Kupffer cell → MCP-1 → Chemotaxis

Ito (fat) cell → Myofibroblast → TGFβ → Extracellular matrix production

Collagen type I, III, IV → Proteoglycans → Matrix glycoproteins

Fibroblast proliferation

Fibrosis

Cholestasis

Cirrhosis

Portal hypertension

Nodular regeneration with loss of lobular structure

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Liver Failure (see also p. 170 ff.)

Causes of acute liver failure (→ A) are poisoning and inflammation, for example, fulminant cholangitis or viral hepatitis (especially in hepatitis B and E). The causes of chronic liver failure that is accompanied by fibrosis (cirrhosis) of the liver (→ p. 172) are (→ A):
- inflammation, for example, chronic persistent viral hepatitis;
- alcohol abuse, the most common cause;
- in susceptible patients, side effects of drugs, for example, folic acid antagonists, phenylbutazone;
- Cardiovascular causes of impairment of venous return, for example, in right heart failure (→ p. 170)
- a number of inherited diseases (→ chap. 8), for example, glycogen storage diseases, Wilson’s disease, galactosemia, hemochromatosis, α1-antitrypsin deficiency;
- intrahepatic or posthepatic cholestasis (→ p. 168) for prolonged periods, for example, in cystic fibrosis (→ p. 162), a stone in the common bile duct (→ p. 164 ff.), or tumors.

The most serious consequences of liver failure are:
- **Protein synthesis** in the liver is reduced. This can lead to hypoalbuminemia that may result in ascites, i.e., an accumulation of extracellular fluid in the abdominal cavity, and other forms of edema (→ p. 234). Plasma volume is reduced as a result, secondary hyperaldosteronism develops causing hypokalemia, which in turn encourages alkalosis (→ A, left). In addition, the reduced ability of the liver to synthesize causes a fall in the plasma concentration of clotting factors.
- **Cholestasis** occurs (→ p. 168), producing not only liver damage but also aggravating any bleeding tendency, because the lack of bile salts decreases micellar formation and with it the absorption of vitamin K from the intestine, so that γ-carboxylation of the vitamin K-dependent clotting factors prothrombin (II), VII, IX, and X is reduced.
- **Portal hypertension** develops (→ p. 170) and may make the ascites worse because of lymphatic flow impairment. It may cause thrombocytopenia resulting from splenomegaly, and may lead to the development of esophageal varices. The deficiency in active clotting factors, thrombocytopenia, and varices are likely to cause severe bleeding. Finally, portal hypertension can cause an exudative enteropathy. This will increase the ascites due to loss of albumin from the plasma, while at the same time favoring bacteria in the large intestine being “fed” with proteins that have passed into the intestinal lumen, and thus increasing the liberation of ammonium, which is toxic to the brain.
- The hyperammonemia, which is partly responsible for the encephalopathy (apathy, memory gaps, tremor, and ultimately liver coma) is increased because
  - gastrointestinal bleeding also contributes to an increased supply of proteins to the colon;
  - the failing liver is no longer sufficiently able to convert ammonium ($\text{NH}_3\cdot\text{NH}_4^+$) to urea;
  - the above-mentioned hypokalemia causes an intracellular acidosis which activates ammonium formation in the cells of the proximal tubules and at the same time causes a systemic alkalosis. A respiratory component is added to the latter if the patient hyperventilates due to the encephalopathy.

Further substances that are toxic to the brain bypass the liver in portal hypertension and are therefore not extracted by it as would normally be the case. Those substances, such as amines, phenols, and short-chain fatty acids, are also involved in the encephalopathy. Lastly, the brain produces “false transmitters” (e.g., serotonin) from the aromatic amino acids, of which there are increased amounts in plasma when liver failure occurs. These transmitters probably play a part in the development of the encephalopathy.

Kidney function is impaired, giving rise to the hepatorenal syndrome (→ p. 118).
A. Causes and Consequences of Liver Failure

1. Inflammations (viral hepatitis, cholangitis, etc.)
2. Toxins (e.g. organic nutrients)
3. Alcohol
4. Venous congestion (e.g. in right heart failure)
5. Various inherited diseases

Liver Failure

- Chronic
- Acute
- Cirrhosis

Causes and Consequences:

- Hypoalbuminemia
- Portal hypertension
- Cholestasis
- Fat absorption
- Vitamin K deficiency
- Varices
- Exudative enteropathy
- Clotting factors
- Gastrointestinal bleeding
- Hyperaldosteronism
- Hypokalemia
- Renal NH$_4^+$ production
- Hyperammoniemia
- Alkalosis
- Hyperventilation
- Encephalopathy

Hyperammoniemia

Exudative enteropathy

Gastrointestinal bleeding

Hyperaldosteronism

Hypokalemia

Renal NH$_4^+$ production

Hyperammoniemia

Alkalosis

Hyperventilation

Encephalopathy

Aromatic amino acids

Urea

NH$_4^+$ + HCO$_3^-$

H$_2$N

CO

NH$_2$

Vitamin K deficiency

Fat absorption

Varices

Exudative enteropathy

Gastrointestinal bleeding

Hyperaldosteronism

Hypokalemia

Renal NH$_4^+$ production

Hyperammoniemia

Alkalosis

Hyperventilation

Encephalopathy

Aromatic amino acids

Urea

NH$_4^+$ + HCO$_3^-$
Overview

The left ventricle (LV) of the heart pumps the blood through the arterial vessels of the systemic circulation into the capillaries throughout the body. Blood returns to the heart via the veins and is then pumped by the right ventricle (RV) into the pulmonary circulation and thus returns to the left heart (→ A).

The total blood volume is about 4.5–5.5 L (ca. 7% of fat-free body mass; → p. 28), of which about 80% is held in the so-called low pressure system, i.e., the veins, right heart, and the pulmonary circulation (→ A). Because of its high compliance and large capacity, the low pressure system serves as a blood store. If the normal blood volume is increased, e.g., by blood transfusion, more than 98% of the infused volume goes to the low pressure and less than 2% to the high pressure system. Conversely, if the blood volume is decreased, it is almost exclusively the low pressure system that is reduced. When cardiac and pulmonary function is normal, the central venous pressure (normally 4–12 cm H₂O) is a good measure of the blood volume.

Cardiac output (CO) is the product of heart rate and stroke volume and at rest amounts to ca. 70 [min⁻¹] · 0.08 [L], i.e., ca. 5.6 L/min (more precisely, a mean of 3.4 L/min per m² body surface area, a value called cardiac index (CI). CO can be increased many times over by a rise in heart rate and/or stroke volume (SV).

CO is distributed among the organs that are arranged in parallel within the systemic circulation (→ A, Q values), their share being dependent on how vital they are, on the one hand, and on the momentary demands, on the other. Maintenance of an adequate blood supply to the brain takes priority (ca. 13% of resting CO), as this is not only a vital organ, but also because it reacts especially sensitively to oxygen deficiency, and nerve cells, once destroyed, cannot usually be replaced (→ p. 2 ff). Blood flow through the coronary arteries of the heart muscle (at rest ca. 4% of CO; → p. 216) must not fall, because the resulting abnormal pump function can impair the entire circulation. The kidneys receive ca. 20–25% of CO. This proportion, very high in relation to their weight (only 0.5% of body weight) largely serves their control and excretory functions. If there is a risk of imminent circulatory shock (→ p. 231), renal blood supply may be temporarily reduced in favor of the heart and brain. When physical work is markedly increased, blood flow through the skeletal muscles is raised to ca. ¼ of the (now greater) CO. During digestion the gastrointestinal tract receives a relatively large proportion of CO. It is obvious that these two groups of organs cannot both have maximal blood perfusion at the same time. Blood flow through the skin (ca. 10% of CO at rest) serves, in the first instance, to remove heat. It is therefore raised during increased heat production (physical exercise) and/or at high ambient temperature (→ p. 20 ff.), but can, on the other hand, be reduced in favor of vital organs (pallor, e.g., in shock; → p. 230 ff).

The entire CO flows through the pulmonary circulation, since it is connected in series with the systemic circulation (→ A). Via the pulmonary artery low-oxygen (“venous”) blood reaches the lungs, where it is enriched with oxygen (“arterialized”). In addition, a relatively small volume of arterialized blood from the systemic circulation reaches the lung via the bronchial arteries that supply the lung tissue itself. Both supplies then drain into the left atrium (LA) via the pulmonary veins.

Flow resistance in the pulmonary circulation is only ¼ of total peripheral resistance (TPR), so that the mean pressure that has to be generated by the RV in the pulmonal artery (ca. 15 mmHg = 2 kPa) is much less than that which needs to be generated by the LV in the aorta (100 mmHg ≈ 13.3 kPa). The main resistance in the systemic circulation is due to the small arteries and arterioles (→ A, upper right), which for this reason are called resistance vessels.
A. Cardiovascular System

Volume distribution

- Heart (diastole): 7%
- Small arteries and arterioles: 8%
- Large arteries: 5%
- Capillaries: 9%
- Lung: 7%
- Brain: 64%
- Small arteries and arterioles: 47%
- Capillaries: 27%
- Arteries: 19%
- Veins: 7%

Distribution of vascular resistance in the systemic circulation:

- Pulm. art. pressure: 25/10 mmHg (mean pressure 15 mmHg)
- Aortic pressure: 120/80 mmHg (mean pressure 100 mmHg)
- Coronary circulation: Q = 4% V̇O₂ = 11%
- Brain: Q = 13% V̇O₂ = 21%
- Lung: V̇O₂ = 27%
- Heart (diastole): 64%
- Small arteries and arterioles: 47%
- Large arteries: 27%
- Capillaries: 7%
- Arteries: 19%
- Veins: 7%

Organ perfusion in % of cardiac output (resting CO ≈ 5.6 L/min in person weighting 70 kg)

- Heart (diastole): 7%
- Small arteries and arterioles: 8%
- Large arteries: 5%
- Capillaries: 9%
- Lung: 7%
- Brain: 64%
- Small arteries and arterioles: 47%
- Capillaries: 27%
- Arteries: 19%
- Veins: 7%

Organ perfusion in % of cardiac output (resting CO = 5.6 L/min)

- Heart (diastole): 7%
- Small arteries and arterioles: 8%
- Large arteries: 5%
- Capillaries: 9%
- Lung: 7%
- Brain: 64%
- Small arteries and arterioles: 47%
- Capillaries: 27%
- Arteries: 19%
- Veins: 7%

Organ perfusion in % of total O₂ consumption (total consumption at rest = 0.25 L/min)

- Heart (diastole): 7%
- Small arteries and arterioles: 8%
- Large arteries: 5%
- Capillaries: 9%
- Lung: 7%
- Brain: 64%
- Small arteries and arterioles: 47%
- Capillaries: 27%
- Arteries: 19%
- Veins: 7%
Phases of Cardiac Action (Cardiac Cycle)

Resting heart rate is ca. 70 beats per minute. The four periods of ventricular action thus take place within less than one second (→ A): the iso(volu)metric (I) and ejection (II) periods of the systole, and the iso(volu)metric relaxation (III) and filling (IV) periods of the diastole, at the end of which the atria contract. These mechanical periods of cardiac activity are preceded by the electrical excitation of the ventricles and atria, respectively.

The cardiac valves determine the direction of blood flow in the heart, namely from the atria into the ventricles (period IV) and from the latter into the aorta and pulmonary artery (period II), respectively. During periods I and III all valves are closed. Opening and closing of the valves is determined by direction of the pressure gradient between the two sides of the valves.

Cardiac cycle. At the end of the diastole (period IVc), the sinus node passes on its action potential to atrial muscle (P wave in the electrocardiogram [ECG]: → A1), the atria contract, and immediately thereafter the ventricles are stimulated (QRS complex in the ECG). The ventricular pressure starts to rise and when it exceeds that in the atria the atrioventricular (tricuspid and mitral) valves close. This ends diastole, the end-diastolic volume (EDV) in the ventricle averaging ca. 120 mL (→ A4), or 70 mL/m² body surface area (b.s.a.) at rest.

There follows the iso(volu)metric period of the systole (I) during which the ventricular myocardium contracts without change in the volume of the ventricular cavity (all valves are closed [iso(volu)metric contraction; first heart sound]; → A6) so that the intraventricular pressure rapidly rises. The left ventricular pressure will exceed the aortic pressure when it reaches about 80 mmHg (10.7 kPa), while the right ventricular pressure will exceed that in the pulmonary artery at about 10 mmHg. At this moment the semilunar (aortic and pulmonary) valves open (→ A).

This starts the ejection period (II), during which the left ventricular and aortic pressures reach a maximum of ca. 120 mmHg (16 kPa). The largest proportion of the stroke volume (SV) is rapidly ejected during the early phase (IIa; → A4), flow velocity in the aorta rising to its maximum (→ A5). The ventricular pressure then begins to fall (remainder of the SV is ejected more slowly, IIb), finally to below that in the aorta and pulmonary artery, when the semilunar valves close (second heart sound). The average SV is 80 mL (47 mL/m² b.s.a.), so that the ejection fraction (= SV/EDV) is about 0.67 at rest. Thus, a residual volume of ca. 40 mL remains in the ventricle (endsystolic volume [ESV]: → A4).

Diastole now begins with the iso(volu)metric relaxation period (III). In the meantime the atria have filled again, a process to which the suction effect produced by the lowering of the valve level (momentarily enlarging atrial volume) during the ejection period has contributed the most (drop in the central venous pressure [CVP] from c to x; → A3). Ventricular pressure falls steeply (→ A2), while atrial pressure has risen in the meantime (inflow of blood: v wave in CVP), so that the leaflets of the tricuspid and mitral valves open again.

The filling period (IV) begins. Blood rapidly flows from the atria into the ventricles (drop in pressure y in CVP) so that, at normal heart rate, they are filled to 80% in only a quarter of the duration of diastole (rapid filling phase [IVa]; → A4). Filling then slows down ([IVb]; a-wave of CVP; → A2 and A3). At normal heart rates, atrial contraction contributes ca. 15% of total ventricular filling. At higher heart rates, the duration of the cardiac cycle is shortened, especially that of the diastole, so that the contribution of atrial contraction to ventricular filling becomes more important.

The third and fourth heart sounds (produced by the inflow of blood and by atrial contraction during early diastole, respectively) occur normally in children, but in adults they are abnormal (→ p. 197 f.).

The intermittent cardiac activity produces a pulse wave that spreads along the arterial system at pulse wave velocity (aorta: 3–5 m/s; radial artery: 5–10 m/s). This is much higher than the flow velocity (in aorta: maximally 1 m/s) and is faster the thicker and more rigid the vessel wall is (increase in hypertension and with advancing age) and the smaller the vessel radius.
A. Phases of Cardiac Action (Cardiac Cycle)

- **Isovolumetric contraction**
- **Atrial systole**
- **Isovolumetric relaxation**
- **Passive ventricular filling**
- **Ejection phase**

---

**ECG**

1. **Ventricular systole**
2. **Ventricular diastole**
3. **Aortic pressure**
4. **Pressure in the left ventricle**
5. **Pressure in the left atrium**
6. **Central venous pressure (CVP)**
7. **Volume in left ventricle**
8. **Flow rate in the aorta**
9. **End-diastolic volume (EDV)**
10. **Stroke volume (SV)**
11. **Residual (endsystolic) volume (ESV)**

---

- **Heart sounds**
- **Duration**

<table>
<thead>
<tr>
<th>Heart sounds</th>
<th>Duration (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>50</td>
</tr>
<tr>
<td>II</td>
<td>210</td>
</tr>
<tr>
<td>III</td>
<td>60</td>
</tr>
<tr>
<td>IV</td>
<td>Markedly heart rate-dependent (at 70 min⁻¹): ca. 500 ms</td>
</tr>
</tbody>
</table>

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Origin and Spread of Excitation in the Heart

The heart contains muscle cells (fibers) that produce and distribute excitation impulses (conducting system), as well as working myocardium, which responds to the excitation by contracting. Contrary to the situation in skeletal muscle, excitation originates within the organ (autorhythmicity or autonomy of the heart). Atrial and ventricular myocardium each consists functionally of a syncytium, i.e., the cells are not insulated from one another but connected through gap junctions. A stimulus that originates somewhere within the atria or ventricles thus always leads to complete contraction of both atria or of both ventricles, respectively (all-or-nothing contraction).

Normal excitation of the heart originates within the sinus node, the heart’s pacemaker. Excitation (→A) spreads from there through both atria to the atroventricular node (AV node) and from there, via the His bundle and its two (Tawara) branches, reaches the Purkinje fibers, which transmit the excitation to the ventricular myocardium. Within the myocardium the excitation spreads from inside to outside (endocardium toward epicardium) and from apex toward the base, a process that can be followed—even in the intact organism—by means of the ECG (→p. 184; →C).

The potential in the cells of the sinus node is a pacemaker potential (→B1, bottom). It has no constant resting potential, but rises after each repolarization. The most negative value of the latter is called maximal diastolic potential (MDP) ca. −70 mV. It rises steadily until the threshold potential (TP) ca. −40 mV is reached once more and an action potential (AP) is again triggered.

The following changes in ionic conductance (g) of the plasma membrane and thus of ionic currents (I) cause these potentials (→B1, top): Beginning with the MDP, nonselective conductance is increased and influx (I; f = funny) of cations into the cell leads to slow depolarization (prepotential = PP). Once the TP has been reached, g Na now rises relatively rapidly, the potential rising more steeply so that an increased influx of Ca2+ (I ca) produces the upstroke of the AP. While the potential overshoots to positive values, leading to an outward K+ flux I k, the pacemaker cell is again repolarized to the MDP.

Each AP in the sinus node normally results in a heart beat, i.e., the impulse frequency of the pacemaker determines the rate of the heart beat. The rate is lower if

- the rise of the slow depolarization becomes less steep (→B3a),
- the TP becomes less negative (→B3b),
- the MDP becomes more negative so that spontaneous depolarization begins at a lower level (→B3c), or
- repolarization in an AP starts later or is slower.

What the first three processes have in common is that the threshold is reached later than before.

All parts of the excitation/conduction system have the capacity of spontaneous depolarization, but the sinus node plays the leading role in normal cardiac excitation (sinus rhythm is ca. 70–80 beats per minute). The reason for this is that the other parts of the conduction system have a lower intrinsic frequency than the sinus node (→Table in C; causes are that slow depolarization and repolarization are flatter; see above). Excitation starting from the sinus node will thus arrive at more distal parts of the conducting system, before their spontaneous depolarization has reached the TP. However, if conduction of the sinus impulse is interrupted (→p. 186ff.), the intrinsic frequency of more distal parts of the conduction system take over and the heart then beats in AV rhythm (40–60 beats per minute) or, in certain circumstances, at the even lower rate of the so-called tertiary (ventricular) pacemakers (20–40 beats per minute).

In contrast to the sinus and AV nodes with their relatively slowly rising AP, due largely to an influx of Ca2+ (→A), there are in the working myocardium so-called rapid, voltage-gated Na+ channels that at the beginning of the AP briefly cause a high Na+ influx and therefore, compared with the pacemaker potential, a relatively rapid rise in the upstroke of the AP (→A). The relatively long duration (compared with skeletal muscle) of myocardial AP, giving
A. Cardiac Excitation

ECG

Pacemaker potential (spontaneous depolarization)

Action potentials

100 mV

Myocardium relatively refractory: vulnerable period

Stable resting potential

B. Pacemaker Potential and Excitation Rate in the Heart

1 Ionic currents and pacemaker potential

(after Francesco)

Inward current

Outward current

Membrane potential (mV)

Duration of myocardial action potential depends on the rate of excitation

(after Trautwein et al.)

2 3 Heart rate changes due to changes in pacemaker potential

Rising slope (dV/dt) of prepotential

Threshold potential

Maximal diastolic potential

4 Factors influencing conduction of the action potentials (AV node)

Steep: rapid conduction

Shallow: slow conduction

e.g. Sympathetic stimulation, temperature ↓, quinidine

e.g. Parasympathetic stimulation, temperature ↑, Vagus n.

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it the shape of a *plateau*, has an important function in that it prevents circles of myocardial excitation (*reentry*; → p. 186 ff.). This also holds true for very high and low heart rates, because the duration of AP adapts to the heart rate (→ B2).

The AP results in Ca\(^{2+}\) being taken up from the extracellular space via voltage-gated Ca\(^{2+}\) channels that are sensitive to dihydropyridine. In consequence, the cytosolic Ca\(^{2+}\) concentration rises locally (Ca\(^{2+}\) “spark”), whereupon the ligand-gated and ryanodine-sensitive Ca\(^{2+}\) channels of the sarcoplasmic reticulum, acting as Ca\(^{2+}\) store, open up (so-called trigger effect). Ca\(^{2+}\), which enters from there into the cytosol, finally triggers the electromechanical coupling of cardiac contraction. The cytosolic concentration of Ca\(^{2+}\) is also determined by the Ca\(^{2+}\) uptake into the Ca\(^{2+}\) stores (via Ca\(^{2+}\)-ATPase) as well as by Ca\(^{2+}\) transport into the extracellular space. The latter is brought about both by a Ca\(^{2+}\)-ATPase (exchanges 1 Ca\(^{2+}\) for 2 H\(^{+}\)) and by a 3 Na\(^{+}\)/Ca\(^{2+}\) exchange carrier that is driven by the electrochemical Na\(^{+}\)-K\(^{+}\) gradient, thus indirectly by Na\(^{+}\)-K\(^{+}\)-ATPase, across the cell membrane.

Although the heart beats autonomously, adaptation of cardiac activity to changing demands is mostly effected through efferent cardiac nerves. The following qualities of cardiac activity can be modified by nerves:

- **Rate** of impulse formation of the pacemaker and thus of the heart beat (chronotropism);
- **Velocity** of impulse conduction, especially in the AV node (dromotropism);
- The force of myocardial contraction at a given distension, i.e., the heart's contractility (inotropism);
- **Excitability** of the heart in the sense of changing its excitability threshold (batmotropism).

These changes in cardiac activity are caused by parasympathetic fibers of the vagus nerve and by sympathetic fibers. **Heart rate** is increased by the activity of sympathetic fibers to the sinus node (positive inotropic effect via β\(_{1}\)-receptors) and decreased by parasympathetic, muscarinic fibers (negative chronotropic effect). This is due to changes in the slow depolarization rise and altered MDP in the sinus node (→ B3a and B3c, respectively). Flattening of the slow depolarization and the more negative MDP under vagus action are based on an increased g\(_{K}\), while the increased steepness of slow depolarization under sympathetic action or adrenalin influence is based on an increase in g\(_{Ca}\) and, in certain circumstances, a decrease in g\(_{K}\). The more subordinate (more peripheral) parts of the conduction system are acted on chronotropically only by sympathetic fibers, which gives the latter a decisive influence in any possible takeover of pacemaker function by the AV node or tertiary pacemakers (see above).

The parasympathetic fibers of the left vagus slow down while the sympathetic fibers accelerate **impulse transmission in the AV node** (negative or positive dromotropic action, respectively). The main influence is on the MDP and the steepness of the AP upstroke (→ B3c and B4). Changes in g\(_{K}\) and g\(_{Ca}\) play an important role here as well.

In contrast to chronotropism and dromotropism, the sympathetic nervous system, by being positively inotropic, has a direct effect on the working myocardium. The increased contractility is due to an *increase in Ca\(^{2+}\) influx*, mediated by β\(_{1}\)-adrenergic-receptors, from outside the cell that allows an increase in the Ca\(^{2+}\) concentration in the cytosol of the myocardial cells. This Ca\(^{2+}\) influx can be inhibited pharmacologically by blocking the Ca\(^{2+}\) channels (so-called Ca\(^{2+}\) antagonists).

Contractility is also increased by prolonging the AP (and as a result shortening Ca\(^{2+}\) influx), as well as inhibiting Na\(^{+}\)-K\(^{+}\)-ATPase, for example, by means of the cardiac glycosides digoxin and digitoxin (smaller Na\(^{+}\) gradient across the cell membrane → lower efficiency of 3 Na\(^{+}\)/Ca\(^{2+}\) exchange → decreased Ca\(^{2+}\) extrusion → increased cytosolic Ca\(^{2+}\) concentration).

At a lower heart rate the Ca\(^{2+}\) influx over time is low (few APs), so that there is a relatively long period in which Ca\(^{2+}\) outflux can take place between APs. Thus, the mean cytosolic concentration of Ca\(^{2+}\) becomes lower and contractility is held low as a result. The vagus nerve can also act via this mechanism; however, it does so indirectly through negative inotropy (frequency inotropism). The converse is true for sympathetic stimulation.
C. Spread of Excitation in the Heart

Normal sequence of activation

<table>
<thead>
<tr>
<th>Sinus node</th>
<th>Time (ms)</th>
<th>ECG</th>
<th>Conduction velocity ($\text{m} \cdot \text{s}^{-1}$)</th>
<th>Inherent rate ($\text{min}^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impulse formation</td>
<td>0</td>
<td>P wave</td>
<td>0.05</td>
<td>60–100</td>
</tr>
<tr>
<td>Impulse arrival at right atrium</td>
<td>50</td>
<td></td>
<td>0.8–1.0 in atrium</td>
<td></td>
</tr>
<tr>
<td>left atrium</td>
<td>85</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AV node</td>
<td>50</td>
<td>PQ segment (excitation delayed)</td>
<td>0.05</td>
<td>40–55</td>
</tr>
<tr>
<td>Impulse arrival</td>
<td>125</td>
<td></td>
<td>1.0–1.5</td>
<td></td>
</tr>
<tr>
<td>Impulse transmission</td>
<td>130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>His bundle activated</td>
<td>145</td>
<td></td>
<td>1.0–1.5</td>
<td></td>
</tr>
<tr>
<td>Distal bundle activated</td>
<td>150</td>
<td></td>
<td>3.0–3.5</td>
<td></td>
</tr>
<tr>
<td>Purkinje fibers activated</td>
<td>175</td>
<td>QRS complex</td>
<td>1.0</td>
<td>None</td>
</tr>
<tr>
<td>Subendocardial myocardium completely activated</td>
<td>190</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>right ventricle</td>
<td>205</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>left ventricle</td>
<td>225</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subepicardial myocardium completely activated</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The Electrocardiogram (ECG)

The ECG is a recording of potential differences (in mV) that are generated by the excitation within the heart. It can provide information about the position of the heart and its rate and rhythm as well as the origin and spread of the action potential, but not about the contraction and pumping action of the heart.

The ECG potentials originate at the border between excited and nonexcited parts of the myocardium. Nonexcited or completely excited (i.e., depolarized) myocardium does not produce any potentials which are visible in the ECG. During the propagation of the excitation front through the myocardium, manifold potentials occur, differing in size and direction. These vectors can be represented by arrows, their length representing the magnitude of the potential, their direction indicating the direction of the potential (arrow head: +). The many individual vectors, added together, become a summated or integral vector (→ A, red arrow). This changes in size and direction during excitation of the heart, i.e., the arrow head of the summated vector describes a loop-shaped path (→ A) that can be recorded oscillographically in the vectorcardiogram.

The limb and precordial leads of the ECG record the temporal course of the summed vectors, projected onto the respective plane (in relation to the body) of the given lead. A lead parallel to the summated vector shows the full deflection, while one at a right angle to it shows none. The Einthoven (or standard limb) leads I, II, and III are bipolar (→ C1,2) and lie in the frontal plane. For the unipolar Goldberger (limb) leads, aVL, aVR, and aVF (a = augmented) (→ C3), one limb electrode (e.g., the left arm in aVL) is connected to the junction of the two other limb electrodes. These leads, too, lie in the frontal plane. The unipolar precordial leads V1–V6 (Wilson leads; → C4) lie approximately in the horizontal plane (of the upright body). They mainly record those vectors that are directed posteriorly. As the mean QRS vector (see below) mainly points downward to the left and posteriorly, the thoracic cage is divided into a positive and a negative half by a plane which is vertical to this vector. As a result, the QRS vector is usually negative in V1–V3, positive in V5–V6.

An ECG tracing (→ B and p. 183 C) has waves, intervals, and segments (deflection upward +, downward −). The P wave (normally < 0.25 mV, < 0.1 s) records depolarization of the two atria. Their repolarization is not visible, because it is submerged in the following deflections. The Q wave (mV < ¼ of R), the R and S waves (R + S > 0.6 mV) are together called the QRS complex (< 0.1 s), even when one of the components is missing. It records the depolarization of the ventricles; the T wave records their repolarization. Although the two processes are opposites, the T wave is normally in the same direction as that of the QRS complex (usually + in most leads), i.e., the sequence of the spread of excitation and of repolarization differs: the APs in the initially excited fibers (near the endocardium) last longer than those excited last (near the epicardium). The PQ segment (fully depolarized atria) and the ST segment (fully depolarized ventricles) are approximately at the zero mV level (isoelectric line). The PQ interval (< 0.2 s; → B) is also called (atrioventricular) transmission time. The QT interval (→ B) depends on heart rate. It is normally 0.35–0.40 seconds at 75 beats per minute (time taken for ventricular depolarization and repolarization).

The six frontal limb leads (standard and augmented) are included in the Cabrera circle (→ C3). The simultaneous summated vector in the frontal plane, for example, the mean QRS vector, can be determined by using the Einthoven triangle or the Cabrera circle (→ C2, red arrow). When the spread of excitation is normal, its position corresponds approximately to the anatomic longitudinal axis of the heart (electrical axis of the heart). The potential of the mean QRS vector is calculated (taking the positivity and negativity of the deflections into account) from the height of the Q, R, and S deflections. The normal positional type of the electrical axis extends from ca. + 90° to ca. − 30° (for arrangement of degrees → C3). Abnormal positional types are marked right axis deviation (>+ 120°), for example, in right ventricular hypertrophy, and marked left axis deviation (more negative than − 30°), for example, in left ventricular hypertrophy. Extensive myocardial infarcts can also change the electrical axis.
A. Vector Loops in Cardiac Excitation

B. ECG Tracing

C. Bipolar Leads (Standard: 1, 2, 3) and Unipolar (Goldberger: 3, precordial: 4)
Abnormalities of Cardiac Rhythm

Disorders of rhythm (arrhythmias or dysrhythmias) are changes in the formation and/or spread of excitation that result in a changed sequence of atrial or ventricular excitation or of atrioventricular transmission. They can affect rate, regularity, or site of action potential formation.

Action potential formation in the sinus node occurs at a rate of 60–100 per minute (usually 70–80 per minute at rest; \( \rightarrow A1 \)). During sleep and in trained athletes at rest (vagotonia) and also in hypothyroidism, the rate can drop below 60 per minute (sinus bradycardia), while during physical exercise, excitement, fever (\( \rightarrow p.20 \)), or hyperthyroidism it may rise to well above 100 per minute (sinus tachycardia; \( \rightarrow A2 \)). In both cases the rhythm is regular, while the rate varies in sinus arrhythmia. This arrhythmia is normal in juveniles and varies with respiration, the rate accelerating in inspiration, slowing in expiration.

Tachycardia of ectopic origin. Even when the stimulus formation in the sinus node is normal (\( \rightarrow A \)), abnormal ectopic excitations can start from a focus in an atrium (atrial), the AV node (nodal), or a ventricle (ventricular). High-frequency ectopic atrial depolarizations (saw-toothed base line instead of regular P waves in the ECG) cause atrial tachycardia, to which the human ventricles can respond to up to a rate of ca. 200 per minute. At higher rates, only every second or third excitation may be transmitted, as the intervening impulses fall into the refractory period of the more distal conduction system, the conduction component with the longest AP being the determining factor. This is usually the Purkinje fibers (\( \rightarrow C \), middle row), which act as frequency filters, because their long action potential stays refractory the longest, so that at a certain rate further transmission of the stimulus is blocked (in Table C between 212 and 229 per minute; recorded in a dog). At higher rates of discharge of the atrial focus (up to 350 per minute = atrial flutter; up to 500 per minute = atrial fibrillation), the action potential is transmitted only intermittently. Ventricular excitation is therefore completely irregular (absolutely arrhythmic). Ventricular tachycardia is characterized by a rapid succession of ventricular depolarizations. It usually has its onset with an extrasystole (IES) see below; \( \rightarrow B3 \), second ES). Ventricular filling and ejection are reduced and ventricular fibrillation occur (high-frequency and uncoordinated twitchings of the myocardium; \( \rightarrow B4 \)). If no countermeasures are taken, this condition is just as fatal as cardiac arrest, because of the lack of blood flow.

Extrasystoles (ES). When an action potential from a supraventricular ectopic focus is transmitted to the ventricles (atrial or nodal extrasystole), it can disturb their regular (sinus) rhythm (supraventricular arrhythmia). An atrial ES can be identified in the ECG by a distorted (and premature) P wave followed by a normal QRS complex. If the action potential originates in the AV node (nodal ES), the atria are depolarized retrogradely, the P wave therefore being negative in some leads and hidden within the QRS complex or following it (\( \rightarrow B1 \), blue frame; see also A). Because the sinus node is also often depolarized by a supraventricular ES, the interval between the R wave of the ES (= R\textsubscript{ES}) and the next normal R wave is frequently prolonged by the time of transmission from ectopic focus to the sinus node (postextrasystolic pause). The intervals between R waves are thus: \( R\textsubscript{ES} R \Rightarrow R \Rightarrow \) and \( R \Rightarrow R\textsubscript{ES} + R\textsubscript{ES} R \Rightarrow \) 2 R–R (\( \rightarrow B1 \)). An ectopic stimulus may also occur in a ventricle (ventricular extrasystole; \( \rightarrow B2,3 \)). In this case the QRS of the ES is distorted. If the sinus rate is low, the next sinus impulse may be normally transmitted to the ventricles (interposed ES; \( \rightarrow B2 \)). At a higher sinus rate the next (normal) sinus node action potential may arrive when the myocardium is still refractory, so that only the next but one sinus node impulse becomes effective (compensatory pause). The R–R intervals are: \( R \Rightarrow R\textsubscript{ES} + R\textsubscript{ES} R \Rightarrow 2 R \Rightarrow R \). (For causes of ES, see below).

Conduction disorders in the AV node (AV block) or His bundle can also cause arrhythmias. First degree (1\(^\circ\)) AV block is characterized by an abnormally prolonged AV transmission (PQ interval > 0.2 s); second degree (2\(^\circ\)) AV block by intermittent AV transmission (every second or third P wave); and third degree (3\(^\circ\)) AV block by completely blocked AV transmission (\( \rightarrow B5 \)). In the latter case the heart will...
A. Normal Stimulus Formation with Normal Transmission

1 Normal sinus rhythm

2 Sinus tachycardia

B. Ectopic Origin of Stimulus (1–5) and Abnormal Conduction (5)

1 Nodal (AV) extrasystole with postextrasystolic pause

2 Interposed ventricular extrasystole

3 Ventricular tachycardia after extrasystole

4 Ventricular fibrillation

5 Complete AV block with idioventricular rhythm
temporarily stop (Adams–Stokes attack), but ventricular (tertiary) pacemakers then take over excitation of the ventricles (ventricular bradycardia with normal atrial rate). Partial or complete temporal independence of the QRS complexes from the P waves is the result (→ B5). The heart (i.e., ventricular) rate will fall to 40–60 per minute if the AV node takes over as pacemaker (→ B), or to 20–40 per minute when a tertiary pacemaker (in the ventricle) initiates ventricular depolarization. This could be an indication for employing, if necessary implanting, an artificial (electronic) pacemaker. Complete bundle branch block (left or right bundle) causes marked QRS deformation in the ECG, because the affected part of the myocardium will have an abnormal pattern of depolarization via pathways from the healthy side.

Changes in cell potential. Important prerequisites for normal excitation of both atrial and ventricular myocardium are: 1) a normal and stable level of the resting potential (−80 to −90 mV); 2) a steep upstroke (dV/dt = 200–1000 V/s); and 3) an adequately long duration of the AP.

These three properties are partly independent of one another. Thus the “rapid” Na+ channels (→ p. 180) cannot be activated if the resting potential is less negative than about −55 mV (→ H9). This is caused mainly by a raised or markedly lowered extracellular concentration of K+ (→ H8), hypoxia, acidosis, or drugs such as digitalis. If there is no rapid Na+ current, the depolarization is dependent on the slow Ca2+ influx (L type Ca2+ channel; blockable by verapamil, diltiazem or nifedipine). The Ca2+ influx has an activation threshold of 30 to 40 mV, and it now generates an AP of its own, whose shape resembles the pacemaker potential of the sinus node. Its rising gradient dV/dt is only 1–10 V/s, the amplitude is lower, and the plateau has largely disappeared (→ H1). (In addition, spontaneous depolarization may occur in certain conditions, i.e., it becomes a source of extrasystoles; see below.) Those APs that are produced by an influx of Ca2+ are amplified by norepinephrine and cell stretching. They occur predominantly in damaged myocardium, in whose environment the concentrations of both norepinephrine and extracellular K+ are raised, and also in dilated atrial myocardium. Similar AP changes also occur if, for example, an ectopic stimulus or electric shock falls into the relative refractory period of the preceding AP (→ E). This phase of myocardial excitation is also called the vulnerable period. It is synchronous with the rising limb of the T wave in the ECG.

Causes of ESs (→ H4) include:
- A less negative diastolic membrane potential (see above) in the cells of the conduction system or myocardium. This is because depolarization also results in the potential losing its stability and depolarizing spontaneously (→ H1);
- Depolarizing after-potentials (DAPs). In this case an ES is triggered. DAPs can occur during repolarization (“early”) or after its end (“late”).

Early DAPs occur when the AP duration is markedly prolonged (→ H2), which registers in the ECG as a prolonged QT interval (long QT syndrome). Causes of early DAPs are bradycardia (e.g., in hypothyroidism, 1° and 2° AV block), hypokalemia, hypomagnesemia (loop diuretics), and certain drugs such as the Na+ channel blockers quinidine, procainamide, and disopyramide, as well as the Ca2+ channel blockers verapamil and diltiazem. Certain genetic defects in the Na+ channels or in one of the K+ channels (HERG, Kvlq, or min K+ channel) lead to early DAPs due to a lengthening of the QT interval. If such early DAPs occur in the Purkinje cells, they trigger ventricular ES in the more distal myocardium (the myocardium has a shorter AP than the Purkinje fibers and is therefore already repolarized when the DAP reaches it). This may be followed by burst-like repetitions of the DAP with tachycardia (see above). If, thereby, the amplitude of the (widened) QRS complex regularly increases and decreases, a spindle-like ECG tracing results (tordades de pointes).

The late DAPs are usually preceded by post-hyperpolarization that changes into postdepolarization. If the amplitude of the latter reaches the threshold potential, a new AP is triggered (→ H3). Such large late DAPs occur mainly at high heart rate, digitalis intoxication, and increased extracellular Ca2+ concentration. Oscillations of the cytosolic Ca2+ concentration seem to play a causative role in this.
C. Conduction Block at High Rate of Excitation

1. Rapid spread of excitation and long refractory period: protection against reentry

D. Reentry

2. Basic causes of reentry
   - pathway too long
   - refractory time too short
   - spread of excitation too slow
**Consequences of an ES.** When the membrane potential of the Purkinje fibers is normal (frequency filter; see above), there will be only the one ES, or a burst of ESs with tachycardia follows (→ H6,7). If, however, the Purkinje fibers are depolarized (anoxia, hypokalemia, hyperkalemia, digitalis; → H8), the rapid Na⁺ channel cannot be activated (→ H9) and as a consequence dV/dt of the upstream and therefore the conduction velocity decreases sharply (→ H10) and ventricular fibrillation sets in as a result of reentry (→ H11).

**Reentry in the myocardium.** A decrease in dV/dt leads to slow propagation of excitation (θ), and a shortening of the AP means a shorter refractory period (tᵣ). Both are important causes of reentry, i.e., of circular excitation. When the action potential spreads from the Purkinje fibers to the myocardium, excitation normally does not meet any myocardial or Purkinje fibers that can be reactivated, because they are still refractory. This means that the product of θ · tᵣ is normally always greater than the length s of the largest excitation loop (→ D1). However, reentry can occur as a result if
- the maximal length of the loop s has increased, for example, in ventricular hypotrophy,
- the refractory time tᵣ has shortened, and/or
- the velocity of the spread of excitation θ is diminished (→ D2).

A strong electrical stimulus (electric shock), for example, or an ectopic ES (→ B3) that falls into the vulnerable period can trigger APs with decreased upstroke slope (dV/dt) and duration (→ E), thus leading to circles of excitation and, in certain circumstances, to ventricular fibrillation (→ B4, H11). If diagnosed in time, the latter can often be terminated by a very short high-voltage current (defibrillator). The entire myocardium is completely depolarized by this countershock so that the sinus node can again take over as pacemaker.

**Reentry in the AV node.** While complete AV block causes a bradycardia (see above), partial conduction abnormality in the AV node can lead to a tachycardia. Transmission of conduction within the AV node normally takes place along parallel pathways of relatively loose cells of the AV node that are connected with one another through only a few gap junctions. If, for example, because of hypoxia or scarring (possibly made worse by an increased vagal tone with its negative dromotropic effect), the already relatively slow conduction in the AV node decreases even further (→ Table, p. 183), the orthograde conduction may come to a standstill in one of the parallel pathways (→ F, block). Reentry can only occur if excitation (also slowed) along another pathway can circumvent the block by retrograde transmission so that excitation can reenter proximal to the block (→ F, reentry). There are two therapeutic ways of interrupting the tachycardia: 1) by further lowering the conduction velocity θ so that retrograde excitation cannot take place; or 2) by increasing θ to a level where the orthograde conduction block is overcome (→ Fa and b, respectively).

In Wolff–Parkinson–White syndrome (→ G) the circle of excitation has an anatomic basis, namely the existence of an accessory, rapidly conducting pathway (in addition to the normal, slower conducting pathway of AV node and His bundle) between right atrium and right ventricle. In normal sinus rhythm the excitation will reach parts of the right ventricular wall prematurely via the accessory pathway, shortening the PR interval and deforming the early part of the QRS complex (δ wave; → G1). Should an atrial extrasystole occur in such a case, (→ G2; negative P wave), excitation will first reach the right ventricle via the accessory pathway so early that parts of the myocardium are still refractory from the preceding normal action potential. Most parts of the ventricles will be depolarized via the AV node and the bundle of this so that the QRS complex for the most part looks normal (→ G2,3). Should, however, the normal spread of excitation (via AV node) reach those parts of the ventricle that have previously been refractory after early depolarization via the accessory pathway, they may in the meantime have regained their excitability. The result is that excitation is now conducted retrogradely via the accessory pathway to the atria, starting a circle of excitation that leads to the sudden onset of (paroxysmal) tachycardia, caused by excitation reentry from ventricle to atrium (→ G3).
E. Another AP Triggered Shortly Before or at the End of an Action Potential (AP)

- **Stimulus**
  - Absolutely refractory
  - Relatively refractory
  - AP duration shortened
  - Refractory period shortened

- **Graph**
  - Rise of dV/dt less steep → Spread of excitation slowed down

F. Block in AV Node: Reentry with Tachycardia and Drug Treatment

- **Normal**
- **Tissue damage**
- **Reentry**
- **Block**
- **Tachycardia**

- **Treatment a**
- **Treatment b**

G. Reentry in Wolff-Parkinson-White Syndrome

- **Accessory pathway** between atrium and ventricle
- **Ectopic atrial extrasystole**
- **Reentry**
- **Tachycardia**
H. Causes and Consequences of Extrasystoles

1. Action potential in normal myocardium
   - Arrival of stimulus
   - Membrane potential decreased
   - Spontaneous depolarization

2. Bradycardia, hypokalemia, antiarrhythmic drugs
   - Delayed repolarization
   - Early depolarizing afterpotential

3. Stimulus
   - Myocardium
   - Threshold
   - Resting potential
   - Late depolarizing afterpotential
   - Spontaneous action potential

4. ECG
   - Myocardium
   - ES
   - dV/dt
   - t_R
   - Extrasystole

Anoxia, acidosis, digitalis, etc.
Stable Stimulus
Late depolarizing afterpotential
Spontaneous depolarization

ECG
Myocardium
ES
dV/dt
t_R
Extrasystole
Abnormalities of Cardiac Rhythm IV + V

- Single extrasystole
- Tachycardia
- Reentry
- Synchronized myocardial excitation
- Depolarized Purkinje fibers
- Normal potential of Purkinje fibers
- Hypokalemia
- Hyperkalemia
- Digitalis
- Anoxia etc.

- Membrane potential
- Normal EK⁻
- Extracellular K⁺ concentration (mmol/L)
- Potential (mV)

- Ability to activate rapid Na⁺ current
- Diastolic potential

- Purkinje fibers
- dV/dt

- Ventricular fibrillation
- Desynchronized myocardial excitation
- Reentry
Mitral Stenosis

The most common cause of mitral (valvar) stenosis (MS) is rheumatic endocarditis, less frequently tumors, bacterial growth, calcification, and thrombi. Very rare is the combination of congenital or acquired MS with a congenital atrial septal defect (→ p. 204; Lutembacher’s syndrome).

During diastole the two leaflets of the mitral valve leave a main opening and, between the chordae tendineae, numerous additional openings (→ A1). The total opening area (OA) at the valve ring is normally 4–6 cm². When affected by endocarditis, the chordae fuse, the main opening shrinks, and the leaflets become thicker and more rigid. The echocardiogram (→ A3) demonstrates slowing of the posterior diastolic movement of the anterior leaflet, deflection A getting smaller or disappearing and E–F becoming flatter. The amplitude of E–C also gets smaller. The posterior leaflet moves anteriorly (normally posteriorly). In addition, thickening of the valve is also seen (pink in A3). A recording of the heart sounds (→ A2) shows a loud and (in relation to the onset of QRS) a delayed first heart sound (up to 90 ms, normally 60 ms). The second heart sound is followed by the so-called mitral opening snap (MOS), which can best be heard over the cardiac apex. If the OA is less than ca. 2.5 cm², symptoms develop on strenuous physical activity (dyspnea, fatigue, hemoptysis, etc.). These arise during ordinary daily activities at an OA of < 1.5 cm², and at rest when the OA < 1 cm². An OA of < 0.3 cm² is incompatible with life.

The increased flow resistance caused by the stenosis diminishes blood flow across the valve from left atrium to left ventricle during diastole and thus reduces cardiac output. Three mechanisms serve to compensate for the decreased cardiac output (→ A, middle):

- Peripheral oxygen extraction, i.e., arteriovenous oxygen difference (AVO₂) can increase (while cardiac output remains reduced).
- Diastolic filling time per unit of time can be increased by reducing the heart rate (→ A4, green arrow) so that the stroke volume is raised more than proportionately, thus increasing cardiac output.
- The most effective compensatory mechanism, which is obligatory on physical exercise and with severe stenosis, is an increase in left atrial pressure (PₐL) and therefore of the pressure gradient between atrium and ventricle (PₐL – PᵥL, → A2, pink area). The diastolic flow rate (Qᵥ) is therefore raised again, despite the stenosis (the result is a mid-diastolic murmur [MDM]: → A2).

However, the further course of the disease is determined by the negative effects of the high PₐL: the left atrium hypertropies and dilates (P mitrale in the ECG; → A2). It may ultimately be so damaged that atrial fibrillation occurs, with disappearance of the presystolic crescendo murmur (PSM: → A2), which had been caused by the rapid inflow (poststenotic turbulence) during systole of the regularly beating atra. Lack of proper contraction of the fibrillating atria encourages the formation of thrombi (especially in the atrial appendages), and thus increases the risk of arterial emboli with infarction (especially of the brain; → A, bottom; see also p. 240). The heart (i.e., ventricular) rate is also increased in atrial fibrillation (tachyarrhythmia; → p. 186), so that the diastolic duration of the cardiac cycle, compared with systole, is markedly reduced (greatly shortened diastolic filling time per unit time; → A4, red arrow). PₐL rises yet again to prevent a fall in the cardiac output. For the same reason, even at regular atrial contraction, any temporary (physical activity, fever) and especially any prolonged increase in heart rate (pregnancy) causes a severe strain (PₐL ↑↑).

The pressure is also raised further upstream. Such an increase in the pulmonary veins produces dyspnea and leads to varicosity of bronchial veins (causing hemoptysis from ruptured veins). It may further lead to pulmonary edema (→ p. 80), and finally pulmonary hypertension may result in increased stress on the right heart and right heart failure (→ p. 214).

Without intervention (surgical valvotomy, balloon dilation, or valve replacement) only about half of the patients survive the first 10 years after the MS has become symptomatic.
A. Causes and Consequences of Mitral Stenosis

Rheumatic endocarditis, thrombi, calcification, etc.

**Plate 7.11 Mitral Stenosis**

Normal: 4–6 cm²

Mitral opening area

Symptoms:

- >2.5 cm²: none
- 1–2.5 cm²: during exercise
- <1 cm²: at rest

**Mitral stenosis**

Diastolic flow rate (Qd) → CO

Heart rate → AVD O₂ ↑ → Left atrial pressure (P LA) ↑ → LA hypertrophy

Compensation

- Left atrial damage
- Pulmonary capillary pressure ↑
- Pulmonary hypertension
- Right heart pressure load

Diastolic filling time/time (after van der Werf)

Cardiac output

Arterial emboli

Brain

Coronaries

Spleen

Kidney

Mesentery

Other arteries

Pulmonary edema

Right heart failure

**ECG**

P mitrale

mmHg

ECG

Heart murmur

Heart rate

Stroke volume

LA hypertrophy

Physical exertion, fever, pregnancy

Atrial fibrillation

Atrial thrombi

Right heart failure

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Mitral Regurgitation

In mitral regurgitation (MR, also sometimes called mitral insufficiency) the mitral valve has lost its function as a valve, and thus during systole some of the blood in the left ventricle flows back (“regurgitates”) into the left atrium. Its causes, in addition to mitral valve prolapse (Barlow’s syndrome) which is of unknown etiology, are mainly rheumatic or bacterial endocarditis, coronary heart disease (→ p. 218 ff.), or Marfan’s syndrome (genetic, generalized disease of the connective tissue).

The mitral valve is made up of an annulus (ring) to which an anterior and a posterior leaflet are attached. These are connected by tendinous cords (chordae tendineae) to papillary muscles that arise from the ventricular wall. The posterior walls of the LA and LV are functionally part of this mitral apparatus.

Endocarditis above all causes the leaflets and chordae to shrink, thicken, and become more rigid, thus impairing valve closure. If, however, leaflets and chordae are greatly shortened, the murmur starts at the onset of systole (SM: → A, left). In mitral valve prolapse (Barlow’s syndrome) the chordae are too long and the leaflets thus bulge like a parachute into the left atrium, where they open. The leaflet prolapse causes a mid-systolic click, followed by a late systolic murmur (LSM) of reflux. In Marfan’s syndrome the situation is functionally similar with lengthened and even ruptured chordae and a dilated annulus. In coronary heart disease ischemic changes in the LV can cause MR through rupture of a papillary muscle and/or poor contraction. Even if transitory ischemia arises (angina pectoris; → p. 218 ff.), intermittent mitral regurgitation (Jekyll–Hyde) can occur in certain circumstances (ischemia involving a papillary muscle or adjacent myocardium).

The effect of MR is an increased volume load on the left heart, because part of the stroke volume is pumped back into the LA. This regurgitant volume may amount to as much as 80% of the SV. The regurgitant volume/time is dependent on

– the mitral opening area in systole,
– the pressure gradient from LV to LA during ventricular systole, and
– the duration of systole.

Left atrial pressure (P_{LA}) is raised if there is additional aortic stenosis or hypertension, and the proportion of ventricular systole in the cardiac cycle (systolic duration/time) is increased in tachycardia (e.g., on physical activity or tachyarrhythmia due to left atrial damage), such factors accentuating the effects of any MR.

To maintain a normal effective stroke volume into the aorta despite the regurgitation, left ventricle filling during diastole has to be greater than normal (rapid filling wave [RFW] with closing third heart sound; → A). Ejection of this increased enddiastolic volume (EDV) by the left ventricle requires an increased wall tension (Laplace’s law), which places a chronic load on the ventricle (→ heart failure, p. 224).

In addition, the left atrium is subjected to greater pressure during systole (→ A, left; high v wave). This causes marked distension of the left atrium (300–600 mL), while P_{LA} is only moderately raised owing to a long-term gradual increase in the distensibility (compliance) of the left atrium. As a result, chronic MR (→ A, left) leads to pulmonary edemas and pulmonary hypertension (→ p. 214) much less commonly than mitral stenosis (→ p. 154) or acute MR does (see below). Distension of the left atrium also causes the posterior leaflet of the mitral valve to be displaced so that the regurgitation is further aggravated (i.e., a vicious circle is created). Another vicious circle, namely MR → increased left heart load → heart failure → ventricular dilation → MR↑↑, can also rapidly decompensate the MR.

If there is acute MR (e.g., rupture of papillary muscle), the left atrium cannot be stretched much (low compliance). P_{LA} will therefore rise almost to ventricular levels during systole (→ A, right; very high v wave) so that the pressure gradient between LV and left atrium is diminished and the regurgitation is reduced in late systole (spindle-shaped systolic murmur; → A, right SM). The left atrium is also capable of strong contractions (→ A, right; fourth heart sound), because it is only slightly enlarged. The high P_{LA} may in certain circumstances rapidly cause pulmonary edema that, in addition to the fall in cardiac output (→ shock, p. 230 ff.), places the patient in great danger.
Plate 7.12 Mitral Regurgitation

A. Causes and Consequences of Mitral Regurgitation

**Endocarditis**

- Valve ring: deformed, stiffened
- Leaflets: shrunk, thickened, stiffened, prolapsing

**Valvar prolapse** (Barlow)

- Left atrium: distended
- Valve ring: deformed, stiffened
- Leaflets: shrunk, thickened, stiffened, prolapsing

**Coronary heart disease**

- Left ventricle:
  - ischemia, fibrosis, aneurysm
- Chordae:
  - too long, too short, rupture
- Papillary muscle:
  - fibrosis, rupture

**Marfan’s syndrome**

- Left atrium:
  - distended

**Left ventricle:**

- ischemia, fibrosis, aneurysm

**Chordae:**

- too long, too short, rupture

**Papillary muscle:**

- fibrosis, rupture

**Right heart failure**

- Pulmonary edema
- Tachycardia
- Regurgitant volume

**Left heart failure**

- Atrial pressure ($P_{LA}$)
- Vascular edema
- Pulmonary hypertension

**Diastole**

- Regurgitant volume

**Systole**

- Heart sounds
- Time (s)

**Mitral regurgitation**

- Forward CO
- Systolic pressure

**Atrial pressure ($P_{LA}$)**

- Dsypnea, hemoptysis
- Pulmonary edema
- Tachycardia
- Regurgitant volume

**Regurgitant volume**

- Left heart failure
- Right heart failure

**Atrial dilation**

- Atrial pressure ($P_{LA}$)
- Volume load

**Atrial damage**

- Volume load
- Mitral regurgitation

**Tachyarrhythmia**

- Volume load
- Mitral regurgitation

**Regurgitant volume**

- Volume load
- Mitral regurgitation

Heart sounds

- Time (s)

ECG

- P ‘mitrale’
Aortic Stenosis

The normal opening area of the aortic valve is 2.5–3.0 cm². This is sufficient to eject blood, not only at rest (ca. 0.2 L/s of systole), but also on physical exertion, with a relatively low pressure difference between left ventricle and aorta \( (P_{LV} - P_{Ao}) \rightarrow A \), blue area). In aortic stenosis (AS) 20% of all chronic valvar defects the emptying of the left ventricle is impaired. The causes of AS \( \rightarrow A \), top left) can be, in addition to subvalvar and supravalvar stenosis, congenital stenosing malformations of the valve (age at manifestation is < 15 years). When it occurs later (up to 65 years of age) it is usually due to a congenital bicuspid malformation of the valve that becomes stenotic much later through calcification (seen on chest radiogram). Or it may be caused by rheumatic–inflammatory stenosing of an originally normal tricuspid valve. An AS that becomes symptomatic after the age of 65 is most often caused by degenerative changes along with calcification.

In contrast to mitral stenosis \( \rightarrow p.194 \), long-term compensation is possible in AS, because the high flow resistance across the stenotic valve is overcome by more forceful ventricular contraction. The pressure in the left ventricle \( (P_{LV}) \) and thus the gradient \( P_{LV} - P_{Ao} \rightarrow A, 2 \), is increased to such an extent that a normal cardiac output can be maintained over many years \( (P_{LV} \text{ up to } 300 \text{ mmHg}) \). Only if the area of the stenosed valve is less than ca. 1 cm² do symptoms of AS develop, especially during physical exertion (cardiac output \( \uparrow \rightarrow P_{LV} \uparrow \)).

The consequences of AS include concentric hypertrophy of the left ventricle as a result of the increased prestenotic pressure load \( \rightarrow p.224 \). This makes the ventricle less distensible, so that the pressures in the ventricle and atrium are raised even during diastole \( \rightarrow A, P_{LV}, P_{IA} \). The strong left atrium contraction that generates the high end-diastolic pressure for ventricular filling causes a fourth heart sound \( \rightarrow A \) and a large a wave in the left atrium pressure \( \rightarrow A \). The mean atrial pressure is increased mainly during physical exertion, thus dyspnea develops. Poststenotically, the pressure amplitude and later also the mean pressure are decreased (pallor due to centralization of circulation; \( \rightarrow p.232 \). In addition, the ejection period is lengthened causing a small and slowly rising pulse \( \text{pulsus parvus et tardus} \). At auscultation there is, in addition to the sound created by the strong atrial contraction, a spindle-shaped rough systolic flow murmur \( \rightarrow A, \text{SM} \) and, if the valve is not calcified, an aortic opening click \( \rightarrow A \). The transmural pressure of the coronary arteries is diminished in AS for two reasons:

- The left ventricular pressure is increased not only in systole but also during diastole, which is so important for coronary perfusion \( \rightarrow p.216 \).
- The pressure in the coronary arteries is also affected by the poststenotically decreased (aortic) pressure.

Coronary blood flow is thus reduced or, at least during physical exertion, can hardly be increased. As the hypertrophied myocardium uses up abnormally large amounts of oxygen, myocardial hypoxia \( \text{angina pectoris} \) and myocardial damage are consequences of AS \( \rightarrow p.218 \).

Additionally, on physical exertion a critical fall in blood pressure can lead to dizziness, transient loss of consciousness \( \text{syncope} \), or even death. As the cardiac output must be increased during work because of vasodilation in the muscles, the left ventricular pressure increases out of proportion (quadratic function; \( \rightarrow A \)). Furthermore, probably in response to stimulation of left ventricular baroreceptors, additional “paradoxic” reflex vasodilation may occur in other parts of the body. The resulting rapidly occurring fall in blood pressure may ultimately be aggravated by a breakdown of the already critical oxygen supply to the myocardium \( \rightarrow A \). Heart failure \( \rightarrow p.224 \), myocardial infarction \( \rightarrow p.220 \), or arrhythmia \( \rightarrow p.186 \), all of which impair ventricular filling, contribute to this vicious circle.
A. Causes and Consequences of Aortic Stenosis

1. Causes of Aortic Stenosis:
   - Congenital
   - Acquired postnatally
     - Rheumatic inflammatory
     - Calcifying
     - Degenerative calcifying

2. Consequences of Aortic Stenosis:
   - Heart sound and murmur
   - Transmural coronary artery pressure
   - Paradoxical vasodilation
   - Stimulation of ventricular baroreceptors
   - Systemic hypotension
   - Ventricular hypertrophy
   - Transmural coronary artery pressure
   - Left heart hypertrophy
   - Physical exercise
   - Coronary blood flow
   - Cardiac O₂ consumption
   - Myocardial hypoxia (angina pectoris)
   - Vasodilation during exercise
   - Arrhythmia
   - Ventricular filling
   - Blood pressure
   - Syncope
   - Left heart failure

Graphs:
- Flow rate (L/s in systole) vs. Systolic pressure gradient
- ECG with measurements
- Pressure changes in LV, LA, Ao

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Aortic Regurgitation

After closure of the aortic valve the aortic pressure ($P_{Ao}$) falls relatively slowly, while the pressure in the left ventricle ($P_{LV}$) falls rapidly to just a few mmHg (→ p. 179), i.e., there is now a reverse pressure gradient ($P_{Ao} > P_{LV}$). In aortic valve regurgitation (AR, also called insufficiency) the valve is not tightly closed, so that during diastole a part of what has been ejected from the left ventricle during the preceding ventricular systole flows back into the LV because of the reverse pressure gradient (regurgitant volume; → A).

Causes. AR can be the result of a congenital anomaly (e.g., bicuspid valve with secondary calcification) or (most commonly) of inflammatory changes of the cusps (rheumatic fever, bacterial endocarditis), disease of the aortic root (syphilis, Marfan’s syndrome, arthritis such as Reiter’s syndrome), or of hypertension or atherosclerosis.

The consequences of AR depend on the regurgitant volume (usually 20–80 mL, maximally 200 mL per beat), which is determined by the opening area and the pressure difference during diastole ($P_{Ao} – P_{LV}$) as well as the duration of diastole. To achieve an adequate effective stroke volume (= forward flow volume) the total stroke volume (→ A2, SV) must be increased by the amount of the regurgitant volume, which is possible only by raising the end-diastolic volume (→ A2, orange area). This is accomplished in acute cases to a certain degree by the Frank–Starling mechanism, in chronic cases, however, by a much more effective dilational myocardial transformation. (Acute AR is therefore relatively poorly tolerated: cardiac output ↓; $P_{LA}$ ↑). The endsystolic volume (→ A2, ESV) is also greatly increased. According to Laplace’s law (→ p. 225), ventricular dilation demands greater myocardial force as otherwise $P_{LV}$ would decrease. The dilation is therefore accompanied by left ventricular hypertrophy (→ p. 224f.). Because of the flow reversal in the aorta, the diastolic aortic pressure falls below normal. To maintain a normal mean pressure this is compensated by a rise in systolic pressure (→ A1). This increased pressure amplitude can be seen in the capillary pulsation under the finger nails and pulse-synchronous head nodding (Quincke’s and Musset’s sign, respectively). At auscultation an early diastolic decrescendo murmur (EDM) can be heard over the base of the heart, produced by the regurgitation, as well as a click and a systolic murmur due to the forced large-volume ejection (→ A1, SM).

The above-mentioned mechanisms allow the heart to compensate for chronic AR for several decades. In contrast to AS (→ p. 198), patients with AR are usually capable of a good level of physical activity, because activity-associated tachycardia decreases the duration of diastole and thus the regurgitant volume. Also, peripheral vascular dilation of muscular work has a positive effect, because it reduces the mean diastolic pressure gradient ($P_{Ao} – P_{LV}$). On the other hand, bradycardia or peripheral vasoconstriction can be harmful to the patient.

The compensatory mechanisms, however, come at a price. Oxygen demand rises as a consequence of increased cardiac work (= pressure times volume; → A2, orange area). In addition, the diastolic pressure, which is so important for coronary perfusion (→ p. 216), is reduced and simultaneously the wall tension of the left ventricle is relatively high (see above)—both causes of a lowered transmural coronary artery pressure and hence underperfusion which, in the presence of the simultaneously increased oxygen demand, damages the left ventricle by hypoxia. Left ventricular failure (→ p. 224) and angina pectoris or myocardial infarction (→ p. 220) are the result. Finally, decompensation occurs and the situation deteriorates relatively rapidly (vicious circle): as a consequence of the left ventricular failure the endsystolic volume rises, while at the same time total stroke volume decreases at the expense of effective endsystolic volume (→ A2, red area), so that blood pressure falls (left heart failure) and the myocardial condition deteriorates further. Because of the high ESV, both the diastolic $P_{LV}$ and the $P_{LA}$ rise. This can cause pulmonary edema and pulmonary hypertension (→ p. 214), especially when dilation of the left ventricle has resulted in functional mitral regurgitation.
A. Causes and Consequences of Aortic Regurgitation

- Congenital
- Rheumatic fever
- Bacterial endocarditis
- Marfan’s syndrome
- Syphilis
- Arthritis etc.

**Aortic valve**

**Regurgitant volume**

**Diastolic blood pressure**

**Effective stroke volume**

**Compensation**
- Ventricular dilation
- Laplace’s law
- Wall tension
- LV hypertrophy
- 
- 
- 
- 
- Total stroke volume
- Effective stroke volume normalized

**Decompensation**
- Left heart failure
- Effective stroke volume
- Ventricular dilation
- Functional mitral regurgitation
- Ventricular compliance
- Left atrial pressure
- Pulmonary edema
- Left heart failure

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Defects of the Tricuspid and Pulmonary Valves

In principle the consequences of stenotic or regurgitant valves of the right heart resemble those of the left one (→ p. 194–201). Differences are largely due to the properties of the downstream and upstream circulations (pulmonary arteries and venae cavae, respectively).

The cause of the rare tricuspid stenosis (TS) is usually rheumatic fever in which, as in tricuspid regurgitation (TR) of the same etiology, mitral valve involvement usually coexists. TR may also be congenital, for example, Ebstein’s anomaly, in which the septal leaflet of the tricuspid valve is attached too far into the right ventricle (atrialization of the RV). However, most often TR has a functional cause (dilation and failure of the right ventricle). Pulmonary valve defects are also uncommon. Pulmonary stenosis (PS) is usually congenital and often combined with a shunt (→ p. 204), while pulmonary regurgitation (PR) is most often functional (e.g., in advanced pulmonary hypertension).

Consequences. In TS the pressure in the right atrium (P_{RA}) is raised and the diastolic flow through the valve is diminished. As a result, cardiac output falls (valve opening area, normally ca. 7 cm², reduced to < 1.5 – 2.0 cm²). The low cardiac output limits physical activity. A rise in mean P_{RA} to more than 10 mmHg leads to increased venous pressure (high a wave in the central venous pulse; → p. 179), peripheral edema, and possibly atrial fibrillation. The latter increases the mean P_{RA}, and thus the tendency toward edema. Edemas can also occur in TR, because the P_{RA} is raised by the systolic regurgitation (high v wave in the central venous pulse). Apart from the situation in Ebstein’s anomaly, serious symptoms of TR occur only when there is also pulmonary hypertension or right heart failure (→ p. 214). PR increases the volume load on the right ventricle. As PR is almost always of a functional nature, the effect on the patient is mainly determined by the consequences of the underlying pulmonary hypertension (→ p. 214). Although, PS, similar to AS, can be compensated by concentric ventricular hypertrophy, physical activity will be limited (cardiac output ↓), and fatigue and syncope may occur.

At auscultation the changes due to valvar defects of the right heart are usually louder during inspiration (venous return increased).

- TS: First heart sound split, early diastolic tricuspid opening sound followed by diastolic murmur (tricuspid flow murmur) that increases in presystole during sinus rhythm (atrial contraction);
- TR: Holosystolic murmur of regurgitant flow; presence (in adults) or accentuation (in children) of third heart sound (due to increased diastolic filling) and of the fourth heart sound (forceful atrial contraction);
- PS: Occurrence or accentuation of fourth heart sound, ejection click (not in subvalvar or supravalvar stenosis); systolic flow murmur;
- PR: Early diastolic regurgitation murmur (Graham–Steell murmur).

Circulatory Shunts

A left-to-right shunt occurs when arterialized blood flows back into the venous system without having first passed through the peripheral capillaries. In right-to-left shunts systemic venous (partially deoxygenated) blood flows directly into the arterial system without first passing through the pulmonary capillaries. In the fetal circulation (→ A) there is

- low resistance in the systemic circulation (placental!),
- high pressure in the pulmonary circulation (→ B 2),
- high resistance in the pulmonary circulation (lungs unexpanded and hypoxic vasoconstriction; → C),
- right-to-left shunt through the foramen ovale (FO) and ductus arteriosus Botalli (DA).

At birth the following important changes occur:

1. Clamping or spontaneous constriction of the umbilical arteries to the placenta increases the peripheral resistance so that the systemic pressure rises.
2. Expansion of the lungs and rise in the alveolar P_{O₂} lower the pulmonary vascular resistance (→ C), resulting in an increase in blood flow through the lungs and a drop in the pressure in the pulmonary arteries (→ B 1, 2).
A. Fetal Circulation

- **O₂** saturation (full saturation = 1.0)
- 1. O₂ flow (ml/min)
- 2. Systolic pressure (mmHg)
- 3. Muscle thickness in vessel wall

B. Pulmonary Circulation

- Pulmonary artery:
  1. Blood flow (L/min)
  2. Systolic pressure (mmHg)
  3. Muscle thickness in vessel wall

C. Fetal Hypoxic Vasoconstriction

- Ventricular septal defect
- Normal
- Pulmonary vascular resistance (mmHg · mL⁻¹ · min⁻¹)

Data from fetal lamb (after Levine)
3. As a result, there is physiological reversal of the shunt through the foramen ovale (FO) and ductus arteriosus (DA), from right-to-left to left-to-right (left atrium to right atrium and aorta to pulmonary artery).

4. These shunts normally close at or soon after birth, so that systemic and pulmonary circulations are now in series.

Abnormal shunts can be caused by patency of the duct (patent or persisting DA [PDA]; → E) or of the FO (PFO), by defects in the atrial or ventricular septum (ASD or VSD), or by arterio-venous fistulae, etc. Size and direction of the shunt in principle depend on: 1) the cross-sectional area of the shunt opening; and 2) the pressure difference between the connected vessels or chambers (→ D). If the opening is relatively small, 1) and 2) are the principal determining factors (→ D1). However, if the shunt between functionally similar vascular spaces (e.g., aorta and pulmonary artery; atrium and atrium, ventricle and ventricle) is across a large cross-sectional area, pressures in the two vessels or chambers become (nearly) equalized. In this case the direction and volume of the shunt is determined by 3) outflow resistance from the shunt-connected vessels or chambers (→ D2; e.g., PDA), as well as 4) their compliance (= volume distensibility; e.g., of the ventricular walls in VSD; → D3).

The ductus arteriosus (DA) normally closes within hours, at most two weeks, of birth due to the lowered concentration of the vasodilating prostaglandins. If it remains patent (PDA), the fetal right-to-left shunt turns into a left-to-right shunt (→ E, top), because the resistances in the systemic and pulmonary circuits have changed in opposite directions. At auscultation a characteristic flow murmur can be heard, louder in systole than diastole (“mechanical murmur”). If the cross-sectional area of the shunt connection is small, the aortic pressure is and remains much higher than that in the pulmonary artery (→ D1, AP), the shunt volume will be small and the pulmonary artery pressure nearly normal. If the cross-sectional area of the shunt connection is large, the shunt volume will also be large and be added to the normal ejection volume of the right ventricle, with the result that pulmonary blood flow and inflow into the left heart chambers are much increased (→ E, left). In compensation the left ventricle ejection volume is increased (Frank–Starling mechanism; possibly ventricular hypertrophy), and there will be a lasting increased volume load on the left ventricle (→ E, left), especially when the pulmonary vascular resistance is very low postnatally (e.g., in preterm infants). As the ability of the neonate’s heart to hypertrophy is limited, the high volume load can often lead to left ventricular failure in the first month of life.

If, on the other hand, the pulmonary vascular resistance (R pulm) remains relatively high postnatally (→ E, right), and therefore the shunt volume through the ductus is relatively small despite a large cross-sectional area, a moderately increased left ventricular load can be compensated for a long time. However, in these circumstances the level of pulmonary artery pressure will become similar to that of the aorta. Pulmonary (arterial) hypertension occurs (→ E, right and p. 214). This, if prolonged, will lead to damage and hypertrophy of the pulmonary vessel walls and thus to a further rise in pressure and resistance. Ultimately, a shunt reversal may occur with a right-to-left shunt through the ductus (→ E, bottom left). Aortic blood distal to the PDA will now contain an admixture of pulmonary arterial (i.e., hypoxic) blood (cyanosis of the lower half of the body; clubbed toes but not fingers). The pressure load on the right heart will after a period of compensating right ventricular hypertrophy ultimately lead to right ventricular failure. If functional pulmonary valve regurgitation occurs (caused by the pulmonary hypertension), it may accelerate this development because of the additional right ventricular volume load. Early closure of the PDA, whether by pharmacological inhibition of prostaglandin synthesis, by surgical ligation or by transcatheter closure, will prevent pulmonary hypertension. However, closure of the ductus after shunt reversal will aggravate the hypertension.

A large atrial septal defect initially causes a left-to-right shunt, because the right ventricle being more distensible than the left ventricle offers less resistance to filling during diastole and can thus accommodate a larger volume than the left ventricle. However, when this volume load causes hypertrophy of the right ventricle its compliance is decreased, right atrial pressure rises and shunt reversal may occur.
D. Determining Factors for Direction and Size of Circulatory Shunts

- **Septal defect small**
  - $P_{lt} > P_{rt}$ remains
  - $\Delta P$ determines shunt volume

- **Septal defect large**
  - $P_{lt} \approx P_{rt}$
  - Outflow resistance $R$ or compliance $C$ determine shunt volume

E. Consequences of Postnatal Patent Ductus Arteriosus (PDA)

- **Prenatal ductus arteriosus: right-to-left shunt**
- **Birth** → **Vascular resistance: peripheral pulmonary** → **Postnatally: left-to-right shunt**

- **Persisting** → **Left-to-right shunt**
- **Spontaneous closure after birth**

- **$R_{pulm}$ small**
  - Pulmonary blood flow $\uparrow$
  - Left heart: volume load
  - (Left ventr. hypertrophy) Left ventricular failure

- **$R_{pulm}$ large**
  - Pulmonary artery: pressure load
  - Damage, hypertrophy
  - Pulmonary hypertension

- **Shunt reversal: right-to-left shunt**
- **Cyanosis of lower half of body**

- **Right heart: hypertrophy, failure**
  - Functional pulmonary regurgitation
  - Volume load on right ventricle
Arterial Blood Pressure and its Measurement

The systemic arterial blood pressure rises to a maximum (the **systolic pressure** $P_s$), during the ejection period, while it falls to a minimum (the **diastolic pressure** $P_d$) during diastole and the iso(volu)metric period of systole (aortic valve closed) (→ A). Up to about 45 years of age the resting (sitting or recumbent) $P_d$ ranges from 60–90 mmHg (8–12 kPa); $P_s$ ranges from 100–140 mmHg (13–19 kPa) (→ p.208). The difference between $P_d$ and $P_s$ is the **blood pressure amplitude** or **pulse pressure**.

The **mean blood pressure** is decisive for peripheral arterial perfusion. It can be determined graphically (→ A) from the invasively measured blood pressure curve (e.g., arterial catheter), or while recording such a curve by dampening down the oscillations until only the mean pressure is recorded.

In the vascular system the flow fluctuations in the great arteries are dampened through the “windkessel” (compression chamber) effect to an extent that precapillary blood no longer flows in spurts but continuously. Such a system consisting of highly compliant conduits and high-resistance terminals, is called a **hydraulic filter**. The arteries become more rigid with age, so that the $P_s$ rise per volume increase ($\Delta P/\Delta V =$ elastance) becomes greater and compliance decreases. This mainly increases $P_s$ (→ C), without necessarily increasing the mean pressure (the shape of the pressure curve is changed). Thoughtless pharmacological lowering of an elevated $P_s$ in the elderly can thus result in dangerous underperfusion (e.g., of the brain).

**Measuring blood pressure.** Blood pressure (at the level of the heart) is routinely measured according to the **Riva-Rocci** method, by sphygmomanometer (→ B). An inflatable cuff is fitted snugly around the upper arm (its width at least 40% of the arm’s circumference) and under manometric control inflated to ca. 30 mmHg (4 kPa) above the value at which the palpated radial pulse disappears. A stethoscope having been placed over the brachial artery near the elbow, at the lower edge of the cuff, the cuff pressure is then slowly lowered (2–4 mmHg/s). The occurrence of the first pulse-synchronous sound (clear, tapping sound; phase 1 of Korotkoff) represents $P_s$ and is recorded. Normally this sound at first becomes softer (phase 2) before getting louder (phase 3), then becomes muffled in phase 4 and disappears completely (phase 5). The latter is nowadays taken to represent $P_d$ and is recorded as such.

**Sources of error when measuring blood pressure.** Complete disappearance of the sound sometimes occurs at a very low pressure. The difference between phases 4 and 5 (normally about 10 mmHg) is increased by conditions and diseases that favor flow turbulence (physical activity, fever, anemia, thyrotoxicosis, pregnancy, aortic regurgitation, AV fistula). If blood pressure is measured again, the cuff pressure must be left at zero for one to two minutes, because venous congestion may give a falsely high diastolic reading. The cuff should be 20% broader than the diameter of the upper arm. A cuff that is too small (e.g., in the obese, in athletes or if measurement has to be made at the thigh) also gives falsely high diastolic values, as does a too loosely applied cuff. A false reading can also be obtained when the auscultatory sounds are sometimes not audible in the range of higher amplitudes (auscultatory gap). In this case the true $P_s$ is obtained only if the cuff pressure is high enough to begin with (see above).

It is sufficient in follow-up monitoring of systemic hypertension (e.g., in labile hypertension from which fixed hypertension can often develop; → D and p.208) to measure blood pressure in one arm only (the same one every time, if possible). Nevertheless, in cases of stenosis in one of the great vessels there can be considerable, diagnostically important, **differences in blood pressure between left and right arm** (pressure on the right > left, except in dextrocardia). This occurs in *supravalvar aortic stenosis* (mostly in children) and the *subclavian steal syndrome*, caused by narrowing in the proximal subclavian artery, usually of atherosclerotic etiology (ipsilateral blood pressure reduced). **Blood pressure differences between arms and legs** can occur in congenital or acquired (usually atherosclerotic) stenoses of the aorta distal to the origin of the arteries to the arms.
Plate 7.17 Measuring Arterial Blood Pressure

A. Aortic Pressure Curve (Invasive Measurement)

B. Measuring Blood Pressure with Sphygmanometer (after Riva-Rocci)

C. Age-related Blood Pressure

D. Incidence of Fixed Hypertension
Hypertension

Hypertension (H.), used as a term by itself, refers to an abnormally high arterial pressure in the systemic circulation (for pulmonary hypertension, → p. 214). In the industrialized countries it affects about 20% of the population. As H. almost always begins insidiously, yet can be treated effectively, the upper limit of normal blood pressure needs to be determined. The World Health Organisation (WHO) has proposed the following values for all age groups (mmHg/7.5 = kPa):

<table>
<thead>
<tr>
<th>diastolic pressure</th>
<th>normal (P_d [mmHg])</th>
<th>Threshold hypertension</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>ijastolic pressure</td>
<td>&lt; 90</td>
<td>90 – 95</td>
<td>&gt; 95</td>
</tr>
<tr>
<td>systolic pressure</td>
<td>&lt; 140</td>
<td>140 – 160</td>
<td>&gt; 160</td>
</tr>
</tbody>
</table>

Cases of alternating normal and elevated levels (labile H.) are included in the column ‘Threshold hypertension’. Patients with a labile H. often develop fixed H. later (→ p. 207 D). As P_s regularly rises with age (→ p. 207 C), the upper limit of P_s in adults has been widely set at 150 mmHg for those aged 40 – 60 years and at 160 mmHg for those aged over 60 years (P_s at 90 mmHg for both adult groups). Lower values have been set for children. Assessment of blood pressure should be based on the mean values of at least 3 readings on two days (see also p. 206).

The product of cardiac output (= stroke volume [SV] · heart rate) and total peripheral resistance (TPR) determines blood pressure (Ohm’s law). H. thus develops after an increase in cardiac output or TPR, or both (→ A). In the former case one speaks of hyperdynamic H. or cardiac output H., with the increase in P_s being much greater than that in P_d. In resistance H., P_s and P_d are either both increased by the same amount or (more frequently) P_d more than P_s. The latter is the case when the increased TPR delays ejection of the stroke volume.

The increase of cardiac output in hyperdynamic hypertension is due to an increase in either heart rate or extracellular volume, leading to an increased venous return and thus an increased stroke volume (Frank–Starling mechanism). Similarly, an increase in sympathetic activity of central nervous system origin and/or raised responsiveness to catecholamines (e.g., caused by cortisol or thyroid hormone) can cause an increase in cardiac output (→ A, left).

Resistance hypertension is caused mainly by abnormally high peripheral vasoconstriction (arterioles) or some other narrowing of peripheral vessels (→ A, right), but may also be due to an increased blood viscosity (increased hematocrit). Vasoconstriction mainly results from increased sympathetic activity (of nervous or adrenal medullary origin), raised responsiveness to catecholamines (see above), or an increased concentration of angiotensin II. Auto-regulatory mechanisms also include vasoconstriction. If, for example, blood pressure is increased by a rise in cardiac output (see above), various organs (e.g., kidneys, gastrointestinal tract) “protect” themselves against this high pressure (→ A, middle). This is responsible for the frequently present vasoconstrictor component in hyperdynamic H. that may then be transformed into resistance H. (→ A). Additionally, there will be hypertrophy of the vasoconstrictor musculature. Finally, H. will cause vascular damage that will increase TPR (fixation of the H.).

Some of the causes of hypertension are known (e.g., renal or hormonal abnormalities; → B2,3), but these forms make up only about 5 – 10% of all cases. In all others the diagnosis by exclusion is primary or essential hypertension (→ B1). Apart from a genetic component, more women than men and more urbanites than country dwellers are affected by primary H. In addition, chronic psychological stress, be it job-related (pilot, bus driver) or personality-based (e.g., “frustrated fighter” type), can induce hypertension. Especially in “salt-sensitive” people (ca. ¼ of patients with primary H.; increased incidence when there is a family history) the high NaCl intake (ca. 10 – 15 g/d = 170 – 250 mmol/d) in the western industrialized countries might play an important role. While the organism is well protected against Na⁺ loss (or diminished extracellular volume) through an increase in aldosterone, those with an increased salt sensitivity are apparently relatively unprotected against a high
A. Principles of the Development of Hypertension

Arterial blood pressure =
Cardiac output (CO) \times \text{Total peripheral resistance (TPR)}

Extracellular volume $\uparrow$

Central blood volume $\uparrow$

Catecholamines

Venous tone $\uparrow$

CNS

Hyperdynamic hypertension

T₃, T₄, cortisol

CO $\uparrow$

Angiotensin II

Vascular hyperreactivity

Adrenal medulla

Vasoconstriction

TPR $\uparrow$

Vicious circle

Hypertrophy of vessel musculature and vascular damage: fixation of hypertension

Organ perfusion

Vascular resistance (radius)

constant

pressure dependent

Systemic blood pressure

Resistance hypertension

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NaCl intake. In these patients, aldosterone release is so strongly inhibited even at “normal” Na\(^+\) intake (>100 mmol/d) that it cannot be lowered any further. A diet with low NaCl intake would in this case bring NaCl balance into the aldosterone regulatory range.

The actual connection between NaCl sensitivity and primary H. has not been fully elucidated, but the possibility is being considered that responsiveness to catecholamines is raised in people sensitive to NaCl. This results, for example, on psychological stress, in a greater than normal rise in blood pressure, on the one hand, due directly to the effect of increased cardiac stimulation (→ B, upper right) and, on the other hand, indirectly as a result of increased renal absorption and thus retention of Na\(^+\) (rise in extracellular volume leads to hyperdynamic H.). The increased blood pressure leads to pressure diuresis with increased Na\(^+\) excretion, restoring Na\(^+\) balance (Guyton). This mechanism also exists in healthy people, but the pressure increase required for excretion of large amounts of NaCl is much lower (→ C, a → b). In primary H. (as in disorders of renal function) the NaCl-dependent increase in blood pressure is greater than normal (→ C, c → d). A diet that is low in Na\(^+\) can thus lower (not yet fixed) H. in these cases (C, c → e). A simultaneously elevated K\(^+\) supply accentuates this effect for unknown reasons. The cellular mechanism of salt sensitivity still awaits clarification. It is possible that changes in cellular Na\(^+\) transport are important. In fact cellular Na\(^+\) concentration is raised in primary H., which decreases the driving force for the 3 Na\(^+\)/Ca\(^{2+}\) exchange carrier in the cell membrane, as a result of which the intracellular Ca\(^{2+}\) concentration rises, which in turn increases the tone of the vasoconstrictor muscles (Blaustein). It is possible that digitalis-like inhibitors of Na\(^+\)-K\(^+\)-ATPase are involved (ouabain?). They may be present in larger amounts, or there may be a special sensitivity to them in primary H. Atriopeptin (→ atrial natriuretic peptide [ANP]), which has vasodilator and natriuretic effects, is probably not involved in the development of primary H. Although the concentration of renin is not elevated in primary H., blood pressure can be reduced even in primary H. by inhibiting the angiotensin-converting enzyme (ACE inhibitors; see below) or angiotensin receptor antagonists.

The various forms of secondary hypertension make up only 5–10% of all hypertensive cases (→ B₂, 3, 4), but contrary to primary H. their cause can usually be treated. Because of the late consequences of H. (→ E), such treatment must be initiated as early as possible. Renal hypertension, the most common form of secondary H., can have the following, often partly overlapping, causes (→ B₂, see also p.114): Every renal ischemia, for example, resulting from aortic coarctation or renal artery stenosis, but also from narrowing of the renal arterioles and capillaries (glomerulonephritis, hypertension-induced atherosclerosis), leads to the release of renin in the kidneys. It splits the decapeptide angiotensin I from angiotensinogen in plasma. A peptidase (angiotensin-converting enzyme, ACE), highly concentrated especially in the lungs, removes two amino acids to form angiotensin II. This octapeptide has a strong vasoconstrictor action (TPR rises) and also releases aldosterone from the adrenal cortex (Na\(^+\) retention and increase in cardiac output), both these actions raising the blood pressure (→ B₂). In kidney disease with a significant reduction of the functioning renal mass, Na\(^+\) retention can therefore occur even during normal Na\(^+\) supply. The renal function curve is steeper than normal, so that Na\(^+\) balance is restored only at hypertensive blood pressure levels (→ C, c → d). Glomerulonephritis, renal failure, and nephropathy of pregnancy are some of the causes of the primarily hypertensive form of renal H. Renal H. can also be caused by a renin-producing tumor or (for unknown reasons) by a polycystic kidney. The kidney is also central to other forms of hypertension that do not primarily originate from it (primary H., hyperaldosteronism, adenogenital syndrome, Cushing’s syndrome). Furthermore, in every case of chronic H. secondary changes will occur sooner or later (vascular wall hypertrophy, atherosclerosis): they fix the H. even with effective treatment of the primary cause. If unilateral renal artery stenosis is repaired surgically rather late, for example, the other kidney, damaged in the meantime by the hypertension, will maintain the H.

Hormonal hypertension can have several causes (→ B₃):
**B. Causes of Hypertension**

1. **Primary hypertension**
   - Na\(^+\) uptake too high, K\(^+\) uptake too low
   - Genetic factors
   - Psychological stress, abnormal regulation (?), norepinephrine, hypersensitivity
   - Cardiac stimulation

2. **Renal hypertension**
   - Renal artery stenosis etc.
   - Various renal diseases
   - Renal ischemia
   - Renin
   - Angiotensin II
   - Aldosterone
   - Na\(^+\) retention
   - Functioning renal mass

3. **Hormonal hypertension**
   - 11-desoxy-corticosterone (DOC)
   - ACTH
   - Cortisol deficiency
   - Adrenal cortical tumor
   - Primary hyperaldosteronism (Conn’s s.)
   - Cushing’s syndrome
   - Adrenal medullary tumor

4. **Other forms of hypertension:**
   - Cardiovascular, neurogenic, drugs

**90% Primary ('essential') hypertension**

**7% Renal hypertension**

**3% Hormonal and other causes**

**ECV ↑**

**CO ↑**

**TPR ↑**

**v**

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In the adrenogenital syndrome (→ B3a) cortisol formation in the adrenal cortex is blocked, and thus adrenocorticotropic hormone (ACTH) release is not inhibited. As a result excessive amounts of mineralocorticoid-active precursors of cortisol and aldosterone, for example, 11-deoxycorticosterone (DOC), are produced and released (→ p. 264 ff.). This leads to Na⁺ retention, hence to an increase in extracellular volume (ECV) and thus to cardiac output H.

Primary hyperaldosteronism (Conn’s syndrome; → B3b). In this condition an adrenal cortical tumor releases large amounts of aldosterone without regulation. Also in this case Na⁺ retention in the kidney leads to cardiac output H.

Cushing’s syndrome (→ B3c). Inadequate ACTH release (neurogenic cause; hypophyseal tumor) or an autonomous adrenal cortical tumor increase plasma glucocorticoid concentration, resulting in a raised catecholamine effect (cardiac output increased), and the mineralocorticoid action of high levels of cortisol (Na⁺ retention) lead to H. (→ p. 264 ff.). A similar effect occurs from eating large amounts of liquorice, because the glycyrrhizinic acid contained in it inhibits renal 11β-hydroxysteroid dehydrogenase. As a result, cortisol in the kidneys is not metabolized to cortison but rather has its full effect on the renal mineralcorticoid receptor.

Pheochromocytoma (→ B3d) is an adrenomedullary tumor that produces catecholamines, resulting in uncontrolled high epinephrine and norepinephrine levels and thus both cardiac output hypertension and resistance hypertension.

Contraceptive pills can cause Na⁺ retention and thus cardiac output hypertension.

Neurogenic hypertension. Encephalitis, cerebral edemas or hemorrhage, and brain tumors may lead to a massive rise in blood pressure via central nervous stimulation of the sympathetic nervous system. An abnormally high central stimulation of cardiac action as part of the hyperkinetic heart syndrome may also cause H.

The consequences of hypertension (→ E) most importantly result from atherosclerotic damage in arterial vessels (→ p. 236 ff.), which can be observed well by means of fundoscopy. Because of the resulting increase in flow resistance, every form of hypertension ultimately creates a vicious circle. Vascular damage finally leads to ischemia of various organs and tissues (myocardium, brain, kidneys, mesenteric vessels, legs), renal ischemia accelerating the vicious circle. Damage to the vascular walls together with hypertension can, for example, lead to brain hemorrhage (stroke) and in the large arteries (e.g., aorta) to the formation of aneurysms and ultimately their rupture (→ p. 238). Life expectancy is therefore markedly reduced. American life insurance companies, monitoring the fate of 1 million men whose blood pressure had been normal, slightly, or moderately elevated when aged 45 years (→ D), found that of those men who definitely had normal blood pressure (ca. 132/85 mmHg) nearly 80% were still alive 20 years later, while of those with initially raised blood pressure (ca. 162/100 mmHg) fewer than 50% had survived.
C. Na⁺ Uptake and Blood Pressure

- Primary hypertension or abnormal renal function
- Normal uptake
- High uptake

D. Mortality and Hypertension

E. Consequences of Hypertension

- Arterial hypertension
- Hypertensive encephalopathy
- Left ventricular hypertrophy, heart failure
- Renal ischemia
- Renal failure
- Myocardial infarction
- Peripheral vascular disease
- Bleeding
- Malacia
- Apoplexy

**Plate 7.20 Hypertension III**

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Pulmonary Hypertension

The mean pulmonary artery pressure ($P_{PA} = 15$ mmHg = 2 kPa) is determined by three variables, namely pulmonary vascular resistance (PVR), cardiac output, and left atrial pressure ($P_{LA} = ca. 5$ mmHg = 0.7 kPa).

According to Ohm’s law $\Delta P = PVR \cdot CO$.

$$\Delta P = P_{PA} - P_{LA}$$

$$P_{PA} = PVR \cdot CO + P_{LA}$$

Pulmonary hypertension (PHT) develops when one (or several) of the above variables is raised so much that at rest $P_{PA}$ is over 20 mmHg; on exercise it is above 32 mmHg (see pulmonary edema, p. 80). In principle, PHT can have three causes (→ A):

- **PVR rise**, so-called obstructive PHT, caused, for example, by pulmonary embolism or emphysema. PVR may further increase because of the resulting hypoxemia and its consequences (pulmonary hypoxic vasoconstriction, increased hematocrit).
- **$P_{LA}$ rise**, so-called passive PHT, for example, in mitral stenosis (→ A, upper right and p. 194).
- **Cardiac output increase**, except in left-to-right shunt (→ p. 204). A rise in cardiac output alone will lead to (hyperkinetic) PHT only in extreme cases, because the pulmonary vasculature is very distensible and additional blood vessels can be recruited. A rise in cardiac output (fever, hyperthyroidism, physical exertion) can, however, aggravate an existing PHT due to other reasons.

**Acute PHT** almost always results from a reduction in the cross-sectional area of the vascular bed (of at least 50%, because of the high vascular distensibility), as by pulmonary embolism, i.e., migration of thrombi or (rarely) other emboli from their site of origin into the pulmonary arteries (→ A, top and p. 240). If embolism arises, it is likely that additional (hypoxic?) vasoconstriction will develop, which will then reduce the vascular cross-sectional area even more. Sudden vascular obstruction causes acute cor pulmonale (acute right heart load). In acute PHT the right ventricular systolic pressure can rise to over 60 mmHg (8 kPa), but may become normal again within 30–60 minutes in certain circumstances, for example, if the thrombus has moved more distally, thus increasing the vascular cross-sectional area. Pressure may also be reduced by thrombolysis or possibly by diminished vasoconstriction. Embolism may result in pulmonary infarction, especially when medium-sized vessels are obstructed and at the same time the blood supply to the bronchial arteries is reduced (e.g., in pulmonary venous congestion or systemic hypotension). However, massive pulmonary embolism may also lead to acute right heart failure (→ A, bottom right), so that flow into the left ventricle and thus its output falls. This in turn leads to a decrease in systemic blood pressure and to circulatory shock and its consequences (→ p. 230).

Among the **causes of chronic PHT** are:

- **a** Lung disease (asthma, emphysema, chronic bronchitis or fibrosis, together accounting for > 90% of chronic cor pulmonale cases);
- **b** Chronic thromboembolism and systemic vascular disease;
- **c** Extrapulmonary causes of abnormal pulmonary function (thoracic deformity, neuromuscular disease, etc.);
- **d** Removal of lung tissue (tuberculosis, tumors);
- **e** Chronic altitude hypoxia with hypoxic constriction that can also, to an extent, be involved in causes a – c;
- **f** Idiopathic primary PHT of unknown etiology.

Causes b and e lead to precapillary PHT; cause a usually to capillary PHT. In all these disorders the resistance in the pulmonary circulation is chronically elevated, due to either exclusion of large segments of the lung, or generalized vascular obstruction. The **consequence of chronic PHT** is right ventricular hypertrophy (chronic cor pulmonale; → A, bottom left) and ultimately right ventricular failure (→ A, bottom right). In contrast to a – f, the cause of passive PHT is primarily not in the lung but in the left heart (postcapillary PHT). Thus, almost all patients with mitral valve disease (→ p. 196 ff.) or left heart failure (→ p. 224 ff.) develop PHT.
A. Causes and Consequences of Pulmonary Hypertension

- Altitude
- Embolism
- Lung disease and other ventilatory disorders
- Mitral valve disease
  - Left heart failure

- Hypoxic vasoconstriction
- Vascular obstruction
- Numbers of vessels or their cross-sectional area

- Hematokrit
- Blood viscosity
- Hypoxia
- Physical activity, fever, left-to-right shunt

- Cardiac output (CO)
- Pulmonary vascular resistance (PVR)
- Left atrial pressure (P_LA)

\[
\text{Pulmonary hypertension} = \text{Mean pulmonary a. pressure (P_{AP})}
\]

\[
\text{chronic} = \text{acute}
\]

- Right heart: increased load
- Hypertrophy
- Dilation

- Cyanosis
- Congestion of neck veins
- Liver congestion
- Edema
- Heart failure

- Increased central venous pressure
- Right heart failure
- Shock
Coronary Circulation

The myocardial blood supply comes from the two coronary arteries that arise from the aortic root (→ B, D). Usually the right coronary artery supplies most of the right ventricle, the left one most of the left ventricle. The contribution of the two arteries to the supply of the interventricular septum and the posterior wall of the left ventricle varies.

Coronary blood flow, $Q_{\text{cor}}$, has a few special features:

1. Phasic flow. $Q_{\text{cor}}$ changes markedly during the cardiac cycle (→ A), especially due to the high tissue pressure during systole that, in areas close to the endocardial regions of the left ventricle, reaches ca. 120 mmHg (→ B). While the main epicardial branches of the coronary arteries and the flow in the subepicardial regions are largely unaffected by this (→ B), vessels near the endocardium of the left ventricle are "squeezed" during systole, because during this phase the extravascular pressure (= left ventricular pressure) surpasses the pressure in the lumen of the coronary arteries. Blood supply to the left ventricle is therefore largely limited to the diastole (→ A). Conversely, the high systolic tissue pressure presses the blood out of the coronary sinus and other veins, so that most of it flows into the right occurs during systole.

2. Adaptation to $O_2$ demand is achieved largely by changes in vascular resistance. $O_2$ demand of an organ can be calculated from the blood flow through it, $Q$, multiplied by the arteriovenous $O_2$ concentration difference ($C_a - C_v$)$_o$. If $O_2$ demand rises, for example, through physical activity or hypertension (→ C, right and p. 218), both variables may in principle be increased, but ($C_a - C_v$)$_o$ and thus oxygen extraction (= 100 · [(C$_a$ – C$_v$)/C$_a$] = 60%) is very high even at rest. During physical work, $O_2$ supply to the myocardium, and thus cardiac work, can essentially only be increased by an increase in $Q_{\text{cor}}$ (= aortic pressure $P_{Ao}$/coronary resistance $R_{\text{cor}}$). If $P_{Ao}$ remains unchanged, $R_{\text{cor}}$ must be reduced (vasodilation; → C, left), which is normally possible down to ca. 20–25% of the resting value (coronary reserve). In this way $Q_{\text{cor}}$ can be increased up to four to five times the resting value, i.e., it will be able to meet the ca. four to fivefold increase in $O_2$ demand of the heart at maximal physical work (→ p. 219 A, normal).

3. $Q_{\text{cor}}$ is closely linked to myocardial $O_2$ demand. The myocardium works aerobically, i.e., there must be a rapid and close link between the momentary energy demand and $Q_{\text{cor}}$. Several factors are involved in this autoregulation:

   - **Metabolic factors.** First of all, $O_2$ acts as a vasoconstrictor, i.e., $O_2$ deficiency dilates the coronary arteries. AMP, a metabolic breakdown product of ATP, cannot be sufficiently regenerated to ATP during hypoxia, and thus the concentration of AMP and its breakdown product adenosine rises in the myocardium. Adenosine acts as a vasodilator on the vascular musculature via $A_2$ receptors (cAMP increase). Finally, the accumulation of lactate and $H^+$ ions (both of them products of the anaerobic myocardial metabolism; → p. 219 C) as well as prostaglandin I$_2$, will locally cause vasodilation.

   - **Endothelium-mediated factors.** ATP (e.g., from thrombocytes), ADP, bradykinin, histamine, and acetylcholine are vasodilators. They act indirectly by releasing nitric oxide (NO) that secondarily diffuses into the vascular muscle cells, where it increases guanylyl cyclase activity, and thus intracellularly raises the concentration of cyclic guanosine monophosphate (cGMP). Finally, cGMP activates protein kinase G, which relaxes the vascular musculature.

   - **Neurohumoral factors.** Epinephrine and noradrenaline, circulating and released from the sympathetic nerve fiber endings, respectively, act as vasoconstrictors on the $\alpha_1$-adrenoceptors that prevail in epicardial vessels, and as vasodilators at $\beta$-adrenoceptors that predominate in subendocardial vessels.

If $O_2$ supply can no longer keep in step with oxygen demand, for example, at a high heart rate with a long systole, or in atherosclerotic obstruction of the coronary arteries, **coronary is sufficiency** (hypoxia) results (→ C, D and p. 218 ff.).
A. Coronary Blood Flow

B. Pressure Gradients in Myocardium

C. Components of \( O_2 \) Balance in Myocardium

D. Atherosclerosis of Coronary Arteries
Coronary Heart Disease

During physical work or psychological stress, the myocardial oxygen demand rises, particularly because heart rate and myocardial contractility will have been increased by sympathetic stimulation. In response to this the coronary vascular resistance can in the normal heart drop to as low as ca. 20% of its resting level so that, with the corresponding increase in coronary perfusion, the O₂ balance will be restored even during this period of increased demand. The capacity to increase perfusion to up to five times the resting value is called coronary reserve. The wide range in coronary blood flow is due to the fact that the distal coronary vessels are constricted at rest and dilate only on demand (→A; normal vs. ¼ resistance).

Diminished coronary reserve is characteristic of coronary heart disease (CHD) and leads to O₂ supply no longer being able to meet any increased O₂ demand. This ischemic anoxia manifests itself in pain mainly in the left chest, arm, and neck during physical work or psychological stress (angina pectoris; see below)

The main cause of CHD is narrowing of the proximal large coronary arteries by atherosclerosis (→p. 217 D and 236 ff.). The poststenotic blood pressure (Pₚₚ) is therefore significantly lower than mean diastolic arterial pressure (Pₐ₀; →A). To compensate for this raised resistance or reduced pressure, the coronary reserve is encroached upon, even at rest. The price paid for this is a diminution in the range of compensatory responses, which may ultimately be used up. When the luminal diameter of the large coronary arteries is reduced by more than 60–70% and the cross-sectional area is thus reduced to 10–15% of normal, myocardial ischemia with hypoxic pain occurs even on mild physical work or stress. If synchronously O₂ supply is reduced, for example, by a lowered diastolic blood pressure (hypotension, aortic regurgitation), arterial hypoxemia (staying at high altitude), or decreased O₂ capacity (anemia), O₂ balance is disturbed, even when there is only mild coronary artery stenosis (→p. 217 C).

If the pain ceases when the physical or psychological stress is over, the condition is called stable angina pectoris. When a patient with chronic stable angina pectoris suddenly has stronger and more frequent anginal pain (unstable angina pectoris), it is often a premonitory sign of acute myocardial infarction, i.e., complete occlusion of the relevant coronary artery (see below).

However, complete coronary occlusion does not necessarily lead to infarction (see below), because in certain circumstances a collateral blood supply may develop as long-term adaptation so that, at least at rest, the O₂ demand can be met (→B). The affected region will, however, be particularly in danger in cases of hypoxemia, a drop in blood pressure, or an increased O₂ demand.

Pain resulting from a lack of O₂ can also occur at rest due to a spasm (α₁-adrenoreceptors; →p. 216) in the region of an only moderate atherosclerotic narrowing of the lumen (vasospastic, Prinzmetal’s, or variant angina). While shortening of the arterial muscle ring by, for example, 5% increases the resistance of a normal coronary artery about 1.2fold, the same shortening in the region of an atheroma that is occluding 85% of the lumen will increase the resistance 300 times the normal value (→D). There are even cases in which it is largely (or rarely even exclusively) a coronary spasm and not the atheromatous occlusion that leads to an episode of vasospastic angina.

Another cause of diminished coronary reserve is an increased O₂ demand even at rest, for example, in hypertension or when there is an increased ventricular volume load. The ventricular wall tension, i.e., the force that the myocardium must generate per wall cross-sectional area (N·m⁻²) to overcome an elevated aortic pressure or to eject the increased filling volume, is then significant. In accordance with Laplace’s law, the wall tension (K) of an approximately spherical hollow organ can be calculated from the ratio of (transmural pressure · radius)/(2 · wall thickness) (→p. 217 C)

Thus if, without change in wall thickness, the ventricular pressure (Pᵥᵥ) rises (aortic valve stenosis, hypertension; →p. 198 and 208) and/or the ventricular radius increases (greater filling in mitral or aortic regurgitation; →p. 196 and 200), the wall tension necessary for maintaining normal cardiac output and
A. Coronary Reserve

<table>
<thead>
<tr>
<th>Poststenotic pressure, ( P_s ) (mmHg)</th>
<th>Normal</th>
<th>1/4 (vasodilation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% closed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% closed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80% closed</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proximal stenosis

B. Collateral Myocardial Perfusion

- Left coronary artery
- Collateral circulation
- Endocardium
- Subendocardial
- Subepicardial
- Ischemic zone

C. Myocardial Energy Metabolism

**Normal**

Glucose → G-6-P → Pyruvate → Acetyl-CoA → \( \text{O}_2 \) → ATP → CO₂

- NAD⁺ → FAD
- ATP → Normal myocardial contraction
- Creatine phosphate store

**Ischemic anoxia** (early stage)

Glucose → G-6-P → Pyruvate → Acetyl-CoA → \( \text{O}_2 \) → ATP → CO₂

- NAD⁺ → FAD
- ATP → ATP deficiency

- Lactate (formation)
- Free fatty acids
- Intracellular fat deposition
- Abnormal myocardial contraction

**Ischemia** (longer than 15–20 min)

- No removal of \( H^+ \) and Lactate
- Acidosis
- Lactate accumulation
- Inhibits glycolysis (and others)
- ATP deficiency

**Infarction**

- Enzyme released into plasma
- Irreversible cell damage

**Angina pectoris**

<table>
<thead>
<tr>
<th>Days</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>CK</td>
</tr>
<tr>
<td>2</td>
<td>SGOT</td>
</tr>
<tr>
<td>6</td>
<td>LDH₁</td>
</tr>
</tbody>
</table>

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thus myocardial \( O_2 \) demand are raised. Should this continue over a long period, the ventricular myocardium will hypertrophy (\( \rightarrow \) p. 224 ff.). This reduces wall tension, at least for a while (compensation). Decompensation occurs when the heart weight has reached the critical value of 500 g, at which time the ventricle dilates (\( \rightarrow \) p. 224 ff.). The radius of the ventricular cavity and thus wall tension increases, so that \( O_2 \) demand now suddenly rises to very high values.

**Consequences and symptoms of myocardial ischemia.** The myocardium covers its energy requirement by metabolizing free fatty acids, glucose, and lactate. These substrates are used for the \( O_2 \)-dependent formation of ATP (\( \rightarrow \) C, normal). When blood supply is interrupted (ischemia), this aerobic energy gain stagnates, so that ATP can only be formed anaerobically. Lactic acid is now produced, dissociating into \( H^+ \) ions and lactate. In these circumstances not only is lactate not used up, it is actually produced (\( \rightarrow \) C, early “ischemic anoxia”). The ATP yield is thus quite meagre and, furthermore, the \( H^+ \) ions accumulate because of the interrupted blood flow, both events being responsible for abnormal ventricular contraction (reversible cell damage; \( \rightarrow \) C). If the ischemia persists, glycolysis is also inhibited by tissue acidosis, and irreversible cell damage occurs (infarct; see below) with release of intracellular enzymes into the blood (\( \rightarrow \) C, left).

**ATP deficiency** leads to:
- Impairment of the systolic pumping action of the ventricle (forward failure; \( \rightarrow \) p. 224 ff.) as well as
- Decreased compliance of the myocardium during diastole (backward failure; \( \rightarrow \) p. 224 ff.), so that the diastolic atrial and ventricular pressures are raised.
- Congestion in the pulmonary circulation (dyspnea and tachypnea). Just before ventricular systole the lowered compliance in diastole produces a fourth heart sound that originates from the increased atrial contraction (“atrial gallop”). If the papillary muscles are affected by the ischemia, this may result in
  - Mitral regurgitation (\( \rightarrow \) p. 196).
- Finally, disorder of myocardial excitation caused by the ischemia (\( \rightarrow \) E) may precipitate dangerous arrhythmias (ECG; \( \rightarrow \) p. 186 ff.). During the ischemia period the ECG will show an elevation or depression (depending on the lead) of the ST segment as well as flattening or reversal of the T wave (similar to that in F 4). If the resting ECG of a patient with angina is normal, these ECG changes can be provoked by controlled (heart rate, blood pressure) physical exercise.

Stimulation of the nociceptors (by kinins?, serotonin?, adenosine?) will lead not only to
- anginal pain (see above), but also to
- generalized activation of the sympathetic nervous system with tachycardia, sweating, and nausea.

**Therapeutic attempts** at restoring an even \( O_2 \) balance (\( \rightarrow \) p. 217 C) in patients with angina are:
- Lowering myocardial \( O_2 \) consumption (\( \beta \)-adrenergic blockers; organic nitrates that reduce the preload [and to some extent also the afterload] by generalized vasodilatation; \( Ca^{2+} \) channel blockers), and
- Increasing the \( O_2 \) supply (organic nitrate and \( Ca^{2+} \) channel blockers that both function to counteract spasm and to dilate coronary vessels). In addition, the size and position of the atherosclerically stenosed coronary arteries make it possible to dilate them by balloon angioplasty or vascular stents or by revascularization with a surgically created aortocoronary bypass.

### Myocardial Infarction

**Causes.** If the myocardial ischemia lasts for some time (even at rest [unstable angina]; see above), tissue necrosis, i.e., myocardial infarction (MI), occurs within about an hour. In 85% of cases this is due to acute thrombus formation in the region of the atherosclerotic coronary stenosis.

This development is promoted by
- turbulence, and
- atheroma rupture with collagen exposure. Both events
- activate thrombocytes (aggregation, adhesion, and vasoconstriction by release of thromboxan). Thrombosis is also encouraged through
- abnormal functions of the endothelium, thus its vasodilators (NO, prostacyclin) and antithrombotic substances are not present.
D. Acute Ischemia in Coronary Atherosclerosis

- Atheroma
- Thrombus (local, embolic)
- Spasm

<table>
<thead>
<tr>
<th>Circumference of muscle ring</th>
<th>Normal</th>
<th>Dilated</th>
<th>Constricted</th>
<th>Dilated</th>
<th>Constricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Internal radius (mm)</td>
<td>100 %</td>
<td>95 %</td>
<td>100 %</td>
<td>95 %</td>
<td></td>
</tr>
<tr>
<td>Lumen area (mm²)</td>
<td>2</td>
<td>1.9</td>
<td>0.78</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Lumen area reduced by</td>
<td>12.5</td>
<td>11.3</td>
<td>1.9</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Resistance (~ 1/r²)</td>
<td>0 %</td>
<td>10 %</td>
<td>85 %</td>
<td>94 %</td>
<td></td>
</tr>
<tr>
<td>(muscle wall thickness ignored)</td>
<td>(1)</td>
<td>x 1.2</td>
<td>x 43</td>
<td>x 328</td>
<td></td>
</tr>
</tbody>
</table>

E. Excitation of Myocardial Cell in Ischemia

- Normal
- Ischemia after 30 min
- Ischemia after 60 min
- Ischemia after 180 min

Bipolar intramural electrogram

F. ECG in Coronary Infarction

- ECG pattern reverse of that on the opposite side

Stage 1 (hours to days)
Stage 2 (days to weeks)
Stage 3 (months to years)
plasminogen activator [t-PA], antithrombin III, heparin sulfate, protein C, thrombomodulin, and prostacyclin).

Rare causes of MI are inflammatory vascular diseases, embolism (endocarditis; valve prosthesis), severe coronary spasm (e.g., after taking cocaine), increased blood viscosity as well as a markedly raised O₂ demand at rest (e.g., in aortic stenosis).

**ECG (→ F).** A prominent characteristic of transmural infarction (tml) is an abnormal Q wave (→ F1) of > 0.04 seconds and a voltage that is > 25% of overall QRS voltage. It occurs within one day and is due to the necrotic myocardium not providing any electrical signal, so that when this myocardial segment should be depolarized (within the first 0.04 s), the excitation vector of the opposite, normal portion of the heart dominates the summated vector. This “0.04 vector” therefore “points away” from the site of infarction so that, for example, in anterior-wall infarction, it is registered particularly in leads V₅, V₆, I, and aVL as a large Q wave (and small R). (In a transmural infarction of the posterior wall such Q wave changes cannot be registered with the conventional leads). Abnormal Q waves will still be present years later (→ F₂, 3), i.e., they are not diagnostic of an acute infarction. An infarction that is not transmural usually causes no Q changes.

**ST segment elevation** in the ECG is a sign of ischemic but not (yet) dead myocardial tissue. It occurs

- during an anginal attack (see above)
- in nontransmural infarction
- at the very beginning of transmural infarction
- at the margin of a transmural infarction that occurred hours to days before (→ F4)

The ST segment returns to normal one to two days after an MI, but for the next few weeks the T wave will be inverted (→ F₅, F₂).

If sizeable portions of the myocardium die, enzymes are released from the myocardial cells into the bloodstream. It is not so much the level of enzyme concentrations as the temporal course of their maxima that is important in the diagnosis of MI. Myocardial creatine kinase (CK-MB [MB = muscle, brain]) reaches its peak on day 1, aspartate aminotransferase (ASAT) on day 2, and myocardial lactate dehydrogenase (LDH₅) on days three to five (→ C, bottom).

Possible **consequences** of MI depend on site, extent, and scarring of the infarct. In addition to various arrhythmias, among them acutely life-threatening ventricular fibrillation (→ p. 186ff.), there is a risk of a number of **morphological/mechanical complications** (→ G):

- Tearing of the chordae tendineae resulting in acute mitral regurgitation (→ G1 and p. 196);
- Perforation of the interventricular septum with left-to-right shunting (→ G2 and p. 204);
- Fall in cardiac output (→ G, a) that, together with
  - stiffened parts of the ventricular wall (akinesia) due to scarring (→ G, b),
  - will result in a high end-diastolic pressure (→ G3 and p. 224). Still more harmful than a stiff infarct scar is
  - a stretchable infarct area, because it will bulge outward during systole (dyskinesia; → G4), which will therefore—at comparably large scar area—be more likely to reduce cardiac output to dangerous levels (cardiogenic shock) than a stiff scar will (→ G5);
  - Finally, the ventricular wall at the site of the infarct can rupture to the outside so that acutely life-threatening pericardial tamponade occurs (→ G6 and p. 228).
G. Mechanical Consequences in the Heart after Myocardial Infarction (in Left Ventricle)

1. Ischemia, possibly tearing of chordae
   - Acute mitral regurgitation
     - 'Forward' stroke volume
     - Pulmonary congestion
     - Pulmonary edema

2. In ventricular septum
   - Perforation
   - Left-to-right shunt
   - Central blood volume
   - Ventricular diastolic pressure
   - Compliance curve

3.

4. In outer ventricular wall
   - CO↓
   - End-diastolic volume
   - Stiff
   - Distensible

5. CO (L/min)

6. Pericardium
   - Rupture
   - Pericardial tamponade

7. Cardiogenic shock
   - 80%
   - Death after infarction

8. Myocardial infarction (left ventricle)
   - Death after infarction

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Heart Failure

Heart failure (HF) is the state of reduced myocardial performance, and mainly affects the *left ventricle* (LV). Its most common causes (→ A) are coronary heart disease (→ p. 218 ff.) and hypertension (→ p. 208 ff.), but nearly all other forms of cardiac disease (valvar defects, cardiomyopathies; → A) as well as some extracardiac diseases can result in HF. *Right ventricular failure* can occur with right heart defects and shunts (→ p. 202 ff.), and particularly with pulmonary hypertension (→ p. 214). However, the right ventricle may also be affected secondarily by abnormalities in the left ventricle (mitral stenosis, left HF).

In principle a distinction is made between HF due to reduced systolic ejection (systolic or **forward failure**), resulting from either an increased volume load, myocardial disease, an increased pressure load, or impaired diastolic filling of the heart, and HF in which diastolic filling is impaired (diastolic or **backward failure**), for example as a result of greater ventricular wall stiffness. In forward HF the stroke volume, and thus cardiac output, can no longer adequately meet the organism’s requirements. In backward HF this can be counteracted only by increasing the diastolic filling pressure. Usually HF only becomes manifest *initially on severe physical work* (when maximal O₂ uptake and maximal cardiac output is decreased, but otherwise without symptoms; stage I of the NYHA [New York Heart Association] classification). However, symptoms later develop progressively, at first only on ordinary physical activity, later even at rest (NYHA stages II–IV).

**HF caused by volume load.** Aortic and mitral regurgitation, for example, are characterized by the *regurgitant volume* (→ p. 196 and 200) that is added to the effective stroke volume. The enddiastolic volume, and therefore the radius (*r*) of the left ventricle, are increased so that, according to Laplace’s law (→ A), the wall tension (T), i.e., the force that has to be generated per myocardial cross-sectional area, must rise to achieve a normal, effective stroke volume. As this succeeds only inadequately, stroke volume and thus CO (= heart rate · stroke volume) decrease and the blood pressure falls. Sympathetic stimulation occurs as a counterregulatory mechanism, resulting in increased heart rate and peripheral vasoconstriction (see below; → B). If chronic volume load develops, the dilated ventricle reacts with **hypertrophy** to compensate, i.e., with an increased wall thickness (d). However, *r* remains elevated (eccentric hypertrophy; → A1), and this form of HF usually has a less favorable course than one with concentric hypertrophy (see below). If the underlying condition (e.g., valvar defect) is not removed early, HF gets worse relatively rapidly because of the resulting myocardial remodeling (see below). Stiffening of the ventricle, caused by the hypertrophy, is involved in this development. Because of its steeper compliance (= lusitropic = relaxation) curve (→ A3, R becomes R”), it has a diminished enddiastolic volume and thus a small stroke volume (backward HF; see also A5, orange arrows). A vicious circle arises, in that the dilated ventricular wall gives way even more (dilation with myocardial restructuring) and *r* rises steeply. This *decompensation* is characterized by a life-threatening fall in stroke volume despite an enormously elevated enddiastolic volume (→ A5, red arrows).

**HF caused by myocardial disease.** In *coronary heart disease* (ischemia; → p. 218) and after *myocardial infarction* (→ p. 220) the load on the uninvolved myocardium increases, i.e., forward HF develops due to **diminished contractility.** This is reflected by a shift of the contractility (C) curve of the ventricular work diagram (→ A2, C becomes C′). The endsystolic volume and, to a lesser extent, the EDV also rises, while stroke volume falls (→ A2, SV becomes SV; see also A5, lilac arrows). Hypertrophy of the remaining myocardium, a stiff myocardial scar as well as the diminished effect of ATP on actin–myosin separation in the ischemic myocardium will lead to additional backward HF. Finally, a compliant infarct scar may bulge outward during systole (dyskinesia; → p. 223, G4), resulting in additional volume load (regurgitant volume). *Cardio-myopathies* can also lead to HF, volume load being prominent in the dilated form, backward HF in the hypertrophic and restrictive forms.

**HF due to pressure load.** The wall tension (T) of the left ventricle also rises in hypertension or aortic stenosis, because an increased
A. Causes and Mechanical Consequences of Left Ventricular Failure

1. **Eccentric hypertrophy** = cardiac dilation
   - Ventricular radius \( r \) rises
   - Regurgitant volume
   - Volume load
   - Pressure load

2. **Contractility** ↓
   - Systolic or forward failure
   - Diastolic or backward failure
   - Decompensation (structural dilation)

3. **Concentric hypertrophy** (Ventricular radius \( r \) normal or reduced)
   - Hypertrophy \( (d \text{ rises } \rightarrow T \text{ falls}) \)
   - Ventricle less compliant

4. **Aortic or mitral regurgitation**
   - Myocardial infarction
   - Myocardial ischemia
   - Cardiomyopathy
   - Pressure load

5. **Laplace:**
   - Wall tension \( T = \frac{P_{\text{ventr}} \cdot r}{2 \cdot \text{wall thickness } d} \)

- **SV** falls
- **SV** rises
- **ESV** rises
- **EDV** falls

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left ventricular pressure ($P_{lv}$) is required (La-place’s law; $\rightarrow$ A). Forward HF with diminished contractility develops ($\rightarrow$ A2). An analogous situation exists regarding the right ventricle in pulmonary hypertension. Compensatory hypertrophy will also develop when there is an increased pressure load, but it will be “concentric” ($\rightarrow$ A4), because in this case the ventricular volume is not enlarged and may in some circumstances actually be decreased. However, even in concentric hypertrophy the end-diastolic volume will be reduced and thus also the stroke volume (backward HF; $\rightarrow$ A3; see also A5, orange arrows). When there is a high pressure load, myocardial remodeling (see below), and unfavorable capillary blood supply (relative coronary ischemia), a “critical heart weight” of ca. 500 g may be attained, at which the myocardial structure gives way, causing decompensation.

**Neurohumoral consequences of HF.** Next to mechanical cardiac effects ($\rightarrow$ A), HF induces a number of compensatory mechanisms that are primarily directed at restoring cardiac output and blood pressure ($\rightarrow$ B) again. Most important in this is an increased sympathetic tone together with greater release of norepinephrine and epinephrine. Activation of cardiac $\beta_1$-adrenoreceptors will result in:

- **Heart rate being increased** (the symptom being tachycardia); and
- Contractility being raised (positive inotropy), and thus the cardiac output slightly increased.

$\alpha_1$-adrenergic vasoconstriction will produce:

- Reduction in blood flow through skeletal muscle (the symptom being fatigue), skin (the symptom being pallor), and kidneys, with the result that the decreased cardiac output is distributed preferentially to the arteries supplying the heart and brain (centralization);
- **Reduction in renal perfusion**, now leading to activation of the renin–angiotensin–aldosterone system, to an increased filtration fraction, and to increased release of ADH;
- All these mechanisms produce a rise in water and salt absorption. Angiotensin II and ADH also have a vasoconstrictor effect.

**Myocardial remodelling.** Remodelling of the myocardium occurs right at the beginning of HF (NYHA stage I) through mechanical and neurohormonal stimuli. This will decisively influence the progression of HF. Causes of the remodelling are: 1) increased wall tension ($\rightarrow$ A) that, among other effects, raises cytosolic Ca$^{2+}$ concentration, and 2) systemic (catecholamines, ADH, angiotensin II; insulin in type II diabetes) and local growth signals (endothelin, TGF, platelet-derived growth factor [PDGF], fibroblast GF [FGF]), and decrease in growth inhibitors (NO and PG1). The myocardial cells become enlarged (hypertrophy), but refractoriness to catecholamines develops (down-regulation of $\beta_1$-adrenoreceptors, a rise in the antagonistic G proteins, receptor decoupling), and Ca$^{2+}$-ATPase activity falls.

As a consequence, the myocardial action potential is prolonged (due to decreased repolarization currents) and the resting potential is less negative. This can result in arrhythmias (reentry, afterpotentials, ectopic pacemakers; $\rightarrow$ p.186 ff.); in some circumstances even ventricular fibrillation. (The latter occurs in about 50% of patients in HF, causing their sudden cardiac death). Overall there will be weak contractility (among other factors, due to partly functional decoupling between the dihydropyridine and the ryanodine receptors; $\rightarrow$ p.182) as well as reduced relaxation capacity of the myocardium (cytosolic Ca$^{2+}$ concentration increased in diastole). Fibroblast activation (FGF and others) is involved in this and results in an increased deposition of collagen in the ventricular wall and fibrosis of myocardium and blood vessels.

The **systemic consequences and symptoms** of chronic HF are mainly caused by water and salt retention ($\rightarrow$ B, bottom). In left HF the pulmonary capillary pressure is increased. This can cause dyspnea and tachypnea via the J-receptors in the lung and can lead to pulmonary edema (cardiac asthma) with systemic hypoxia and hypercapnia. In right HF peripheral edemas will occur (especially in the lower leg during the day; at night there is excretion of water with nocturnal diuresis).
Heart failure: Neurohumoral Consequences

- Chronic volume or pressure load
- Coronary heart disease etc.
- Primary myocardial damage

**Sympathetic tone↑**

**Organ perfusion↓**
- Skeletal muscle
- Skin
- Heat removal↓
- Kidney

**Symptoms:**
- fatigue
- sweating
- tachycardia

**Salt and water retention**

- ADH↑
- RPF falls more deeply than GFR
- Filtration fraction↑
- Peritubular oncotic pressure↑
- Salt and water resorption↑

**Salt and water retention**

**Symptoms:**
- peripheral edema
- nycturia
- dyspnea
- tachypnea

**Venous pressure↑**

- Systemic
- Pulmonary capillary pressure↑

**Interstitial pulmonary edema**

- Increasing heart failure
- Alveolar pulmonary edema, hypoxia, hypercapnia

**Work of breathing increased**

- Vital capacity↓
- Compliance↓

**Local:**
- endothelin↑
- TGF, FGF↑
- NO, PGI₂↓

**Catecholamines**

- Hyper-volemia

**Distension**

**Remodelling**

**Arrhythmia**

**Renin↑**

**Angiotensin II↑**

**Aldosterone↑**

**GFR↓**

**CO↓**

**Blood pressure↓**

**Sympathetic tone↑**

**Obstruction**

**Atrial pressure↑**

**Volume load**

**Hyper-volemia**

**Distension**

**Remodelling**

**Arrhythmia**

**Renin↑**

**Angiotensin II↑**

**Aldosterone↑**

**GFR↓**

**Salt and water retention**

**Symptoms:**
- peripheral edema
- nycturia
- dyspnea
- tachypnea

**Venous pressure↑**

- Systemic
- Pulmonary capillary pressure↑

**Interstitial pulmonary edema**

- Increasing heart failure
- Alveolar pulmonary edema, hypoxia, hypercapnia

**Work of breathing increased**

- Vital capacity↓
- Compliance↓

**Local:**
- endothelin↑
- TGF, FGF↑
- NO, PGI₂↓

**Catecholamines**

**Hyper-volemia**

**Distension**

**Remodelling**

**Arrhythmia**

**Renin↑**

**Angiotensin II↑**

**Aldosterone↑**

**GFR↓**

**Salt and water retention**

**Symptoms:**
- peripheral edema
- nycturia
- dyspnea
- tachypnea
Pericardial Diseases

The pericardium envelopes the heart as a double-layered, flexible sac: 15 – 50 mL of a serous fluid serves as lubricating film between the two pericardial layers. The intrapericardial pressure (P\textsubscript{per}) is dependent on respiration and varies between + 3.5 and – 3.5 mmHg.

The cause of acute pericarditis (P.) may be infectious (e.g., echovirus, tuberculosis) or non-infectious (e.g., uremia, transmural infarction, tumor, radiotherapy). The usual stages of P. are: 1) vasodilation with increased fluid accumulation (serous P.); 2) increased vascular permeability so that the content of proteins, including fibrinogen or fibrin, in the fluid increases (serofibrinous P.); and 3) immigration of leukocytes (purulent P.). Bleeding is also a possible cause (hemorrhagic P.).

Symptoms of an acute P. are chest pain (aggravated during inspiration and coughing), fever, pericardial rub on auscultation, and an abnormal ECG (ST segment elevation caused by associated inflammatory response of the subendocardial myocardium; PR segment depression because of abnormal atrial depolarization).

Pericardial effusion (> 50 mL of fluid which can be measured by echocardiography) can develop with any acute P. If more than ca. 200 mL accumulates in acute cases (e.g., hemorrhage), P\textsubscript{per} rises steeply because of the rigidity of the pericardial sac (for consequences, see below). But if effusion accumulates in chronic cases, the pericardial sac stretches gradually so that in given circumstances 1 – 2 L can be contained without significant rise in P\textsubscript{per}.

Serious complications of acute P. and of pericardial effusion are pericardial tamponade and constrictive pericarditis, both of which impair cardiac filling (→ A). Causes of pericardial tamponade (PT) include tumor infiltration and viral or uremic P. as well as ventricular rupture after myocardial infarction or chest trauma. A consequence of pericardial tamponade is a rise in ventricular pressure throughout systole to the level of P\textsubscript{per}. The normal “y descent (or dip)” in the central venous pressure (CVP; → p. 179 A3), which represents the fall in pressure after opening of the tricuspid valve, is flattened out so that no such dip is recorded (see below).

Scarring and calcification of the pericardial layers may occur after viral or tubercular P., causing constrictive pericarditis (conP.). This results in the ventricular compliance (= lusitropic = relaxation) curve rising much more steeply (→ A\textsubscript{2}, R becomes R'), so that the diastolic pressure in the ventricle rises again steeply after a brief fall (→ A\textsubscript{1}, dip with short and rapid early diastolic filling) to a plateau (→ A\textsubscript{1}). The y descent of the CVP is more marked in constrictive pericarditis, because—in contrast to pericardial tamponade—there is a greater pressure gradient between atrium and ventricle in early diastole. It is important in the differential diagnosis that in pericardial tamponade (but not in constrictive pericarditis) the systolic blood pressure during inspiration falls by more than 10 (normally 5) mmHg during inspiration, because the increased venous return, increased during inspiration, produces a bulge in the interventricular septum toward the left ventricle, thus lowering its stroke volume more than normal, resulting in a “pulsus paradoxus”.

The cardiac output is diminished in constrictive pericarditis and pericardial tamponade as a result of the decreased ventricular filling (→ A, orange area). Due to increased sympathetic activity, tachycardia and centralization of the circulation develops (shock; → p. 230 ff.). The combination of a fall in blood pressure, tachycardia, and compression of the coronary arteries results in myocardial ischemia with characteristic ECG changes (→ A\textsubscript{4}, 5; → p. 221 F). If pericardial tamponade (especially if acute) is not removed by a pericardial tap, the diastolic ventricular pressure rises ever higher due to a vicious circle, and the cardiac pumping action ceases (→ A\textsubscript{3}). Constrictive pericarditis is treated by means of surgical resection of the pericardium (pericardiectomy).
A. Pericardial Tamponade and Constriction

- **Injury, infarction, after cardiac surgery**
- **Inflammation, tumor, radiotherapy, renal failure, etc.**

- **Effusion, bleeding**
- **Pericardial pressure↑**
- **Hydraulic pressure distribution**
- **Rupture**
- **Exudate**

**Pericardial tamponade**

**Constrictive pericarditis**

1. **Right ventricular pressure in constrictive pericarditis**
   - Plateau
   - Dip
   - (after Spodick)

2. **Diastolic ventricular pressure**
   - Diastolic filling↓
   - Systemic

3. **Decompensation** (esp. acute tamponade)
   - Compression of coronary a.

4. **Myocardial ischemia**
   - Coronary blood flow↓
   - CO↓
   - Tachycardia
   - Vaso-constriction

5. **Ascites, edema**
   - Distension of neck veins
   - Venous pressure↑

6. **Shock**
   - Arterial pressure
   - Venous pressure↑
   - Time

7. **Venous pressure↑**

**ECG**

- **R’ Compliance curve**
- **Constrictive pericarditis**
- **Normal**
- **R’ Dip’**

**Time (s)**

**Pressure (mmHg)**

- **Normal**
- **Plateau**

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Circulatory Shock

(Circulatory) shock is the term given to acute or subacute progressive generalized circulatory failure with an abnormal microcirculation and underperfusion of vital organs. In a wider sense shock also includes disorders of O₂ supply and utilization with (initially) undiminished perfusion.

The cause of shock is usually reduced cardiac output, with the following possible causes:

- In hypovolemia (hypovolemic shock) the central venous pressure is reduced, and thus the venous return decreased. As a result stroke volume falls (Frank–Starling mechanism). The cause of the hypovolemia can be bleeding (hemorrhagic shock) or some other loss of fluid to the outside, such as via the gastrointestinal tract (severe bleeding, massive vomiting, persistent diarrhea), via the kidneys (e.g., diabetes mellitus or insipidus, high-dosage diuretics, polyuria after acute renal failure), or via the skin (extensive burns, profuse sweating without fluid intake). Loss of blood internally can also be a reason for hypovolemic shock, such as hemorrhage into the soft tissues (e.g., in fractures, especially of the thigh and pelvis, or in the region of the retroperitoneum), into the thorax (e.g., rupture of an aortic aneurysm), or into the abdomen (e.g., rupture of the spleen) as well as sequestration of large amounts of fluid in ileus, peritonitis, liver cirrhosis (ascites), or acute pancreatitis.

- Cardiogenic shock. Primary or secondary heart failure can be caused by acute myocardial infarction, acute decompensating heart failure, malignant arrhythmias, cardiomyopathy, acute valvar regurgitation, obstruction of the large vessels (e.g., pulmonary embolism) or by impairment of cardiac filling (mitral stenosis, pericardial tamponade, constrictive pericarditis). In these conditions, in contrast to hypovolemic shock, the central venous pressure is raised (congestive shock).

- Hormonal causes of shock include adrenal hypofunction (Addisonian crisis; → p. 270), diabetic coma (→ p. 288 ff.), hypoglycemic shock (insulin overdosage, insulinoma; → p. 292), hypothyroid or hyperthyroid coma, and coma in hypoparathyroidism or hyperparathyroidism (→ p. 128).

- Metabolic–toxic causes are decompensated liver cirrhosis, acute liver failure, uremia, various forms of poisoning, etc.

- Reduced cardiac output may also be caused by peripheral vascular distention (no pallor) with venous pooling of blood (decreased venous return), as may happen in anaphylactic shock (food or drug allergy), in which vasoactive substances are released (histamine etc).

- In septic–toxic shock the cardiac output is at first raised by the action of toxins of, usually Gram-negative bacteria (tachycardia and reduced total peripheral resistance). The initially normal blood pressure then falls, respiratory failure occurs, and finally a late stage develops with reduced cardiac output and high total peripheral resistance, disseminated intravascular coagulation (DIC), etc. (see below).

- Neurogenic shock is rare, but it may occur when, for example, brain stem or spinal cord trauma or intoxication (barbiturates, narcotics) disturb autonomic nervous system regulation of the heart and circulation and the venous return is markedly reduced.

Symptoms (→ B, left). Hypovolemic and hemorrhagic shock is often associated with a reduced blood pressure (narrow pulse amplitude), increased heart rate, pallor with cold sweat (not in shock that is due to vascular distension), diminished urine output (oliguria), and marked thirst. The resulting (blood) volume deficit can be estimated by means of the shock index (heart rate per minute/systolic blood pressure in mmHg):

- 0.5 = normal or blood loss < 10%;
- 1.0 = blood loss < 20–30% (incipient shock);
- 1.5 = blood loss > 30–50% (manifest shock).

Most of the above symptoms are expressions of counterregulatory mechanisms of the organism against incipient shock: compensated shock (→ A). Rapidly active mechanisms supplement each other to raise the reduced blood pressure, slower ones to counteract the volume deficit.

- Blood pressure compensation (→ A, left). A drop in blood pressure leads to a decrease in the afferent signals of the arterial pressoreceptors. This results in activation of the pressor areas in the central nervous system and to an
A. Compensatory Mechanisms When There Is a Risk of Hypovolemic Shock

- Blood pressure falls
- Blood volume reduced

1. Anaerobic glycolysis → Lactate → pH ↓
2. Presso-receptors
3. Volume receptors
4. Heart
5. Sympathetic stimulation
6. Adrenal medulla
7. Epinephrine
8. Arterial vasoconstriction, esp. kidneys, stomach, intestine and skin
9. Venous vasoconstriction
10. Venous return
11. Peripheral resistance ↑
12. Heart rate ↑
13. Cardiac contractility ↑
14. Capillary pressure ↓
15. Capillary flow into capillaries ↓
16. H2O flow into capillaries
17. GFR ↓
18. Renal perfusion ↓
19. Oliguresis
20. Renin
21. Angiotensin II
22. Aldosterone
23. ADH
24. ADH
25. Thirst
26. Hypothalamus
27. Pressoreceptors
28. Chemo-receptors
29. Medullary centers
30. Venous receptors
31. Heart
32. Blood pressure rises
33. Blood volume increases
34. Water resorption ↑
increased sympathetic tone. Arterial vasoco-
striction (not in shock caused by vascular dis-
tension) directs the reduced cardiac output
away from the skin (pallor), the abdominal or-
gans, and the kidneys to vital organs (coronary
arteries, the brain), bringing about centralization
of the circulation. Vasocostriction of the
venous capacitance vessels (increased cardiac
filling), tachycardia, and positive inotropy, all
the result of sympathetic nervous activity,
raise the previously reduced cardiac output
slightly. Epinephrine released from the adrenal
medulla supplements this nervous system
mechanism.

- Volume compensation (→ A, right). The fall
in blood pressure and arteriolar constriction
with incipient shock diminishes the effective
capillary filtration pressure, and thus intersti-
tial fluid flows into the blood compartment. In
addition, atrial pressure receptors recognize
the volume deficit (decreased atrial pressure),
which inhibits the secretion of atriopeptin and
reflexly brings about ADH secretion (Hen-
ry–Gauer reflex). ADH acts as a vasoconstrictor
and to retain water. The reduction in renal
blood pressure increases the release of renin,
more angiotensin II is formed, the latter stim-
ulating thirst and also having a vasoconstrictor
effect. In addition, it increases the secretion of
aldosterone, which in turn diminishes salt
elimination, and thus water elimination, via
the kidney (→ p.122 ff.). If the risk of shock
can be averted, the lost erythrocytes will be
replaced later (raised renal erythropoietin for-
mation; → p.30 ff.) and the plasma proteins
will be replenished in the liver by increased syn-
thesis.

If the organism is not able, without outside
help (infusions etc.), to prevent the shock with
the above-mentioned homeostatic compensa-
tory mechanisms, manifest (or decompensat-
ed) shock will develop (→ B). If the systolic
blood pressure remains <90 mmHg or the
mean pressure <60 mmHg for a prolonged
period (which can happen despite volume re-
placement [protracted shock]), the conseque-
ces of hypoxia will lead to organ damage
that may culminate in extremely critical mul-
tiorgan failure. Frequent organ damage includes
acute respiratory failure (= shock lung = adult
respiratory distress syndrome [ARDS]) with
hypoxemia, acute renal failure (glomerular fil-
tration rate [GFR] <15 mL/min, despite nor-
malization of blood pressure and volume), liv-
er failure (plasma bilirubin is elevated, pro-
thrombin decreased), brain damage (loss of
consciousness, increasing degree of coma), dis-
seminated intravascular coagulation, acute ul-
cers in the gastrointestinal tract with bleeding.

Several mechanisms are involved in shock,
some of them self-reinforcing. They aggregate
the shock until it can no longer be favorably in-
fluenced, whatever the therapeutic measures
(irreversible or refractory shock). The follow-
ing vicious circles develop, among others:

1. Vasocostriction ⇒ flow velocity ↓ ⇒
   blood viscosity ↑ ⇒ flow resistance ↑ ⇒
   flow velocity ↓ etc. until complete flow
   arrest (stasis with sludge phenomenon)
   (→ C1).
2 a. Volume ↓ ⇒ blood pressure ↓ ⇒ peripher-
   al vasocostriction ⇒ hypoxia ⇒ arteriolar
   opening ⇒ fluid loss into interstitial
   spaces ⇒ volume ↓↓ ⇒ blood pressure ↓↓
   ⇒ hypoxia ↑ (→ C2 a).
2 b. Volume ↓ ⇒ hypoxia ⇒ capillary damage
   ⇒ clot formation ⇒ disseminated intravas-
   cular coagulation ⇒ bleeding into tissues
   ⇒ volume ↓↓ (→ C2 b).
2 c. Hypoxia ⇒ capillary damage ⇒ thrombus
   formation ⇒ hypoxia ↑ (→ C2 c).
3. Cardiac output ↓ ⇒ blood pressure ↓ ⇒
   coronary perfusion ↓ ⇒ myocardial hypox-
   ia ⇒ myocardial acidosis and ATP deficien-
   cy ⇒ cardiac contractility ↓ ⇒ cardiac out-
   put ↓↓ (→ C3, 4).
4 a. Cardiac contractility ↓ ⇒ blood flow ↓ ⇒
   thrombosis ⇒ pulmonary embolism ⇒
   hypoxia ⇒ cardiac contractility ↓↓
   (→ C4 a).
4 b. Hypoxia ⇒ cardiac contractility ↓ ⇒ pul-
   monary edema ⇒ hypoxia ↑ (→ C4 b).
4 c. Cardiac contractility ↓ ⇒ blood pressure ↓
   ⇒ coronary perfusion ↓ ⇒ cardiac contrac-
   tility ↓↓ (C4 c).
B. Causes, Symptoms, and Consequences of Shock

Loss of blood or fluid → Hypovolemia → Vasodilation
Sepsis, anaphylaxis, hyperthermia → Pulmonary edema
Pulmonary edema → Myocardial infarct, AV block, etc.

Symptoms:
- Thirst
- Hypotonia
- Rapid heart rate
- Cold sweat
- Pallor (not in sepsis etc.)
- Skin

Heart rate → Vasoconstriction
Sympathetic tone → Blood pressure

Cardiac filling → Cardiac output → Blood pressure

C. Vicious circles (1–4) which Lead to Irreversible Shock

1. Vasoconstriction
   - Blood flow velocity ↓
   - Blood viscosity ↑
   - Stasis
   - Circulatory failure

2. Hypovolemia
   - Hypoxia
   - Thrombi
   - Capillary damage
   - Precapillary dilation
   - Consumption coagulopathy
   - Volume outflow
   - Bleeding
   - Circulatory failure

3. Hypoxia
   - Blood pressure ↓
   - Myocardial acidosis
   - Myocardial damage
   - Cardiac contractility
   - CO ↓
   - Circulatory failure

4. Cardiac contractility
   - Pulmonary edema
   - Thrombi
   - Respiratory failure
   - Circulatory failure
Edemas

Functional pores in the capillary endothelium allow largely protein-free plasma fluid to filter into the interstitial spaces. About 20 L/d are filtered through all capillaries of the body (excluding the kidneys), of which 90% are immediately reabsorbed. The remaining 2 L/d reach the blood compartment only via the lymph (→ A).

The filtration or reabsorption rate $Q_t$ is determined by the filtration coefficient $K_I$ (= water permeability · exchange area) of the capillary wall, as well as by the effective filtration pressure $P_{\text{eff}}$ ($Q_t = P_{\text{eff}} \cdot K_I$). $P_{\text{eff}}$ is the difference between the hydrostatic pressure difference $\Delta P$ and the oncotic (colloidal osmotic) pressure difference $\Delta \pi$ across the capillary wall (Starling’s law), where $\Delta P = \text{blood pressure in the capillaries} (P_{\text{cap}}) - \text{interstitial pressure} (P_{\text{int}}$, normally $= 0 \text{mmHg}$). $\Delta \pi$ arises due to the protein concentration being higher in plasma than in the interstitial space by $\Delta C_{\text{prot}} (= 1 \text{mmol/L})$, and it is the greater, the closer the reflection coefficient for plasma proteins ($\sigma_{\text{prot}}$) is to 1.0, i.e., the smaller the endothelial permeability for plasma proteins ($\Delta \pi = \sigma_{\text{prot}} \cdot R \cdot T \cdot \Delta C_{\text{prot}}$). At heart level, $\Delta P$ at the arterial end of the capillaries is ca. 30 mmHg; at the venous end it falls to ca. 22 mmHg. $\Delta \pi$ (ca. 24 mmHg; → A, right) counteracts these pressures so that the initially high filtration ($P_{\text{eff}} = +6 \text{mmHg}$) is turned into reabsorption when $P_{\text{eff}}$ becomes negative. (In the lungs $\Delta P$ is only 10 mmHg, so that $P_{\text{eff}}$ is very low.)

Below the level of the heart the hydrostatic pressure of the column of blood is added to the pressure in the capillary lumen (at foot level ca. +90 mmHg). It is especially on standing still that the filtration pressure is very high in the legs. It is compensated by self-regulation in that because of the outflow of water, the protein concentration and thus $\Delta \pi$ is increased along the capillaries. It is also part of self-regulation that $P_{\text{int}}$ rises when filtration is increased (limited compliance of the interstitial space), and as a result $\Delta P$ decreases.

If the amount of filtrate exceeds the sum of reabsorbed volume plus lymphatic outflow, edemas develop, ascites develop in the region of portal vein supply, as do pulmonary edemas in the lungs (→ p. 80). Possible causes of edema are (→ B):

- Blood pressure rise at the arterial end due to precapillary vasodilation ($P_{\text{cap}} \uparrow$), especially during a simultaneous increase in permeability to proteins ($\sigma_{\text{prot}} \downarrow$ and thus $\Delta \pi \downarrow$), for example, in inflammation or anaphylaxis (histamine, bradykinin, etc.).
- Rise in venous pressure ($P_{\text{cap}} \uparrow$ at the capillary end), which may be caused locally by venous thrombosis or systemically (cardiac edema), for example, by heart failure (→ p. 224 ff.). Portal vein congestion leads to ascites (→ p. 170).
- Reduced plasma concentration of proteins (especially albumin) causes $\Delta \pi$ to fall excessively. This may be the result of renal loss of proteins (proteinuria; → p. 104) or of too little hepatic synthesis of plasma proteins (e.g., in liver cirrhosis; → p. 172 ff.), or of an increased breakdown of plasma proteins to meet amino acid demand if there is a protein deficiency (hunger edema).
- Diminished lymphatic flow may also cause local edemas, either by compression (tumors), transection (operations), fibrosis (radiotherapy), or occlusion (Bilharziasis) of the lymphatic vessels.

When edemas form, the interstitial space is enlarged until a new equilibrium is established (filtration = absorption + lymphatic outflow). An increased compliance of the interstitial space encourages edemas to form just as much as a raised hydrostatic pressure in the dependent parts of the body (e.g., ankle edema) does.

As edema fluid originates from blood, the consequence of systemic edema (→ B, bottom) will be a decrease in blood volume, and thus cardiac output. Renal perfusion is reduced not only directly by the fall in CO, but also as a result of sympathetic stimulation. The renal filtration fraction is raised and the renin–angiotensin mechanism is initiated. The resulting $\text{Na}^+$ retention raises the extracellular fluid volume which, while increasing the blood volume, actually makes the edema worse. $\text{Na}^+$ retention in renal failure also results in edema being formed.
**A. Fluid Exchange at Capillaries**

![Diagram showing fluid exchange at capillaries]

Filtration = Reabsorption + Lymphatic drainage

\[ P_{eff} = (P_{cap} - P_{int}) - \sigma \cdot R \cdot T \cdot \Delta C_{Prot} \]

\[ = \Delta P - \Delta \pi \text{ (kPa, mmHg)} \]

**B. Edema Formation**

**Circulation**
- **Systemic:** heart failure etc.
- **Local:** venous thrombosis, inflammation, etc.

**Capillaries**
- **Systemic:** anaphylaxis, sepsis, etc.
- **Local:** inflammation etc.

**Kidney**
- Glomerular damage (nephrotic syndrome)
- **Protein formation**
- **Protein loss**

**Liver**
- Liver damage (e.g., cirrhosis)
- **Local:** (portal vein)
  - **Congestion**
  - **Ascites**

**Na⁺ metabolism**
- Na⁺ uptake high, Na⁺ retention (e.g., renal failure)
- Na⁺ balance positive

**Edema**
- Compression of lymphatic vessels
- Lymphatic drainage
- Lymph
- Obstruction (bilharziasis)
- Obliteration (radiotherapy)

**Systemic**
- Renin-Angiotensin
- **Renal blood flow**
- Blood volume

**Local**
- venous thrombosis,
- inflammation, etc.

**Histamine etc.**
- Venous congestion
- Precapillary vasodilation

**Plasma proteins**
- Protein formation
- Protein loss

**Renal blood flow**
- P_{int}↑

**Sympathetic tone**
- Blood volume↓
- Renal blood flow↓
Atherosclerosis

Atherosclerosis (Ath.; arteriosclerosis) is the cause of more than half of all deaths in the western industrialized nations. It is a slowly progressing arterial disease in which the intima (→ A1) are thickened by fibrous deposits that gradually narrow the lumen and gradually become the site of bleeding and thrombus formation (→ B).

Fatty streaks are the earliest visible sign of Ath. (as early as childhood). They are subendothelial accumulations of large, lipid-containing cells (foam cells; → A2). Later, fibrous plaques or atheroma form (→ A3), which are the cause of the clinical manifestation of Ath. These plaques consist of an accumulation of monocytes, macrophages, foam cells, T lymphocytes, connective tissue, tissue debris, and cholesterol crystals. Plaques are often infected with the bacterium Chlamydia pneumoniae.

The most common site of plaques are the abdominal aorta, coronary arteries, popliteal arteries, and the cerebral circulus arteriosus (in order of frequency).

Of the important risk factors of Ath. (→ C1), five can be influenced, namely hyperlipidemia, hypertension, smoking, diabetes mellitus, and hyperhomocysteinemia. It is not clear whether chlamydia infection plays an important part in the pathogenesis of Ath., or whether it perhaps even triggers its development. Risk factors that cannot be influenced are age, male sex, and a genetic predisposition (→ p. 246 ff.). Subordinate factors are overweight and a sedentary or stressful lifestyle.

Hyperlipidemia. Serum cholesterol levels higher than 265 mg/dl (6.85 mmol/L) in those aged 35–40 years increase the risk of coronary heart disease fivefold compared to values of < 220 mg/dl (5.7 mmol/L). 70% of this cholesterol is transported in low-density lipoproteins (LDLs) and the development of Ath. correlates closely with increased LDL levels. A defect in LDL receptors leads to very early Ath. (→ p. 246 ff.). A special risk factor seems to be lipoprotein(a) (= LDL that contains apolipoprotein Apo(a)). Apo(a) resembles plasminogen and binds to fibrin so that Apo(a) may have an antifibrinolytic and thus thrombogenic effect. (On the role of triglyceride and high-density lipoproteins [HDL], → p. 246 ff.).

Smoking increases the risk of dying from the effects of coronary heart disease 1.4 to 2.4fold (even light smoking), and in heavy smokers up to 3.5fold. Smoking low tar and low nicotine cigarettes does not lower this risk, but it is significantly lowered if smoking is stopped altogether. It is not clear how smoking promotes Ath. Possible causes are sympathetic nervous system stimulation by nicotine, displacement of O2 in the Hb molecule by carbon monoxide, increased platelet adhesiveness, and raised endothelial permeability, induced by constituents in smoke.

Hyperhomocysteinemia (> 14 μg/L plasma, e.g., due to a lack of methylenetetrahydrofolate reductase [MTHFR]), increases the risk of Ath., a rise of 5 μmol/L corresponding to the risk of a 20 mg/dl increase in cholesterol concentration. Homocystein (HoCys) favors plaque formation, probably in several ways (see below). In the commonly occurring thermolabile gene polymorphism of MTHFR, folate deficiency develops (→ p. 34). If the latter is removed, the HoCys level becomes normal.

The pathogenesis of Ath. remains unexplained, but endothelial damage (and chlamydia infection?, see above) could be the primary event and the reaction to it may eventually lead to plaque formation (response to injury hypothesis; → C). Plaques usually develop at sites of high mechanical stress (vessel bifurcation); in this way also hypertension becomes a risk factor. Among the reactions is an increased lipid uptake in the vessel wall as well as adhesion of monocytes and thrombocytes (→ C2, 3), helped by HoCys. The monocytes penetrate into the intima and are transformed into macrophages (→ C4). These liberate reactive O2 radicals, especially the superoxide anion ·O2− (also helped by HoCys), which have a general damaging effect on endothelial cells and inactive endothelium-formed NO on its way to the endothelium and the vascular musculature: NO + ·O2− → ·ONO2− (→ C5). This results in the loss of NO action, namely inhibition of platelet and monocyte adhesion to the endothelium as well as antiproliferative and vasodilating effects on the vascular musculature. The latter favor spasms (→ B and C7). Even in the early stages of Ath., O2 radicals
A. Vascular Wall Changes on Atherosclerosis

1. Normal vascular wall
2. Fatty streaks
3. Fibrous plaque (atheroma)

- Endothelium
- Intima
- Media
- Adventitia
- Lumen
- Necrotic nucleus (foam cells, cell debris, cholesterol crystals)
- Fibrous cover plate (connective tissue, immigrant muscle cells)
- Foam cells (lipid deposits) in the intima
- Endothelial damage and dysfunction

B. Consequences of Atherosclerosis

- Residual lumen
- Plaque
- Plaque enlargement
- Ischemia (→ infarction)
- Spasm
- Hypertension
- Media damage
- Nonatherosclerotic causes
- True aneurysm
- Dissecting aneurysm
- Thrombosis
- Embolism
- Ischemia (→ infarction)
- Rupture
- Thromboembolism
- Rupture, occlusion of side branches, pericardial tamponade, aortic regurgitation, thromboembolism
modify by oxidation of those LDLs that have entered the endothelium (→ C7). Oxidized LDLs damage the endothelium and there induce the expression of adhesion molecules which allow vessel musculature to proliferate. Oxidation also results in altered binding of LDLs. They can no longer be recognized by ApoB 100 receptors (→ p. 246 ff.), but rather by so-called scavenger receptors that are contained in large amounts within the macrophages. Consequently, these now phagocytize large amounts of LDLs and are transformed into sedentary foam cells (→ C9). Lipoprotein(a) can be oxidized and phagocytized in a similar fashion. Simultaneously, chemotactic factors of monocytes and thrombocytes trigger the migration of smooth muscle cells from the media into the intima (→ C6). Here they are stimulated to proliferate by PDGF and other growth-promoting factors (from macrophages, thrombocytes, damaged endothelium, and the muscle cells themselves). They, too, are transformed into foam cells by uptake of oxidized LDLs (→ C10). They form an extracellular matrix (collagen, elastin, proteoglycans) that also contributes to atheroma formation.

The consequences of plaque deposition (→ B) are narrowing of the lumen that can lead to ischemia. Coronary heart disease (→ p. 218 ff.) as well as chronic occlusive arterial disease of the limbs with painful ischemia on exercise (intermittent claudication) are examples of this. Other consequences of plaque formation are stiffening of the vessel wall (calcification), thrombus formation that obstructs the residual lumen and can cause peripheral emboli (e.g., cerebral infarction, stroke) as well as bleeding into the plaques (additional narrowing by the haematoma) and the vessel wall. Thus weakened, the wall may be stretched (aneurysm; see below) and even rupture, with dangerous bleeding into the surrounding tissues, for example, from the aorta (see below) or cerebral vessels (massive intracerebral bleeding, stroke; → p. 360).

An aneurysm is a circumscribed bulging of an arterial vessel due to congenital or acquired wall changes. It takes on the following forms:

- True aneurysm (→ B, left) with extension to all three wall layers (intima, media, and adventitia). In 90–95% of cases it is caused by atherosclerosis with hypertension. Frequently the abdominal aorta is affected. In rare cases it may be congenital or caused by trauma, cystic medial necrosis (Marfan’s, Ehlers–Danlos, or Gsell–Erdheim syndrome), or infection (syphilis, mycosis in immune-deficient patients).

- False aneurysm (pseudoaneurism), consisting of a perivascular hematoma over a tear in the intima and media, connected with the vessel lumen. It is caused by trauma or infection (accident, operation, arterial catheterization).

- Dissecting aneurysm (→ B, middle), usually in the ascending aorta in which, after perforation of the intima, blood under high (arterial) pressure “burrows” a path within the (usually degenerative) media so that intima and adventitia become separated along an advancing length of wall.

- Arteriovenous aneurysm occurs when an aneurysm ruptures into a vein, producing an arteriovenous fistula.

One of the catastrophic complications of an aneurysm is rupture. If it occurs in a large vessel, hemorrhagic shock will dominate the clinical picture (→ p. 230 ff.). Rupture of an intracranial artery (often the anterior communicating artery) together with subarachnoid bleeding is an acute risk to cerebral function. Rupture of an aneurism near the heart (especially a dissecting aneurism) can cause acute pericardial tamponade (→ p. 228) and, if the aortic root is involved, aortic regurgitation (→ p. 200). Other complications are thrombosis in the aneurism, occlusion at the origin of an artery as well as emboli to distal vessels (ischemia or infarction, respectively; → B, right).
C. Response to Injury Hypothesis of Atherosclerosis Genesis

1. Endothelial damage
2. Lipid permeability
3. Monocyte adhesion and immigration
4. Transformation in macrophages
5. Release of $O_2^-$ radicals
6. Lack of NO action
7. Vasodilation
8. LDL oxidation
9. LDL phagocytosis
10. Plaque (atheroma)

Factors:
- Hypertension
- Hyperlipidemia (LDL)
- Smoking
- Diabetes mellitus
- Hyperhomocysteinemia
- Age
- Genetic risk factors
- Male
- Chlamydia infection?

Processes:
- Oxidized LDL
- Monocyte adhesion and immigration
- Thrombocyte aggregation
- LDL oxidation
- Lipid permeability
- Myocytes
- Change receptor behavior
- Serotonin
- LDL phagocytosis
- Foam cell
- Plaque (atheroma)

Chemicals:
- $O_2^-$
- NO
- ONOO$^-$
- LDL
- Oxidized LDL

Other factors:
- Hyperlipidemia (LDL)
- Hyperhomocysteinemia
- Male
- Genetic risk factors
- Chlamydia infection?
Nonatherosclerotic Peripheral Vascular Diseases

As in atherosclerosis (→ p. 236 ff.), thromboembolism of other etiology can cause acute occlusion of arteries. The emboli usually originate in the heart, for example, the left atrium (in atrial fibrillation; mitral stenosis, → p. 194), the left ventricle (dilated cardiomyopathy, myocardial infarct), or from the cardiac valves (endocarditis, mitral stenosis, valvar prosthesis). Intracardiac shunts (→ p. 202) allow venous thrombi (see below) to pass into the arterial system (paradoxic emboli).

Several forms of vasculitis are initiated by depositions of immune complexes or by cell-mediated immune reactions in the arterial wall. In polyarteritis nodosa (affecting the small and medium-sized arteries) it is mostly the kidneys, heart, and liver that are affected by the resulting ischemia. In temporal or giant-cell arteritis (large arteries, especially in the head region) facial pain and headaches, “claudication” of the muscles of mastication and, in some circumstances, blindness can occur. Takayasu arteritis (large arteries in the thorax–neck region) can lead to cerebral ischemia, angina pectoris, or “claudication” in the arms (pulseless disease). Thromboangiitis obliterans (Buerger’s disease, affecting medium-sized and small arteries of the limbs) occurs mostly in male smokers. In addition to arterial occlusion and migrating superficial thrombophlebitis, Raynaud’s phenomenon occurs, painful vascular spasms (e.g., precipitated by cold) with numbness in the fingers or toes that at first blanch (ischemia), then become cyanotic (hypoxemia), and then turn pink again (reactive hyperemia). Raynaud’s phenomenon also occurs in some connective tissue diseases (scleroderma, systemic lupus erythematoses, rheumatoid arthritis). The phenomenon may occur in younger women as a primary disease, in the absence of any other condition (Raynaud’s disease).

Venous Disease

Because of their thin walls with few muscles, the veins are prone to distension, especially in the legs where the hydrostatic pressure of the column of blood increases the transmural pressure. The legs have deep and superficial veins that are connected by perforating veins (→ A, top right). Venous valves ensure orthograde flow against the force of gravity. The alternating contraction and relaxation of the leg musculature and the movement of the joints are essential driving forces for venous return via the deep veins (“joint–muscle pump”). When the leg muscles are relaxed, the valves in the perforating veins ensure blood flow from the surface to the deep veins and also prevent blood flowing in the opposite direction when the muscles contract (→ A1).

Often on the basis of a genetic predisposition (increased distensibility of the veins), work in a standing or sitting position over many years (lack of “pumping” effect) leads, depending on age, to distension and a winding course of the superficial veins as well as to incompetence of the venous valves and flow reversal (to-and-fro movement of the blood) in both the superficial and the perforating veins (primary varicosity; → A2). Frequently they develop or get worse during pregnancy or in obesity. In addition to cosmetic problems, a feeling of heaviness, burning, pain, and edemas develop in the legs. Inflammation (varicophlebitis) and its spread to the deep veins can lead to chronic venous insufficiency (→ A5; for complications, see below).

If a thrombus forms in the deep veins of the legs (acute phlebothrombosis; → A3), the valves of the perforating veins are torn and blood will drain via the superficial veins, causing secondary varicosity. Causes of phlebothrombosis are damaged veins, immobilization (sitting during long journeys, confinement to bed, paralysis), defective clotting inhibition, operations, trauma or (often undetected) tumors. Contraceptive pills (ovulation inhibitors) increase the risk of phlebothrombosis. A very dangerous acute complication occurs when a thrombus is torn from its attachment, resulting in pulmonary embolism with pulmonary infarction (→ A4). In the long term chronic venous insufficiency develops (→ A5), which through peripheral edema with protein exudation and deposition (including pericapillary fibrin cuff) in the skin, results in fibrosis, dermatosclerosis, tissue hypoxia, and ultimately in leg ulcers (→ A6).
A. Varicosis and Phlebothrombosis

1 Normal flow conditions

- Deep leg vein
- Venous valves
- Perforating v.
- Leg muscles

Superficial leg vein

Flow direction during muscle relaxation (no back-flow on muscle contraction)

2 Primary varicosis

- Venous valve failure
- Flow reversal
- Flow reversal on muscle contraction

3 Acute phlebothrombosis, risk of embolism

- Feeling of heaviness, pain, burning sensation and edema in the legs
- Inflammation (varicophlebitis)

4 Pulmonary embolism and infarction

5 Chronic venous failure

- Fibrosis, tissue hypoxia, ulcus

Genetic risk factors, standing or sedentary occupation over years, pregnancy, overweight

Immobilization, coagulopathy, operation, trauma, contraceptive pill, tumor

Silbernagl/Lang, Color Atlas of Pathophysiology © 2000 Thieme
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Overview

Metabolic abnormalities are frequently caused by faulty endocrine regulation (e.g., diabetes mellitus; \(\rightarrow\) 286ff.), or genetic defects of enzymes (enzymopathies) or of transport proteins, the latter, for example, in cystic fibrosis (\(\rightarrow\) p. 162) and cystinosis (see below). The endocytosis and exocytosis of lipoproteins can also be affected by defects of apolipoproteins or membrane receptors (\(\rightarrow\) p. 246ff.).

If there is an enzyme defect (\(\rightarrow\) A, enzyme X), the substrate (A) to be metabolized accumulates, so that the concentration of A in the cell organelle, in the cell, and/or in the body rises. This can result in

- substrate A being “stored” and thus becoming a problem, if only in terms of space (storage diseases, e.g., glycogen storage disease, lipidoses; \(\rightarrow\) p. 244);
- toxic effects at high concentrations, or precipitation of the substrate because of its low solubility, in this way causing damage (e.g., cystine in cystinuria or uric acid/urate in gout; \(\rightarrow\) p. 120 and 250);
- conversion of the substrate, via another metabolic pathway (enzyme Z), to a metabolite that is harmful at the increased concentration (metabolite E);
- inhibition of the metabolic conversion of another enzyme (enzyme Y) or of a carrier that is essential for the transport of other substances, too (substrate C).

In addition, the primary enzyme defect leads to a deficiency of the substance formed by this metabolic pathway (\(\rightarrow\) A, metabolite B). In glycogen storage disease, for example, it causes glucose or ATP deficiency (\(\rightarrow\) p. 244). A lack of metabolite B may additionally increase the metabolic rate of other enzyme reactions (\(\rightarrow\) A, enzyme Y).

Metabolic disorders play a part in the processes dealt with in almost every chapter in this book. This chapter describes further examples of metabolic abnormalities, their selection made mainly according to the seriousness, treatability (on early diagnosis), and prevalence of the abnormalities.

Amino Acids

Amino acids (AA) are both building blocks and breakdown products of proteins. They are the precursors of hormones and transmitters, purines, amines, heme, etc., and they serve as energy sources. Ammonia, produced during catabolism, is incorporated into urea and excreted in this form. Too many or too few amino acids, a carrier defect (\(\rightarrow\) e.g., p. 96ff.), or abnormal formation of urea (\(\rightarrow\) p. 174) thus usually lead to marked disorders. A lack of essential amino acids may be due to inadequate intake (unbalanced diet).

In phenylketonuria (PKU) the conversion of phenylalanine (Phe) to tyrosine (Tyr) is blocked (\(\rightarrow\) B1). If as a result the Phe concentration in plasma rises above ca. 1 mmol/L, Phe is broken down via secondary pathways, especially phenylpyruvate that appears in urine (= PKU). In addition, Phe blocks the transport of certain amino acids, so that these neither leave parenchymal cells (sequestration) nor are able to enter brain cells (\(\rightarrow\) B). Severe developmental defects in the brain are the result. A lack of melanin (\(\rightarrow\) B), formed from tyrosine, also disturbs pigmentation (light sensitivity). Early diagnosis and a low-Phe diet can prevent these developmental disorders. Rare forms of PKU are due to a defect of dihydripteridine reductase (\(\rightarrow\) B2).

Further metabolic disorders of amino acids include (the corresponding enzyme defect is given in brackets): hyperglycemia (propionyl-CoA-carboxylase), hyperoxaluria (type I: alanine-glyoxylate aminotransferase; type II: D-glycerate dehydrogenase), maple syrup disease (multi-enzyme complex in the breakdown of branched-chain AA), homocystinuria (type I: cystathionine-β-synthase; type II: methionine resynthesis from homocysteine; \(\rightarrow\) p. 34, A2), cystinosis (carrier defect \(\Rightarrow\) lysosomal cystine accumulation), alkaptonuria (homogentisic acid dioxygenase), oculocutaneous albinism (phenoloxidase = tyrosinase), and hyperprolinemia (type I: proline dehydrogenase; type II: follow-on enzyme), type I being a partial form of Alport’s syndrome.
A. Effects of Enzyme Defect

- Deficient Enzyme: $X$
- Substrate: $A$
- Metabolite: $B$
- Deficiency of $B$
- Enzyme $Z$
- Storage of $A$
- Toxicity of $A$
- Precipitation of $A$
- Enzyme $Y$
- Storage of $B$
- Toxicity of $B$

B. Phenylketonuria

- Defect 1: L-phenylalanine-4-monooxygenase
- $NADP^+$ to $NADPH + H^+$
- Dihydropteridine reductase
- $L$-phenylalanine
- $L$-tyrosine
- In urine: Phenylketonuria
- Mental retardation, neurological disorders

C. Galactosemia (see next page for text)

- Defect 1: Galactose-1-uridylyltransferase
- $Galactose$ to $Galactose-1-P$
- $Galactokinase$
- $ATP$ to $ADP$
- $Galactose-1-P$
- $Galactitol$
- $Hepatomegaly, jaundice$
- $Cataract$
- $Damaged tubules$
- $Mental retardation$
**Carbohydratis**

Abnormalities of carbohydrate metabolism are usually caused by enzymopathies or abnormal regulation (see also anemia, → p. 30 ff. or diabetes mellitus, → p. 286 ff.).

In galactosemia (→ p. 243 C) galactose is split off from lactose in the gut and can be changed into glucose or glycogen, especially in the liver. In case of a galactose-1-uridylyl transferase deficiency (→ p. 243 C 1), galactose-1-phosphate accumulates in many organs with the onset of breast-feeding. The organs are damaged as galactose-1-phosphate inhibits enzymes which are active in glucose metabolism. Damage can also be caused by galactititol, formed from galactose-1-phosphate. Early diagnosis and a galactose-free diet can prevent such damage (uridine diphosphate galactose can still be formed). A galactokinase deficiency (→ p. 243 C 2) associated with hypergalactosemia and hypergalactosuria is less serious.

In hereditary fructose intolerance (→ A, center) there is a defect of fructose-1-phosphate aldolase. The breakdown of fructose (fruits, saccharose) is blocked and fructose-1-phosphate accumulates. This inhibits phosphofructokinase and fructose-1,6-diphosphate aldolase in the liver, thus causing hepaticemic hypoglycemia, acute liver failure, or cirrhosis (→ p. 172 ff.). If diagnosed early and the patient put on a fructose-free diet, life expectancy is normal, while fructose infusion can quickly be fatal due to liver failure.

**Glycogen storage diseases.** Glucose is stored in muscles and liver as glycogen. Breaking it down provides glucose that is used locally or reaches other organs (→ A, B). If the breakdown of glycogen is blocked, glycogen overloading and hypoglycemia result. This is caused by enzyme deficiencies.

Several types are distinguished (→ A): type Ia (von Gierke; glucose-6-phosphatase deficiency); type Ib (deficiency of microsomal glucose-6-phosphate translocase [not shown in diagram]); type II (Pompe; lysosomal α-glucosidase deficiency); type III (Forbes, Cori; debrancher enzyme deficiency, the most common type); type V (McArdle; muscle phosphorylase deficiency); type VI (Hers; hepatic phosphorylase deficiency); and type VIII (Huijing; hepatic phosphorylase b kinase deficiency). A very rare deficiency of glycogen synthesis (type IV; Andersen; brancher enzyme deficiency) results in glycogenosis because an abnormal type of glycogen is stored in the brain, heart, muscle, and liver. In type VII (Tauri; muscle phosphofructokinase deficiency), on the other hand, glucose is prevented from being utilized to provide the muscles with energy.

Depending on the primary effects of the enzyme deficiencies, one can simplify the classification by dividing the glycogen storage diseases into liver types (I, III, VI, VIII), muscle types (V, VII), and other types (II, IV) (→ B). In the liver types hepatomegaly (due to excess deposition of glycogen) and hypoglycemia are the prominent features, while in the muscle types it is largely energy deficiency. Physical work does not increase plasma lactate and leads to rapid fatigue, muscle cramps and muscle pain as well as to myoglobinuria (in type V), which may cause renal failure. The effects of type II (cardiomegaly, weakness of respiratory muscles) and type IV (liver failure) often end in death in childhood.

**Lipidoses**

Lipidoses are disorders of fat metabolism, in which defects of enzymes and other proteins cause the accumulation (and thus deposition) of lipids.

In Gaucher’s disease there is a lysosomal β-glucocerebrosidase (β-glucosidase) deficiency, in which glucocerebroside accumulates (adult form) in the spleen, liver, lung, and bone marrow (Gaucher cells), hypersplenism (thrombocytopenia), spontaneous fractures as well as pneumonia and cor pulmonale being some of the consequences. In Niemann–Pick disease (five phenotypes, A–E) there is an accumulation of sphingomyelin and cholesterol in the lysosomes. In types A (80% of all cases of the disease) and B there is a deficiency of sphingomyelinase, while in type C1 the deficiency is of a protein (NPC1) which plays an important role in the intracellular distribution of cholesterol. The effects of type A are enlargement of several organs and severe neurological abnormalities that can be fatal already in childhood. A deficiency of acid lipase is the cause of cholester-ester storage disease (liver cirrhosis and atherosclerosis) and in Wolman’s disease (the infantile form of acid lipase deficiency). The gangliosidoses (e.g., Tay–Sachs and Sandhoff’s disease) are caused by various defects of the hexosaminidases and their activators, or of β-galactosidase. In most forms the accumulated gangliosides lead to very severe cerebral disorders and death in early childhood. In Refsum’s disease the breakdown of phytanic acid is blocked (defect of phytanic acid-α-hydroxylase), as a result of which it accumulates and, incorporated into myelin, leads to polyneuropathy.
A. Causes of Glycogen Storage Diseases I–VIII and Fructose Intolerance

- Lysosomal breakdown
  - Glycogen
  - Enzyme defects
    - Enzymes esp. in liver
    - Enzymes esp. in skeletal muscles
    - Enzymes in many organs

- Limit dextrin
  - Debranching enzyme
  - Glucose-6-phosphatase

- Fructose intolerance
  - Phosphorylase kinase
  - Fructose-1-P
  - Fructose-1-P-aldolase
  - UDP-glucose
  - Lactate
  - Pyruvate → Citrate cycle
  - ATP

- Lysosomal α-glucosidase
  - Phosphofructokinase
  - Fructose-1-P
  - Fructose-1,6-P₂
  - Fructose-1-P-aldolase
  - Glucose-1-P
  - Glucose-6-P

- Glucose
  - Glucose-1-P
  - Glucose-6-P
  - Fructose-6-P
  - UDP-glucose

B. Effects of Glycogen Storage Diseases

- Liver types
  - Hepatomegaly
  - Hypoglycemia

- Muscle types
  - Cramps, weakness
  - Myoglobinuria
  - Renal failure

- Other types
  - Cardiomegaly
  - Cardiorespiratory failure
  - Muscle weakness (respiratory muscles!)

During severe muscle activity:
Abnormalities of Lipoprotein Metabolism

Among the disorders of fat metabolism there are, in addition to the lipidoses (→ p. 244), mainly those diseases in which the concentrations of lipoproteins in serum and thus lipid transport in blood are abnormal. Lipids are transported in blood in globular molecular complexes (microemulsions), the lipoproteins (LPs). Their surface consists largely of amphiphilic lipids (phospholipids and nonesterified cholesterol), while their “core” contains nonpolar (hydrophobic) lipids, i.e., triglycerides (TGs) and cholesterol ester (Chol-E), the transport and storage form of cholesterol. The LPs also contain certain apolipoproteins (Apos). The LPs differ in the size, density (which gives them their name, see below), lipid composition, site of origin as well as their apo(lipo)proteins (see Table), the latter serving as structural elements of the LP (e.g., ApoAl and ApoB48), as ligands (e.g., ApoB100 and ApoE) for LP receptors in the membrane of the LP target cells, and as enzyme activators (e.g., ApoA1, ApoCII).

The chylomicrons transport lipids from the gut (via the gut lymphatics) to the periphery (skeletal musculature, fat tissue), where their ApoCII activates the endothelial lipoprotein lipase (LPL); thus free fatty acids (FFAs) are split off which are taken up by the cells of the muscles and fat tissue (→ A2). In the liver the chylomicron remnants bind to receptors (LDL receptor–related protein [LRP]?) (→ A9) via ApoE, they are endocytosed and in this way deliver their TGs as well as their cholesterol and cholesterol esters. Such imported as well as newly synthesized TG and cholesterol are exported by the liver (→ A4) in very low density LP (VLDL) to the periphery, where they activate LPL with their ApoCII, also leading to the release of fatty acids (→ A3). ApoCII is lost in this process and ApoE is exposed. This leaves VLDL remnants or intermediate density LP (IDL), half of which return to the liver (binding mostly with ApoE to the LDL receptors). They are freshly loaded with lipids in the liver, leaving the liver as VLDL (→ A4). The other half of the IDL is transformed (with loss of ApoE and exposure of ApoB100) on contact with hepatic lipase to low density LP (LDL). Two thirds of these LDLs deliver their cholesterol and Chol-E to the liver (→ A7), one third to extrahepatic tissues (→ A14), both processes requiring the binding of ApoB100 to the LDL receptors. By binding to receptors, mediated by clathrin in the coated pit regions of the cell surface, LDLs undergo endocytosis in which the LDL receptors recirculate to the cell membrane. After fusion of the endosomes with lysosomes, the apolipoproteins are “digested” and the Chol-E split, so that free cholesterol reaches the cytosol (→ A5). As a result of this rise in the concentration of intracellular cholesterol: 1) the key enzyme of cholesterol synthesis is inhibited (3-HMG-CoA reductase); 2) cholesterol is again esterified to its storage form (activation of acyl-CoA-cholesterol-acyl transferase [ACAT]); and 3) LDL receptor synthesis is inhibited.

The high density LPs (HDLs) exchange certain apolipoproteins with chylomicrons and VLDLs and also take up excess cholesterol from extrahepatic cells (→ A10) and blood. By means of their ApoAl they activate the plasma enzyme lecithin-cholesterol acyltransferase (LCAT) which in part esterifies the cholesterol and pass on cholesterol and Chol-E to the liver, among other organs, and to those steroid hormone–producing glands (ovaries, testicles, adrenals) which have HDL receptors (→ A6).

<table>
<thead>
<tr>
<th>Lipoprotein class</th>
<th>% of TG</th>
<th>Apolipoproteins</th>
<th>Formations in or from</th>
<th>Transport function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chylomicrons</td>
<td>90</td>
<td>3</td>
<td>Al, B48, CII + III, E</td>
<td>Gut: TG etc. ⇒ Periphery</td>
</tr>
<tr>
<td>Chyl. remnants</td>
<td></td>
<td></td>
<td>[Chylomicron.]</td>
<td>Lipids: Gut ⇒ Liver</td>
</tr>
<tr>
<td>VLDL</td>
<td>65</td>
<td>15</td>
<td>B100, CII + III, E</td>
<td>Liver: TG etc. ⇒ Periphery</td>
</tr>
<tr>
<td>IDL</td>
<td>10</td>
<td>45</td>
<td>B100, CII, E</td>
<td>[VLDL, HDL]: Lipids: ⇒ Liver, LDL</td>
</tr>
<tr>
<td>LDL</td>
<td>5</td>
<td>20</td>
<td>Al, III + IV, CII, D</td>
<td>HDL: Cholesterol: IDL ⇒ Liver, Periphery</td>
</tr>
<tr>
<td>HDL</td>
<td></td>
<td></td>
<td></td>
<td>HDL: Cholesterol: Periphery ⇒ IDL</td>
</tr>
</tbody>
</table>

* Electrophoretic separation distinguishes between α-lipoproteins (= HDL), pre-β-lipoproteins (= VLDL) and β-lipoproteins (= LDL).
An increase in blood lipids can affect cholesterol, triglycerides or both (hypercholesterolemia, hypertriglyceridemia or combined hyperlipidemia). **Hyperlipoproteinemia** is currently the all-inclusive term.

With most patients who have **hypercholesterolemia** (> 200 – 220 mg/dL serum) there is an increased familial prevalence of the condition, but the cause remains unknown (**polygenic hypercholesterolemia**). However, over-weight and diet play an important role. LDL-cholesterol can be lowered most importantly by a preference in the diet for vegetable (unsaturated) fats. Animal (saturated) fats, on the other hand, raise cholesterol synthesis in the liver and in consequence lower its LDL receptor density (→ A7) so that the concentration of cholesterol-rich LDL in serum is raised (LDL-cholesterol > 135 mg/dL). As a result, there is an increased binding of LDL to the scavenger receptor that mediates the incorporation of cholesterol in macrophages, skin, and vessel walls (→ A8). Hypercholesterolemia is thus a risk factor for **atherosclerosis** (→ p. 236 ff.) and **coronary heart disease** (→ p. 218).

In **familial hypercholesterolemia** (hyperlipoproteinemia type IIa; incidence of homozygotes is 1:10^6; of heterozygotes 1:500) the plasma cholesterol is markedly raised from birth (twice as high in heterozygotes; six times as high in homozygotes) so that myocardial infarction may occur even in children. The primary causes are defects in the gene for the high-affinity LDL receptor which prevents the cellular uptake of LDL (→ A7, 14). The defect can cause: 1) diminished transcription of the receptor; 2) receptor proteins remaining in the endoplasmic reticulum; 3) a reduced incorporation of the receptor into the cell membrane; 4) reduced LDL binding; or 5) abnormal endocytosis. Serum cholesterol rises as a result, firstly, of a reduction in the cellular uptake of cholesterol-rich LDL and, secondly, of extrahepatic tissues synthesizing more cholesterol, because the reduced LDL uptake in these tissues fails to inhibit the action of 3-HMG-CoA reductase (→ A5). **Treatment** consists, in addition to an appropriate diet (see above), of administering ionic exchange resins (cholestyramine) that bind bile salts in the gut and thus prevent their enterohepatic recirculation (→ A1). This increases the fresh synthesis of bile salts from cholesterol in the liver and thus reduces the intracellular cholesterol concentration. In heterozygotes this increases the LDL receptor density (→ A5). However, it also stimulates cholesterol synthesis, but this in turn can be prevented by administering inhibitors of 3-HMG-CoA reductase (e.g., lovastatin) (→ A5). The treatment of homozygotes includes the removal of LDL from plasma by plasmapheresis.

In another single-gene defect, **combined hyperlipidemia** (hyperlipoproteinemia type IIb), the TGs as well as cholesterol are slightly raised. The cause is possibly an overproduction of ApoB, so that an increased synthesis of VLDL occurs (→ A4) and therefore more LDL is also formed. **Familial dys-β-lipoproteinemia** predisposes to hyperlipoproteinemia type III. In this condition, instead of the normal ApoE₄, an ApoE₂ variant is expressed that is not recognized by the E receptor. As a result, the hepatic uptake of chylomicron remnants and of LDL is disturbed (→ A9, 13), so that their plasma concentration rises (high risk of atherosclerosis; → p. 236 ff.).

Primary **hypertriglyceridemia** is due to increased TG synthesis in the liver (→ A11) or (rarely) to abnormalities in the breakdown of chylomicrons and VLDL (hyperlipoproteinemia type I), the result of a deficiency of LPL or ApoCII (→ A2, 3). They predispose a person to, for example, **pancreatitis** (→ p. 158 ff.); in addition HDLs are reduced and thus the atherosclerosis risk is increased (reduced removal of cholesterol from the vessel wall?).

Gene defects can also result in subnormal LP concentrations (**hypolipoproteinemia**). **Familial hypo-α-lipoproteinemia** (Tangier disease) is due to a defect of ApoA and there is a HDL deficiency (→ A10), increasing the atherosclerosis risk. In **A-β-lipoproteinemia** there are no LDLs in plasma (hyalocholesterolemia). This is caused by an abnormal synthesis of ApoB, so that chylomicrons cannot be exported from the gut mucosa, nor can VLDL from the liver. This produces accumulation of TG in both organs.
A. Lipoprotein Metabolism and its Abnormalities

Musculature

Fat cells

Liver

Food fats

Bile salts

Cholesterol

Cholesterol (Chol) + chol. ester (Chol-E)

Primary hypertriglyceridemia

Combined hyperlipidemia

HDL contact in blood

Chylomicron remnants

VLDL

Primary hyperlipoproteinemia

Capillary endothelium

LPL

FFA

Fat cells

Musculature

Chylomicrons

Triglycerides (TG)

Apolipoproteins:

CII

E

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Gout

Gout is the result of chronically elevated uric acid/urate concentration in plasma (hyperuricemia: > 7 mg/dL).

**Uric acid formation.** Uric acid (UA) is the end-product of purine metabolism (→ A1). However, normally 90% of the resulting nucleotide metabolites adenine, guanine, and hypoxanthine are reused in that they are re-formed to AMP, IMP, and GMP by adenine phosphoribosyltransferase (APRT) and hypoxanthine guanine phosphoribosyltransferase (HGPRT), respectively. Only the remainder is converted to xanthine and further to uric acid by xanthine oxidase (XO) (→ A1). The low solubility of urate and especially of uric acid, which decreases even further in the cold and at low pH (pKₐ of urate/uric acid = 5.4), is the reason why gout develops from hyperuricemia.

The renal excretion of uric acid (→ A2) is ca. 10% of the filtered amount, i.e., the UA/urate concentration in the final urine is 10–20 times higher than in plasma. Drugs with uricosuric activity (e.g., benzbromarone) can increase UA/urate excretion and thus lower their plasma concentration.

**Hyperuricemia** occurs in ca. 10% of the population in western industrialized countries; one in 20 develops gout (men > women). 90% of patients with the condition have primary gout (→ A3) with a genetic disposition. The underlying primary hyperuricemia is due to the fact that the renal excretion of UA can match normal UA production only when the UA concentration in plasma, and thus in the glomerular filtrate, is raised (asymptomatic hyperuricemia). If there is a higher purine intake (especially in innards, meat extract, fish, muscles, etc.), this is even more the case, and thus in the long term sodium urate crystals are precipitated again and again. On rare occasions the hyperuricemia is caused by a partial lack of HGPRT, in which case the proportion of re-utilized nucleotide metabolites (see above) falls, and thus more UA is formed (→ A1). (In the Lesch–Nyhan syndrome there is a complete absence of HGPRT. In this disease childhood gout is paralleled by severe central nervous system abnormalities.)

As the solubility of urate is especially low in synovial fluid and at low temperature, and since the digits are cooler than the body core, urate crystals are often formed in the acral joints of the foot (microtophi). Alcohol, which increases adenine nucleotide metabolism, favors crystal deposition as does obesity, certain drugs (e.g., diuretics), and a high lead load. The often increased urinary concentration of UA/urate in hyperuricemia results in the formation of urinary stones (→ A5 and p. 120).

An attack of gout (→ A4) occurs when the urate crystals (possibly as a result of trauma) are suddenly released from the microtophi and are recognized by the immune system as foreign bodies. An aseptic inflammation of the joint develops (arthritis, → A4; see also p. 48 ff.), attracting neutrophils which phagocytize the urate crystals. When the neutrophils subsequently break down, the phagocytized urate crystals are released again, which maintains the process. A very painful, deep-red joint swelling occurs, in 70–90% of first attacks affecting one of the proximal toe joints.

**Acute urate nephropathies** (→ A5). If the UA concentration in plasma and primary urine suddenly rises markedly (usually in secondary gout; see below) and/or (because of low fluid intake), the urine is highly concentrated and the urine pH low (e.g., in protein-rich diet), large amounts of UA/urate may be precipitated in the collecting duct with plugging of the lumen. Acute renal failure may result (→ p. 108).

Repeated attacks of gout (chronic gout) can damage the joints (also hands, knees, etc.) to such an extent that, under constant pain, marked joint deformities with destruction of cartilage and bone atrophy will occur (→ A4, photograph). There may also be circumscribed deposits of urates (tophi) around the joint or at the edge of the auricles as well as in the kidneys (chronic gouty nephropathy).

So-called secondary hyperuricemia or gout is initiated by, for example, leukemia, tumor treatment (raised nucleotide metabolism) or by renal failure with other causes (reduced UA excretion).
A. Acute Primary Gout

1. Nucleotide breakdown

- AMP → APRT → Adenine
- IMP → Inosine → Hypoxanthine
- HGPRT → Xanthine
- GMP → Guanosine → Guanine

2. Uric acid excretion

- Allopurinol
- 10% of filtered urate
- Benz-bromarone

3. High purine intake with food

- Rare: partial HGPRT defects

4. Asymptomatic hyperuricemia

- Alimentary
- Cold
- Thiazides
- Alcohol
- Obesity
- Lead pollution

5. Precipitation of sodium urate crystals in joints (microtophi)

- Trauma?

6. Release of sodium urate crystals: attack of gout

- Complement activation and chemotaxis of:
  - Monocytes/macrophages
  - Neutrophils

- IL-1, 6, 8; TNFα

- Cell damage
- Leukotriene B4, prostaglandins, O₂ radicals
- Phagocytosis of crystals
- Cell death
- Lysosomal enzymes

- Protease release

- Joints: acute inflammation, tissue damage

- Urate precipitation in urine

- Acute urate nephropathy

- Sudden rise in plasma urate

- High urine osmolality

- Low urine pH

- Urate stones
Hemochromatosis

Hemochromatosis is a condition in which there is an excessive accumulation of iron (Fe) in the body, deposited in the parenchymal cells of the liver, pancreas, and other organs. Primary (= idiopathic, = hereditary) hemochromatosis (→ A1) is a common disease (1 in 400), inherited as an autosomal recessive trait. The abnormality consists of a markedly raised intestinal absorption of Fe; in a year 0.5 – 1 g excess Fe is taken up. Fe, ferritin, and transferrin saturation are increased in serum (→ p. 38). If diagnosed early, the increased Fe content (25–50 g) can be normalized by means of weekly bloodlettings over one to two years (serum ferritin < 50 µg/L; transferrin saturation < 50%). Secondary hemochromatoses (→ A2) occur if there is an abnormal utilization of Fe (increased Fe absorption with ineffective erythropoiesis, for example, in β thalassemia or sideroblastic anemia: → p. 36), liver disease (e.g., alcoholic cirrhosis, portocaval shunt), in atransferrinemia (→ p. 38), and porphyria cutanea tarda (→ p. 254) as well as in excessive Fe supply, either orally or parenterally (frequent blood transfusions which are a second cause in conditions of abnormal Fe utilization; long-term hemodialysis; injection of Fe preparations).

Toxic cell damage (→ A3) is the result of increased Fe deposition (especially in the form of hemosiderin [siderosis]). Participating in this are: 1) Fe-mediated formation of O₂ radicals (lipid peroxidation of cellular membranes); 2) DNA damage; and 3) an increased formation of collagen, initiated by Fe.

When the Fe content in the liver has increased to ca. 20 times the normal amount, fibrosis with subsequent cirrhosis develops (→ p. 172 ff.). The risk of lethal hepatocellular carcinoma increases twohundredfold. Pancreatic fibrosis caused by siderosis results in insulin deficiency and thus diabetes mellitus. The incorporation of melanin and hemosiderin in the skin (especially if exposed to the sun) leads to marked pigmentation (“bronzed diabetes”). Siderosis in the heart causes a cardiomyopathy that through arrhythmia and heart failure is a frequent cause of death in young patients. The joint damage (pseudogout) is in part due to vitamin C deficiency brought about by Fe (Fe accelerates ascorbic acid breakdown).

Wilson’s Disease

Copper (Cu) metabolism (→ B). Normal Cu uptake is ca. 2 – 5 mg daily, of which 40 – 60% are absorbed in the stomach and upper duodenum. It is then incorporated mainly into ceruloplasmin (CP) in the liver. It reaches the systemic plasma in this form (ca. 93% of plasma Cu; → B1). CP, which binds six to seven Cu atoms relatively firmly, is apparently important for the oxidation of Fe²⁺ in plasma (→ p. 38), but only a little CP-bound Cu is released into the tissues. This is not true of the portion of Cu that is bound to transthyretin and albumin (ca. 7% of plasma Cu). Old (desilylated) CP is broken down in the liver and the liberated Cu is excreted, firmly bound to biliary proteins (→ B2), in the bile and stool (ca. 1.2 mg/d).

Wilson’s disease (hepatolenticular degeneration) is an autosomal recessive disorder of Cu metabolism in which the liver, central nervous system, eyes, and other organs are overloaded with Cu. The imbalance is caused by genetic defects in the Cu-transporting Cu-ATPase. The defect results in failure to excrete sufficient Cu via the bile, the normal route, and the ability to incorporate Cu into CP is diminished (→ B). As a result, free or only loosely bound Cu accumulates in the liver and then in plasma (at subnormal total Cu concentration) and in other organs (→ B3). In this form it is cytotoxic because it binds to proteins, especially the sulfhydryl groups, and promotes the formation of O₂ radicals (lipid peroxidation). The effects (→ B4) are hemolytic anemia and chronic active hepatitis that can later change to cirrhosis. If the hepatitis takes a fulminant course, large amounts of Cu are suddenly released from the necrotic liver and this may trigger a hemolytic crisis. The accumulation of Cu in the CNS can cause numerous and diverse neurological, neuromuscular, and psychogenic abnormalities. Deposition of granular Cu in Descemet’s membrane of the eye can bring about a Kayser–Fleischer ring around the periphery of the cornea. The kidneys, skeleton, and heart can also be affected.
A. Hemochromatoses

1. Primary hemochromatosis
   - Inherited autosomal recessive disease (Cys-282-Tyr mutation in 83% of patients)

2. Secondary hemochromatoses
   - Ineffective erythropoiesis, chronic liver diseases, porphyria cutanea tarda, parenteral Fe overloading, etc.

   - Raised Fe absorption

   - Hemochromatosis
     - Fe content ↑ (from 2–6 g to >50 g)

   - Venesection (0.5 g Fe/L of blood)

   - Treatment

   - Fe toxicity: lipid peroxidation, DNA damage, collagen formation ↑

   - Liver:
     - Siderosis
     - Fibrosis
     - Cirrhosis
     - Carcinoma
     - Diabetes mellitus
     - Pigmentation
     - Heart failure

   - Pancreas:
     - Siderosis
     - Fibrosis

   - Skin:
     - Siderosis
     - Cardiomyopathy
     - Arrhythmia
     - Pseudogout

   - Heart:
     - Cardiac fibrosis

   - Joints:
     - Vitamin C deficiency

   - Testes:
     - Infertility

   - Bone:
     - Osteoporosis

B. Wilson’s disease

1. Gene defect (chromosome 13):
   - Wilson’s disease

   - Cu absorption: 40–60%

   - Cu intake: 2–5 mg/d

   - Cu excretion ca. 1.2 mg/d

   - Cu incorporation in ceruloplasmin

   - Free Cu ↑

   - Biliary Cu elimination

   - Chronic hepatitis

   - Cirrhosis

   - Hemolysis

   - Neurological disorders

   - Cornea


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Heme Synthesis, Porphyrias

Heme is synthesized in a chain of eight reactions (→ A). In addition to its incorporation into the hemoglobin of the erythroblasts (→ p. 39), heme is synthesized in practically all organs and built into myoglobin, cytochrome P₄₅₀, catalase, peroxidase, or the respiratory-chain cytochrome. Because these hemoproteins are indispensable, complete absence of heme synthesis is incompatible with life. Partial, usually heterozygous, defects of one of the participating enzymes have severe consequences.

Heme synthesis starts with the formation of α-amino-β-ketoadipate that is spontaneously transformed into δ-aminolevulinate (δ-aminolevulinic acid [δ-ALA]). This step, which takes place in the mitochondria, is the rate limiting step of heme synthesis; it is catalyzed in the erythroblasts by δ-ALA synthetase 2 (→ A1) and in the liver by δ-ALA-synthetase 1. The activity of both isoenzymes is reduced by heme, the end-product of the synthesis (negative feedback; → A, left). This happens in part through heme being bound in the cytosol to the heme-regulated element of the proenzyme and hindering the latter from passing into the mitochondria.

Effects of heme synthesis abnormalities differ depending on this feedback, depending on whether the substrate turnover of δ-ALA-synthetase-2 or of one of the subsequent enzyme reactions is reduced. In the former case (→ A₁), the heme deficiency can only inadequately raise the activity of the deficient δ-ALA-synthetase-2, so that a sideroblastic anemia will develop (→ p. 36).

In deficiencies of the follow-on enzymes (→ A₂–₈) a hugely increased availability of δ-ALA (disinhibition of δ-ALA-synthetase) develops due to the intact negative feedback. As a result, the concentrations of the substrates of all subsequent reactions are increased and thus the turnover is increased until enough heme has been produced. It is the high concentrations of the intermediary substances that lead to abnormalities (primary porphyrias; → A₂–₈). Depending on their solubility in water or lipids, the intermediary products are excreted in the urine (δ-ALA, porphobilinogen [PBG]), uroporphyrin), or additionally via the bile in the stool (coproporphyrins, protoporphyrins), respectively. The porphyrins are produced from the respective porphino gens; their excretory pattern is of diagnostic significance.

The concentration of δ-ALA is raised by a deficiency of δ-ALA-dehydratase (= PBG synthetase) (→ A²) as well as by a hypofunction of porphobilinogen deaminase (also called hydroxymethylbilane synthetase), the cause of acute intermittent porphyrias (→ A³), in which the PBG concentration is also increased. This results in neurovisceral dysfunctions (tachycardia, nausea, vomiting, constipation) and neuropsychogenic disorders (paralyses, seizures, coma, hallucinations). One of the causes of these dysfunctions may be the competition between δ-ALA and the structurally similar neurotransmitter γ-aminobutyrate (GABA).

In congenital erythropoietic porphyria (→ A⁴) uroporphyrinogen will be formed nonenzymatically from hydroxymethylbilane, and converted enzymatically to coproporphyrinogen I (analogously to A⁵). Coproporphyrinogen I can no longer be used metabolically and, excreted in the urine, in infants it causes red stains on diapers and later on the teeth. Other effects are skin reactions to light and hemolytic anemia.

In (the more frequent) porphyria cutanea tarda (→ A⁵) the porphyrins cause damage to the skin (poorly healing blisters; → A, photograph) as a result of light absorption (especially at λ = 440 nm). O₂ radicals are involved in the generation of the skin lesions.

In hereditary coproporphyria (→ A⁶), as also in porphyria variegata (→ A⁷) (particularly common in South Africa [ca. three out of every 1000 whites]), δ-ALA, PBG, and the coproporphyrins are all elevated, causing neuropsychogenic and dermatological symptoms in the affected children. In protoporphyria (increase of protoporphyrin; → A⁸) burns, itching, and pain in the skin due to photosensitivity are prominent after exposure to ultraviolet rays.

Acquired porphyrias occur in lead poisoning (→ A², ⁸; high δ-ALA and PBG levels) and in hepatobiliary diseases, in which coproporphyrin excretion in bile is reduced.
A. Abnormalities of Heme Synthesis

1. Sideroblastic anemia
2. δ-ALA-dehydratase deficiency
3. Acute intermittent porphyria
4. Congenital erythropoietic porphyria
5. Porphyria cutanea tarda
6. Hereditary coproporphyria
7. Porphyria variegata
8. Protoporphyrin oxidase

Succinyl-CoA + glycine → δ-ALA-synthase-2

δ-ALA-dehydratase deficiency

Porphobilinogen (PBG) → δ-ALA-dehydratase

Porphyribilinogen (PBG) desaminase

Uroporphyrinogen III-cosynthase

Uroporphyrinogen decarboxylase

Coproporphyrinogen-III-oxidase

Protoporphyrinogen oxidase

Ferrochelatase

Heme → Hemooglobin and other heme proteins

Sideroblastic anemia

Circular Fe incorporation (blue) in erythroblasts

Neurological and psychogenic disorders

Hemolytic anemia, red teeth

Marked photosensitivity

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General Pathophysiology of Hormones

Hormones serve to *regulate* and to *control* organ functions. Their release is dependent on stimulation (or inhibition) through specific factors. Hormones act upon hormone-producing cells themselves (*autocrine*), they influence neighboring cells (*paracrine*), or they reach target cells in other organs via the blood (*endocrine*). In a stricter sense, hormones achieve their effects predominantly via an endocrine path. For endocrine action to be effective the hormones must not be inactivated before reaching their target cells. Some hormones require activation (see below). The transition from endocrine hormones to paracrine mediators and transmitters is a fluid one.

At the target cells the hormones bind to receptors and exert their effects via various mechanisms of *cellular signal transduction*. It is usually through a reduction of stimulating factors that these effects lead to a reduced release of the particular hormone, i.e., there is a *regulating cycle with negative feedback* (→A6). In a few cases there is *positive feedback* (of limited duration), i.e., the hormones cause an increased activity of stimuli and thus promote their own release. The term *controlling* (→A1) is used when hormone release is influenced independently of hormonal effects. Several independent controlling and regulating stimuli can act on the hormone-producing glands.

A *reduced hormone effect* (blue arrows) can be due to *abnormal hormone synthesis and storage*. Other causes can be abnormalities of transport within the synthesizing cells or abnormalities of release (→A5). Hormone deficiency may also arise when the hormonal glands are not stimulated sufficiently to meet the needs of the organism (→A1), when the hormone-producing cells do not react sensitively enough to the stimuli (→A4), or when there are not enough hormone-producing cells (hypoplasia, aplasia; →A2).

Other possible causes are *too rapid inactivation* or *accelerated breakdown* of hormones. In the case of hormones that are bound to plasma proteins (→A7) the duration of action depends on the proportion of bound hormones. In their bound form hormones cannot exert their effect; on the other hand, they escape being broken down or being excreted by the kidney.

Some hormones must first be converted into their effective form at the site of their action (→A8). However, if this *conversion* is not possible, for example, due to enzyme defects, the hormone will have no effect. Hormonal action may also not occur because the *target organ is unresponsive* (e.g., due to defective hormone receptors or faulty intracellular transmission) or *functional incapacity of the target cells or organs* (→A9).

Causes of *increased hormone effects* (violet arrows) include, first of all, *increased hormonal release*. This may be due to an excessive influence of individual stimuli (→A1), increased sensitivity (→A4), or too large a number of hormone-producing cells (hyperplasia, adenoma; →A2). Hormonal excess can also be caused by the production of hormones in undifferentiated tumor cells outside of hormonal glands (ectopic hormonal production; →A3). The small-cell bronchial carcinoma is particularly frequently active endocrinally.

Raised hormonal action is also to be expected if a hormone is *broken down or inactivated too slowly* (→A7; e.g., in dysfunction of the inactivating organ [kidney or liver]). The breaking down can be delayed by binding to plasma proteins, but the protein-bound proportion would not be exerting any action either (see above).

Finally, hormonal effects can be increased by *hypersensitivity of the target organ* (too many hormone receptors or ones that are too sensitive), by increased intracellular transmission, or hyperfunction of the hormone-sensitive cells (→A9).

The *clinical features*, i.e., the sum of the pathophysiological changes in the organism, are the result of reduced or increased hormone-specific effects.
A. Excess and Deficiency of Hormones as Disease-Producing System (Overview)

1. Regulating influences
2. Hypoplasia, aplasia
3. Hyperplasia, adenoma
4. Receptors: density, affinity
5. Hormone synthesis, intracellular transport, release
6. Feedback
7. Hormone concentration
8. Conversion
9. Breakdown

Hormon-producing glandular cell

Clinical features of endocrinal disease
Abnormalities of Endocrinial Regulatory Circuit

Hormones are usually part of regulatory circuits. Disorder of one element in such a circuit leads to characteristic changes in its other elements.

Pituitary-independent release of hormones is usually regulated by those parameters that are influenced by the particular hormone, the latter acting on the target organs, whose functions in turn lead to a reduction in the stimuli leading to hormone release (regulatory circuit with negative feedback). Insulin release serves as an example (→ A1): raised plasma glucose concentration stimulates the release of insulin, the effect of which on the target organ, for example, the liver (increased glycolysis; inhibition of gluconeogenesis and glycogen formation), leads to a reduction in plasma glucose concentration.

If the insulin release is inappropriately high for a given plasma glucose concentration (hyperinsulinism), this will lead to hypoglycemia. In addition to an insulin-producing tumor, the cause may be an overlap of regulatory circuits, in that some amino acids also stimulate insulin release, and some of the insulin effects (stimulation of protein synthesis, inhibition of proteolysis) can produce a reduction in the plasma concentration of amino acids. An abnormal breakdown of amino acids, for example, one due to an enzyme defect, can trigger hypoglycemia via a rise in amino acid concentration in the blood and subsequent stimulation of insulin release (→ A2).

If there is a defective hormonal gland (→ A3), the hormone level and thus the hormonal effect is reduced. In the example illustrated an insufficiency of the beta cells results in hyperglycemia.

In addition, when the responsiveness of the target organs is reduced (→ A4), the hormonal effect is decreased. In this way liver failure can result in hyperglycemia, which in turn will raise plasma insulin concentration. However, the abnormal breakdown of amino acids in liver failure can cause hypoglycemia through hyperaminoacidemia and by stimulating insulin release (see above; → A2).

Hormone release regulated by the hypothalamus and pituitary. The plasma concentration of hormones that are under the influence of the hypothalamus and pituitary gland is always regulated (→ B1). Liberins (releasing hormones), formed in the hypothalamus, cause the release of tropins in the pituitary. These stimulate the release of the respective hormone in the periphery. The hormone and to some extent also the effect produced by the hormone finally inhibit the release of liberins in the hypothalamus and of tropins in the pituitary. The example illustrates the regulation of cortisol from the adrenal cortex.

Reduced release of peripheral hormones may be due to a loss of function in the hypothalamus, pituitary, or peripheral hormonal gland. The primary cause of an increased release of peripheral hormones can be an inadequately high orthotopic or ectopic release (→ p. 257 A3) of liberins, tropins, or peripheral hormones.

If there is an increase in liberin release (→ B2), liberin, tropin, and peripheral hormone concentrations are raised.

If there is a primary increase in tropin release, the concentrations of tropins and of the peripheral hormone will be raised, but that of liberins reduced (→ B3).

If there is a primary rise in peripheral hormone release, the release of liberins and tropins is suppressed (→ B4).

In an analogous manner, a primary deficiency of liberins will lead to tropin and peripheral hormone deficiency, while a primary lack of tropins will result in a reduced release of peripheral hormones, with increased release of liberins; a primary deficiency of peripheral hormones will lead to increased release of liberins and tropins.
A. Abnormalities of Simple Endocrinal Regulatory Circuit

1. Normal regulation

2. Increased secretion in the intertwined regulatory circuit

3. Defect in hormonal gland

4. Target organ defective

B. Abnormalities of Hypothalamus-Regulated Hormones

1. Normal regulation

2. CRH primarily raised

3. ACTH primarily raised

4. Cortisol primarily raised
The Antiuretic Hormone

The antiuretic hormone (ADH, antidiuretin, vasopressin) is formed in the supraoptic and paraventricular nuclei of the hypothalamus and is transported to the posterior lobe of the pituitary gland via the axons of the hormone-producing neurons. ADH causes the incorporation, via V_2-receptors and cAMP, of water channels into the luminal membrane and thus promotes water reabsorption in the distal tubules and in the collecting duct of the kidney. ADH also stimulates the tubular absorption of Na^+ and urea. A high ADH concentration also leads to vasoconstriction (via V_1-receptors and IP_3).

Stimuli for the release of ADH are extracellular hyperosmolarity (or cell shrinkage) and a decreased filling of the two atria, as well as vomiting, pain, stress, and (sexual) arousal. ADH secretion is further stimulated by angiotensin II, dopamine, and some drugs or toxins (e.g., nicotine, morphine, barbiturates). Increased atrial distension as well as γ-aminobutyric acid (GABA), alcohol, and exposure to cold have an inhibitory effect.

ADH excess (→ A1) is often due to raised ADH formation in the hypothalamus, for example, by stress. Furthermore, ADH can be formed ectopically in tumors (especially small-cell bronchial carcinoma), or by lung disease. It leads to reduced water excretion (oliguria). The resulting marked concentration of poorly dissolved urinary constituents can lead to the formation of urinary stones (urolithiasis). At the same time there will be a drop in extracellular osmolarity (hypotonic hyperhydration) and cell swelling occurs. This is especially dangerous if it leads to cerebral edema (→ p. 358).

ADH deficiency (→ A2) occurs if release is reduced, as in genetically determined central diabetes insipidus, in destruction of neurones, for example, by autoimmune disease, or other pituitary gland injury. Exogenous causes include alcohol or exposure to cold. On the other hand, ADH may fail to have an effect on the kidney, even if it is normally secreted, for example, because of defective water channels, or if the concentrating capacity of the kidney is otherwise impaired, as in K^+ deficiency, Ca^{2+} excess, or inflammation of the renal medulla (renal diabetes insipidus). Decreased ADH release or effect results in the excretion of large amounts of poorly concentrated urine and hypertonic dehydration (see also p. 122), leading to cell shrinkage. Patients will be forced to compensate for the renal loss of water by drinking large amounts (polydipsia). If the osmoreceptors in the hypothalamus are destroyed, ADH deficiency is accompanied by hypoposmophobia, and the hypertonic dehydration is especially marked. In psychogenic polydipsia ADH release is inhibited because of the excess water, and thus, contrary to primary ADH deficiency, the result will be hypotonic hyperhydration.

Prolactin

Prolactin (→ B) is formed in the anterior lobe of the pituitary gland. It stimulates growth and differentiation of the mammary gland as well as milk production. It inhibits the pulsatile, but not the basal, release of the gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]; → p. 274). It also inhibits cellular glucose uptake and the cellular immune defenses.

Touching the nipple of a lactating woman and estrogens promote the release of prolactin. Its release is also stimulated by thyroliberin (thyroid-releasing hormone [TRH]), endorphins, vasoactive intestinal peptide (VIP), oxytocin, and angiotensin II as well as by stress, non–rapid eye movement (NREM) sleep, or hypoglycemia. Dopamine inhibits prolactin release. As prolactin increases dopamine metabolism in the hypothalamus, it inhibits its own release (negative feedback).

Excess prolactin (→ B) can be caused by hormone-producing tumors, or by administration of antidopaminergic drugs. Renal and liver failure can also result in an excess of prolactin, possibly via a lack of dopamine. Hypothyroidism raises prolactin release via correspondingly increased TRH secretion. The effects of excess prolactin are milk flow (galactorrhea), tendency toward hyperglycemia, and an inhibition of gonadotropin release, accompanied by hypogonadism, amenorrhea, loss of libido, and impotence.
A. Antidiuretic Hormone (Vasopressin, ADH) Excess and Deficiency

1. ADH ↑
   - Excretion ↓
   - Hypotonic hyperhydration
   - Urolithiasis
   - Cerebral edema

2. ADH ↓
   - Excretion ↑
   - Hypertonic dehydration
   - Cell shrinkage

B. Prolactin Excess

- Liver and renal failure
- Absence of dopaminergic inhibition
- Dopamine antagonists
- Hypothyroidism
  - TRH secretion ↑
- Opiates, stress
- Post-partum, estrogens
- Tumor
- LH, FSH ↓
- Gonadal function ↓
  - Amenorrhea, estrogen deficiency
  - Androgen deficiency, loss of libido, impotence
- Prolactin ↑
  - Galactorrhea (flow of milk)
  - Hyperglycemia
  - Risk of diabetes mellitus developing
  - Inhibition of glucose absorption

- Pain, stress, CNS damage, hypothyroidism, drugs
- Tumors, esp. small-cell bronchial carcinoma
- Genetic defect
- Damage to hypothalamus
- Renal defect
- H₂O excess
- Polydipsia
- Thirst
- Pulmonary disease
- Liver and renal failure
- Autoimmune disease
- Alcohol, cold
- Abnormal excretion
- Hypotonic hyperhydration
- Cell shrinkage
- Renal defect
- Urolithiasis
Somatotropin

Somatotropin (growth hormone [GH]) is formed in the anterior lobe of the pituitary gland. It inhibits the uptake of glucose in fat and muscle cells and promotes lipolysis, gluconeogenesis, collagen synthesis, and the formation of erythropoietin (in part through the mediation of hepatic somatomedins or insulin-like growth factors [IGF], e.g., IGF-1). Somatotropin stimulates the enteric absorption of calcium and phosphates as well as the renal excretion of calcium. It also promotes bone growth (before the end of epiphyseal fusion and thus longitudinal growth) as well as soft tissue growth. Somatotropin promotes T-cell proliferation, interleukin 2 (IL-2) formation and the activity of natural killer cells, cytotoxic T cells, and macrophages. In this way it strengthens immune defense. Estrogens inhibit the formation of somatomedins and thus also reduce the effects of somatotropins.

The normally pulsatile liberation of somatotropin is regulated by the hypothalamic messenger substances somatoliberins (somatocrinin) and somatostatin (inhibitory). The release of somatotropin is stimulated by amino acids, hypoglycemia, glucagon, dopamine, and stress. Hyperglycemia, hyperlipidicademia, obesity, and cold inhibit its release.

An excess of somatotropin is usually due to uncontrolled formation of the hormone, for example, by a pituitary adenoma or, in rare cases, by an ectopic tumor. Increased stimulation of hormone synthesis by somatoliberin is equally rare. Finally, uncontrolled therapeutic administration of somatotropin can also result in an iatrogenic excess of somatotropin (→A1).

Massive somatotropin excess before epiphyseal fusion is completed leads to gigantism (height up to 2.6 m). In adults it results in acromegaly (enlarged cheek bones, mandibula, feet and hands, and supraorbital bulge), cartilage hypertrophy with arthropathy and calcification of cartilage and intervertebral disks (→A2). At the same time there is an increase in the size of soft tissues, for example, tongue, heart, liver, kidneys, thyroid, salivary glands, and skin (→A3). This increase in organ size can lead to further complications. If, for example, vascularization does not increase with myocardial hypertrophy, impaired coronary oxygen delivery will result (angina pectoris; →p.218). Arterial hypertension occurs relatively frequently (in 30% of cases). Thickening of the skin is associated with increased sweat and sebum production. Compression of the median nerve can lead to carpal tunnel syndrome. Decreased glucose uptake in peripheral cells favors the development of hyperglycemia (→A4), in some cases of diabetes mellitus. Increased intestinal absorption results in calcium excess followed by hypercalciuria (→A5). The latter may cause precipitation of calcium salts in urine (nephrolithiasis; →p.120). Somatotropin excess also promotes the development of tumors.

A somatotropin-producing pituitary tumor often causes enlargement of the sella turcica; pressure on the optic chiasma (→A6) can give rise to visual field defects (typically bitemporal hemianopia, as though the patient were wearing blinkers; →p.326). Displacement of other endocrine cells can lead to gonadotropin deficiency, and thus to amenorrhea as well as loss of libido, and impotence (→A7). Conversely, somatotropin-producing tumors can also release other hormones, such as prolactin (→p.260).

Somatotropin deficiency can be genetically determined or due to damage of the hormone-producing cells (e.g., tumor, hemorrhage, radiation), decreased hypothalamic stimulation, or an inhibition of release (cortisol, hypothyroidism). The effect of somatotropin can also be weakened by estrogens. If somatotropin deficiency occurs before epiphyseal fusion, pituitary dwarfism will result. However, a deficiency that occurs after the completion of longitudinal growth will have no visible effect. Nevertheless, decreasing release of somatotropin in the elderly probably contributes to a weakening of the immune system.
A. Somatotropin Excess

Pituitary adenoma

1. Iatrogenic
   - Stress, NREM sleep, hypoglycemia, amino acids

2. Hyperglycemia
3. Secretion of sweat and sebum
   - 3a. Visceromegaly
   - 3b. Carpal tunnel syndrome
   - 3c. Risk of angina pectoris
4. Hyperphosphatemia
5. Acromegaly
   - 5a. Gigantism
   - 5b. Macroglossia
   - 5c. Enlargement of cheek bones, hands and feet
6. Compression of optic chiasma
7. Gonadotropin deficiency
   - 7a. Visual field defects
   - 7b. Amenorrhea, loss of libido and impotence

Rare:
- Ectopic adenoma

Before epiphyseal fusion:
- Visceromegaly
- Hyperglycemia

Somatotropin Excess

- Hypertension
- Calciuria
- Gonadotropin deficiency
  - Amenorrhea, loss of libido and impotence

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Adrenocortical Hormones: Enzyme Defects in Formation

The most important adrenocortical hormones (corticoids) are the glucocorticoids and mineralocorticoids. Androgens, progestogens, and estrogens are also formed in the adrenal cortex.

All adrenocortical hormones (see also p. 272 ff.) are formed from cholesterol. The transport of cholesterol to the mitochondria and subsequent transformation in pregnenolone can be impaired by a deficiency in steroidogenic acute regulatory protein (StAR). Several enzymes, which may be absent in genetic defects, are necessary for the formation of the various hormones.

Enzyme defects lead to decreased synthesis of enzyme products, and thus also of the hormones formed through their action. However, reduced glucocorticoid synthesis leads to inhibition of the formation of corticosteroids (CRH) and of corticotropin (adrenocorticotropic hormone [ACTH]). Corticotropin, in turn, stimulates the growth of the adrenal cortex, the release of cholesterol and the expression of several enzymes involved in the synthesis of adrenocorticoid hormones. As a result of this action, there is a rise in the concentration of enzyme substrates, their precursors, and metabolites as well as of steroids which are active preceding the enzyme defect in the metabolic chain. These steroids have partly hormonal effects, namely glucocorticoid (blue), mineralocorticoid (green), androgenic (red), progestogenic (orange), and estrogenic (violet) ones, as illustrated in Figs. 9.7–9.10. Depending on what activity those products, substrates, precursors, and metabolites possess, there may thus be reduced (↓) or increased (↑) hormonal effects (see Table).

By using ACTH to stimulate adrenocorticotrophic hormone production, glucocorticoid production can be (practically) normalized, in spite of an enzyme defect. More frequently, though, the glucocorticoid action decreases (→ p. 270). If there is an excess of gestagenic metabolites, their weak antimineralocorticoid effect can trigger natriuresis (→ p. 276). Some enzyme defects increase concentrations of androgenic metabolites, with the corresponding consequences for sexual development (→ p. 272 f.). If there is a 3β-hydroxydehydrogenase defect (→ A3), then insufficient amounts of androgens are formed for normal male sexual development to take place; too many androgens are formed for normal female sexual development. Limiting the production of the sexual hormones in the adrenal cortex does not, however, generally impair sexual development, since the sexual hormones are normally mainly formed in the gonads.

The most common enzyme defect is a deficiency of 21β-hydroxylase (cytochrome P450c21). Such a deficiency impairs transformation of progesterone into 11-desoxycorticosterone and of 17-hydroxyprogesterone into 11-desoxycorticosteroids (→ A5). Depending on the extent to which enzyme activity is impaired, there will be a moderate to severe cortisol deficiency. Increased formation of androstendion and testosterone leads to virilization of girls and premature development of male sex characteristics (incomplete precocious puberty) in boys (adrenogenital syndrome; see also p. 272). These effects can already be detected at birth, since the excess androgens are formed intrauterinely.

<table>
<thead>
<tr>
<th>Enzym Defect (→ A1–A8)</th>
<th>Androgenic Action</th>
<th>Glucocorticoid Action</th>
<th>Mineralocorticoid Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 20,22-Desmolase (P450sc, StAR)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>2 17α-Hydroxylase (P450c17)</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>3 3β-Hydroxydehydrogenase</td>
<td>↑ (↓) (↓)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>4 17-Reductase</td>
<td>↓</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5 21β-Hydroxylase (P450c21)</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>6 11β-Hydroxylase (P450c11)</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>7 18-Hydroxylase (P450c11AS)</td>
<td>–</td>
<td>–</td>
<td>↓</td>
</tr>
<tr>
<td>8 18-Methyloxidase (P450c11AS)</td>
<td>–</td>
<td>–</td>
<td>↓</td>
</tr>
</tbody>
</table>
A. Enzyme Defects in Formation of Adrenocortical Hormones

Enzymes:
1. 20,22-Desmolase
2. 17α-Hydroxylase
3. 3β-Hydroxysteroid dehydrogenase
4. 17-Reductase
5. 21β-Hydroxylase
6. 11β-Hydroxylase
7. 18-Hydroxylase
8. 18-Methyloxidase

Hormonal effects:
- androgenic
- estrogenic
- gestagenic
- glucocorticoid
- mineralocorticoid
Adrenocorticotoid Hormones: Causes of Abnormal Release

The glucocorticoids serve, in the first instance, in the adaptation of metabolism, circulation, blood, immune system, etc. to stress, i.e., severe physical and psychological threat. The mineralocorticoids act on mineral and water balance (for mechanism of action see p. 268) by aiding in the renal retention of Na⁺ and the elimination of K⁺ and other ions.

The release of glucocorticoids (e.g., cortisol) is regulated by ACTH from the pituitary gland, which is, in turn, under the control of corticotropin-releasing hormone (CRH) from the hypothalamus (→ A). The most important stimulus for the release of CRH, and thus of ACTH and cortisol, is stress. Other stimuli are epinephrine, ADH, histamine, pyrogens, pain, fall in blood pressure, and hypoglycemia (→ A1). The organism’s diurnal rhythm also plays a role: release of cortisol is highest in the early morning hours and then slowly falls during the day (→ A2). The release is inhibited by morphine.

An excess of glucocorticoids often has an iatrogenic cause (therapeutic administration of glucocorticoids for immunosuppression; → A4), but it can also be the result of a hormone-producing tumor in the adrenal gland or other organs (especially small-cell bronchial carcinoma; → A3) (Cushing’s disease; → p. 268). The cause may be an excess stimulation of the adrenal by ACTH (secondary Cush- ing syndrome, for example, due to a pituitary tumor, other causes of CRH release, or ectopic formation of ACTH or, rarely, of CRH).

An important stimulus for the release of the mineralocorticoid aldosterone is angiotensin II, which is formed in increased amounts via the renin–angiotensin system when the renal perfusion pressure is reduced (→ A5). Aldosterone release is also stimulated by ADH, whose secretion is stimulated by angiotensin II. Aldosterone release is increased by hyperkalemia, but decreased by dopamine and the atrial natriuretic factor (ANF).

A selective excess of mineralocorticoids in the majority of cases occurs in the form of secondary hyperaldosteronism caused by increased renin release. In hypovolemia (e.g. in dehydration) the increased release of aldosterone is adequate for controlling volume, but usually too high for K⁺ balance. If hypovolemia occurs, the resulting “intertwining” of the regulatory circuits for plasma volume and potassium (→ p. 258) regularly leads to hypokalemia. Even if blood volume is normal or increased, renal perfusion may be impaired and thus renin release increased in a number of renal diseases. If the pumping action of the heart is reduced (→ p. 224), or in peripheral vasodilation (e.g., in sepsis or liver failure; → p. 118) the blood pressure can be maintained only by massive activation of the sympathetic system, resulting in renal vasoconstriction, renin release, and hyperaldosteronism. Another cause may be an aldosterone-producing tumor in the adrenal (Conn’s syndrome). Furthermore, a defect of 11β-hydroxysteroid dehydrogenase (→ p. 212) may result in an increased mineralocorticoid effect. The enzyme is normally formed in the target cells of aldosterone and inactivates cortisol. This fits into the mineralocorticoid receptor and its mineralocorticoid action is normally stopped only by enzymatic inactivation. Because its concentration in blood is more than a hundred times higher than that of aldosterone, cortisol will cause a massive mineralocorticoid effect if 11β-hydroxysteroid dehydrogenase is defective. In a rare genetic defect (glucocorticoid remediable hyperaldosteronism), the expression of aldosterone producing enzymes is driven by an ACTH-sensitive promoter, leading to enhanced aldosterone production, whenever ACTH is high. Treatment of the patients with glucocorticoids suppresses ACTH release and thus hyperaldosteronism. In yet another rare genetic disease the mineralocorticoid receptor is sensitive to progesterone, leading to pseudohyperaldosteronism which exacerbates in pregnancy.

A deficiency of adrenal hormones (→ B) can be the consequence of adrenal insufficiency (Addison’s disease; → p. 270; e.g., in genetic defects, autoimmune adrenal disease, tuberculosis, metastases, surgical removal) or of enzyme defects in adrenal hormone synthesis (→ p. 264). In addition, there may be insufficient stimulation by ACTH, as in damage to the pituitary gland or hypothalamus. Aldosterone release can also be reduced as a result of hypokalemia or decreased angiotensin II formation.
A. Causes of Cortisol and Aldosterone Excess

1. Psychological and physical stress
   - Corticotropin (ACTH)
   - Corticosteroid Hormones

2. Morphine
   - Diurnal rhythm of plasma glucocorticoids

3. Pituitary adenoma
   - Bronchial carcinoma and others

4. Therap. cortisol administration
   - Cortisol
   - Aldosterone

5. Enzyme defects
   - Hyperkalemia

B. Causes of Cortisol and Aldosterone Deficiency

1. Damage to pituitary
   - Damage to hypothalamus

2. Enzyme defects
   - Hypervolemia
   - Hypokalemia

3. Adrenal insufficiency (e.g. inflammations, surgical removal)

4. Hypokalemia

5. Angiotensinogen
   - Angiotensin I
   - Angiotensin II

6. Angiotensinogen
   - Angiotensin I
   - Angiotensin II

7. Angiotensinogen
   - Angiotensin I
   - Angiotensin II

8. Angiotensinogen
   - Angiotensin I
   - Angiotensin II
Excess Adrenocorticoid Hormones: Cushing’s Disease

Glucocorticoids (especially cortisol) stimulate gluconeogenesis in the liver and inhibit glucose uptake in peripheral cells. They also stimulate lipolysis, the breakdown of proteins in the periphery, and the formation of plasma proteins (e.g., angiotensinogen) in the liver. They promote the formation of erythrocytes, thrombocytes, and neutrophil granulocytes (neutrophils). At the same time they reduce the number of eosinophil granulocytes (eosinophils) and basophil granulocytes (basophils), lymphocytes, and monocytes. They also, via the formation of the proteins lipocortin and vasocortin, suppress the release of histamine, interleukins, and lymphokines. By inhibiting phospholipase A₂ they suppress the formation of prostaglandins and leukotrienes. They diminish antibody formation and thus act as immunosuppressives. Glucocorticoids suppress inflammation by inhibiting connective tissue proliferation, but at the same time impede collagen synthesis and repair. They stimulate the secretion of acids and pepsin in the stomach and slow down mucus production. In addition, they decrease the plasma levels of calcium and phosphate, in part by inhibiting calcitriol formation. They also sensitize blood vessels and the heart to catecholamines, partly by inhibiting prostaglandin synthesis, stimulate the release of norepinephrine, and increase the excitability of the nervous system.

Mineralocorticoids (especially aldosterone) further renal retention of Na⁺ and water. They thus facilitate a rise in blood pressure. They also stimulate renal elimination of K⁺, Mg²⁺, and H⁺ and simultaneously the intracellular uptake of potassium. However, at high plasma levels cortisol also exerts a significant mineralocorticoid effect, even though it is largely inactivated in the target cells of the mineralocorticoids (→ p. 266). Dehydro-epiandrosterone (DHEA), the precursor of the steroid sex hormones, is also formed in the adrenals, in addition to mineralocorticoids and glucocorticoids.

The metabolic effects of glucocorticoid excess favor the development of diabetes mellitus (→ p. 286 ff.), i.e., steroid diabetes, in which the release of insulin is increased (→ A2). The free fatty acids formed by stimulated lipolysis are utilized in the liver to generate very low density lipoproteins (VLDL) which are passed into the blood (→ A3). In addition, the liver forms ketone bodies from fatty acids. A redistribution of fat tissue occurs due to differing sensitivities of peripheral fatty tissue for glucocorticoids and insulin. This results in centripetal fat stores, rounded or moon faces and fat deposits in the neck (“buffalo” hump), while the limbs are noticeably thin. Peripheral protein breakdown (→ A5) leads to muscle wasting, osteoporosis (loss of bone matrix), striae (breakdown of subcutaneous connective tissue), and purpura (increased vascular fragility). Because repair is impeded, wound healing is delayed. The effect on bone is aggravated by CaHPO₄ deficiency and in children results in delayed growth. The effects on blood lead to polycythemia (→ A1), thrombocytosis, and raised coagulability (→ A6). Weakened immune defenses encourage infections (→ A4).

Sensitization of the circulation to catecholamines causes, among other things, an increase in cardiac contractility as well as peripheral vasconstriction, and thus leads to hypertension (→ A7), which, together with hyperlipidemia and raised coagulability of blood, promotes the development of atherosclerosis, thrombosis, and vascular occlusions (→ A6). Due to stimulation of hydrochloric acid and pepsin secretion and the inhibition of mucus secretion in the stomach, gastric and/or duodenal (peptic) ulcers develop (→ A8). The effects on the nervous system can trigger an endocrine psychogenic syndrome.

An increased mineralocorticoid effect causes hypervolemia, which in turn leads to hypertension; it also causes hypokalemia, hypomagnesemia, and alkalosis, which in turn lead to increased neuromuscular excitability (→ A10). The effects are, among others, abnormal action potential formation and conduction in the heart.

An excess of androgens (→ A9) can lead to masculinization and amenorrhea (virilism) in women, and to an accelerated onset of sexual characteristics in male children (incomplete precocious puberty; → p. 272).
A. Effects and Symptoms of Adrenocortical Hormone Excess

1. Polycythemia, leukocytosis, eosinopenia
2. Gluconeogenesis
   - Hyperglycemia
   - Diabetes
3. Insulin
   - Free fatty acids
   - Ketone bodies
   - VLDL
   - Lipogenesis
4. Lymphopenia, inhibition of immune defenses
5. Neuropsychological disorders
   - Muscle weakness: thin limbs
   - Striae
   - Purpura
   - Delayed wound healing
6. Striae
7. Thrombocytosis
   - Clotting
8. Gastric acid and pepsin secretion
   - Mucus secretion
9. Androgens
   - Hirsutism, amenorrhea
   - Precocious pseudopuberty
10. Cardiac output
    - Peripheral resistance
    - Atherosclerosis
    - Blood pressure

Additional symptoms and effects:
- Neuromuscular excitability
- Renal damage
- Diffuse muscle wasting
- Delayed wound healing
- Purpura
- Thrombocytosis
- Polycythemia, leukocytosis
- Eosinopenia
- Red blood cell sensitization to catecholamines
- Osteoporosis
- Skin clenching
- Cardiac output
- Muscle atrophy
- Delayed wound healing
- Neuropsychological disorders
- Susceptibility to infection
- Precocious pseudopuberty
- Hirsutism, amenorrhea
Deficiency of Adrenocorticoid Hormones: Addison’s Disease

For the effects of the adrenocorticoid hormones, see p. 268.

**Glucocorticoid deficiency** frequently leads to hypoglycemia as a result of disinhibited glycolysis and reduced gluconeogenesis (→ A1). This is especially marked in secondary deficiency of adrenocorticoid hormones due to pituitary insufficiency, because it is associated with decreased somatotropin secretion, the hyperglycemic effect of which will be absent (→ p.262). The hypoglycemia activates the sympathetic nervous system and inhibits the release of insulin, and thus also of its influence on lipolysis and protein breakdown. The reduced lipolytic and proteolytic action of cortisol is more than compensated by a decreased insulin and an increased epinephrine effect. Lipolysis and protein breakdown are thus stimulated. Further effects of the raised epinephrine release are tachycardia and sweating (→ A2). The reduced sensitivity to catecholamines of the heart and blood vessels leads to a fall in blood pressure despite the release of epinephrine. Due to the diminished secretion of hydrochloric acid, pathogens that have been swallowed will be less effectively killed in the stomach and more commonly cause gastrointestinal infections (→ A6). Diarrhea and vomiting occur with corresponding loss of water and electrolytes. The lack in glucocorticoid effect on blood-forming cells results in anemia, neutropenia, eosinophilia, and lymphocytosis (→ A4). Other symptoms are fatigue and weakness. Furthermore, depression is caused by the lack of glucocorticoid action on the brain. However, while cortisol deficiency persists, sensitivity of the target cells is raised and they thus delay the onset of symptoms.

In primary adrenocorticoid insufficiency (Addison’s disease) the diminished negative feedback from cortisol leads to a massive rise in the synthesis of pro-opiomelanocortin (POMC), the precursor of ACTH. This increases formation not only of ACTH, but also of α-melanotropin (α-MSH or melanocortin). α-MSH as well as ACTH itself cause brown discoloration of the skin (→ A3), because of which Addison’s disease has been called “bronze disease”. If one adrenal cortex is absent, ACTH causes hypertrophy of the intact adrenal cortex. If both adrenals are absent, ACTH can even cause the ectopic formation of adrenocortical hormones, but this is usually inadequate. In secondary adrenocorticoid insufficiency skin pigmentation is decreased because of a lack of α-MSH and ACTH.

**Mineralocorticoid deficiency** leads to renal salt loss and renal retention of K⁺, Mg²⁺, and H⁺ (→ A5). Na⁺ reabsorption in the sweat glands and gut is also impaired. This results in salt deficiency, hypotonic dehydration, hypovolemia, drop in blood pressure, and in the increase of intracellular volume (→ p.122ff.). This can lead to a decrease in renal perfusion and glomerular filtration rate, causing an increase of plasma creatinine concentration. Also, due to the impaired renal perfusion the release of renin and angiotensin I–II will be raised. As angiotensin II stimulates ADH release and ADH leads to renal water retention the release of angiotensin II contributes to hyponatremia. The retention of K⁺, Mg²⁺, and H⁺ leads to reduced neuromuscular excitability as well as abnormalities of action potential formation and conduction in the heart due to hyperkalemia, hypermagnesemia, and acidosis (→ A8 and p.124ff.). In combined mineralocorticoid and glucocorticoid deficiency, the increased fat and protein breakdown and loss of fluid cause weight loss, and arterial hypotension and anemia reduce physical fitness.

A lack of androgens manifests itself especially in sparse pubic hair as well as muscle wasting and loss of libido (→ A7). However, lack of adrenal androgens is of no consequence in men, as long as testosterone production in the testes is normal.

Acute worsening of the symptoms leads to Addisonian crisis with extreme weakness, fall in blood pressure, tachycardia, diarrhea, hypoglycemia, hyponatremia, hyperkalemia, and oliguria. It is frequently the consequence of an infection that normally, but not in patients with Addison’s disease, leads to an increase in cortisol release.
A. Effects and Symptoms of Adrenocortical Hormone Deficiency

1. Increased glycolysis → Hypoglycemia
2. Lipolysis → Tachycardia
3. Melanotrophic effect → Brown discoloration of the skin
4. Anemia, neutropenia, eosinophilia, thrombopenia, lymphocytosis
5. Renal Na⁺ retention → Acidosis, hyperkalemia, hypermagnesemia
6. Gastrointestinal infections → Hydrochloric acid
7. Androgen deficiency → Pubic hair
8. Abnormal action potential generation and conduction in the heart → Neuromuscular excitability

Decreased gluconeogenesis

Proopiomelanocortin → ACTH → MSH → Proopiomelanocortin

Muscle weakness → Weight loss

Electrolyte disturbances

Hypotonic dehydration

GFR↓

Reduced catecholamine sensitivity

Blood pressure↓
Causes and Effects of Androgen Excess and Deficiency

**Follitropin** (FSH) and **lutropin** (LH) are released in the anterior pituitary, stimulated by pulsatile release of gonadoliberrin (gonadotropin—releasing hormone, GnRH) ($\rightarrow \text{A1}$). The pulsatile secretion of these gonadotropins is inhibited by **prolactin** ($\rightarrow$ p. 260). LH controls the release of **testosterone** from the Leydig cells in the testes. Testosterone, by means of a negative feedback, inhibits the release of GnRH and LH ($\rightarrow \text{A2}$). The formation of **inhibin**, which inhibits the release of FSH, and of **androgen-binding protein** (ABP) is promoted by FSH in the testicular Sertoli cells ($\rightarrow \text{A3}$).

**Testosterone** or dihydrotestosterone (5-α-DHT) which is formed from testosterone in the Sertoli cells and in some organs, promotes the **growth of the penis, seminiferous tubules, and scrotum** ($\rightarrow \text{A4}$). Testosterone and FSH are both necessary for the **formation and maturation of spermatozoa**. In addition, testosterone stimulates the **secretory activity of the prostate** (reduced viscosity of the ejaculate) and the **seminal vesicle** (admixture of fructose and prostaglandins), as well as the secretory activity of the sebaceous and sweat glands in the axillae and the genital region. Testosterone increases skin thickness, scrotal pigmentation, and erythropoiesis. It also influences **height and stature** by promoting muscle and bone growth (protein anabolism), longitudinal growth, and bone mineralization as well as fusion of the epiphyseal plates. Testosterone stimulates **laryngeal growth** (deepening of the voice), **hair growth** in the pubic and axillary regions, on the chest and in the face (beard); its presence is essential for **hair loss in the male**. The hormone stimulates **libido and aggressive behavior**. Lastly, it stimulates the renal retention of electrolytes, reduces the concentration of high density lipoprotein (HDL) in blood, and influences fat distribution.

**Decreased release of androgens** can be due to a **lack of GnRH**. Even **nonpulsatile GnRH secretion** stimulates androgen formation inadequately. Both can occur with damage to the hypothalamus (tumor, radiation, abnormal perfusion, genetic defect) as well as psychological or physical stress. Persistently high concentrations of GnRH (and its analogs) decrease gonadotropin release by down-regulation of the receptors. Other causes are **inhibition of pulsatile gonadotropin release** by prolactin as well as **damage** to the hypophysis (trauma, infarct, autoimmune disease, tumor, hyperplasia) or to the testes (genetic defect, severe systemic disease). Lastly, androgen effects can be impaired by **enzyme defects in hormone synthesis**, for example, genetic reductase deficiency ($\rightarrow$ p. 264) or by a **defect of the testosterone receptors**.

**Effects of deficient testosterone action** in the male fetus are **absent sexual differentiation** ($\rightarrow$ p. 278); in juveniles they are failure of the voice to break and absence of adult body hair, delayed bone growth, but also ultimately excess longitudinal growth of the limbs due to delayed epiphyseal fusion. Other effects (in juveniles and adults) are **infertility**, decreased libido and aggressiveness, reduced muscle and bone mass, and slightly decreased hematocrit. If there is no androgen effect at all, there will not even be any feminine pubic and axillary hair.

Possible **causes of androgen excess** are **enzyme defects in steroid hormone synthesis** ($\rightarrow$ p. 264), a **testosterone-producing tumor**, or **iatrogenic androgen supply** ($\rightarrow \text{A2}, \text{A3}$).

**Effects of testosterone excess** are **male sex differentiation** and hair growth, even in the female, an increase in erythropoiesis, muscle and bone mass as well as of libido and aggressiveness. Amenorrhea ($$\varnothing$$) and **impaired fertility** ($$\varnothing$$ and $$\varnothing$$) are caused by inhibition of GnRH and gonadotropin release.

The **generative function of the testes** can, however, also be impaired without appreciable abnormality of the sex hormones, as in undescended testis (**cryptorchidism**), genetic defects, or damage to the testes (e.g., inflammation, radiation, abnormal blood perfusion due to varices).
A. Androgen Excess and Deficiency

Libido and aggressive behavior
Bone growth
Electrolyte retention
Epiphyseal fusion
Protein synthesis
Muscle growth
Erythropoiesis
Skin thickness
Sebaceous glands
HDL

Persistently increased GnRH analogues
Damage to pituitary

Spermogenesis
Testicular damage, genetic damage
Inhibin
ABP
Lumen

Testosterone
Protein synthesis
Electrolyte retention
Bone growth
Libido and aggressive behavior

Damage to hypothalamus, genetic defects
Cachexia,

Gonadoliberin (GnRH)
Luteinizing hormone (LH)
Follicle-stimulating hormone (FSH)
Prolactin
Leydig cells
Sertoli cells of the seminiferous tubules
Testosterone
Blut
DHT

Lumen
Penis, scrotum, seminiferous tubules
Prostate, seminal vesicles

Reductase deficiency
Iatrogenic supply
Hypothalamic damage, genetic defects
Prolactin Receptor defect
Sertoli cells of the seminiferous tubules
Spermiogenesis

Testosterone

Adreno-genital syndrome
Tumors

Feminization of the male due to testosterone deficiency
Infertility
Masculinization of the female due to testosterone excess

Persistently increased GnRH analogues
Damage to pituitary

Feminine fat distribution
Absence of male hair
Male voice
Hair on chest
Amenorrhea
Rhomboid pubic hair
Hyper-trophic clitoris

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Release of Female Sex Hormones

The gonadotropic hormones FSH and LH are released from the anterior lobe of the pituitary gland in a pulsatile manner (every 60 to 90 min for 1 min) after pulsatile stimulation by GnRH from the hypothalamus at the same frequency (→ A2; see also p. 272). FSH and LH are essential for the maturing of the follicles and for the temporal coordination of the production of female sex hormones. In the female organism FSH promotes the maturation of the follicles and estrogen production in the granulosa cells of the follicles (→ A2). The estrogens (estrone, estradiol, estriol) at first stimulate the further release of gonadotropins (positive feedback) until the maturation of a follicle leads to ovulation and corpus luteum formation. Progestogens (progesterone and analogs), formed by the corpus luteum under the influence of LH, and the estrogens (after ovulation) inhibit further release of gonadotropins (→ A3). The concentration of gonadotropins falls again, as does, after some delay, that of the estrogens and progestogens (→ A4). As a rule this cycle takes 28 days, although the interval between menstruation and ovulation varies greatly. The granulosa cells also form inhibin and activin, while the theca cells form the androgens androstenedione and testosterone. Activin promotes gonadotropin release, while inhibin suppresses it (see p. 272 for the effect of testosterone). Prolactin produced in the anterior pituitary inhibits the pulsatile release of gonadotropins. It also decreases the ovary’s responsiveness to gonadotropins.

An excess of female sex hormones is usually due to an exogenous supply (contraceptive pills). In addition, some tumors produce sex hormones.

A lack of estrogens and progestogens is frequently the result of a decreased GnRH release in severe psychological or physical stress (e.g., malnutrition, serious systemic disease, high-performance sport). GnRH release can also be reduced through the influence of the neurotransmitters norepinephrine, dopamine, serotonin, and endorphins (→ A1).

However, it is not only reduced, but also persistently high concentrations of GnRH (or its analogs) that decrease the release of gonadotropins (down-regulation of the GnRH recep-

tors). Even if the hypothalamus is undamaged, gonadotropin release can be impaired by damage to the pituitary (hemorrhage, ischemia, inflammation, trauma), by displacement of gonadotropin-producing cells by tumors, or by inhibition due to a raised concentration of sex hormones (ovulation inhibitors, anabolic substances with androgen action, tumors, adreno-genital syndrome; → p. 264).

If androgen production is raised, the release of FSH is inhibited and follicle maturation is thus interrupted. Polycystic ovaries are formed. Some of the androgens are transformed into estrogens which, via stimulation of LH release, promote further formation of ovarian androgens.

It is relatively common for a reduction in gonadotropin release to be due to raised prolactin secretion, for example, as a result of the absence of inhibition of pituitary secretion of prolactin or a prolactin-producing pituitary tumor (→ p. 260). Gonadotropin release can be inhibited by dopaminergic drugs that cause a rise in prolactin secretion. Lastly, gonadotropin release can be inhibited by damage to the pituitary through head trauma, abnormal anlage or maturation, radiation, tumors, degenerative or inflammatory disease, or defective biosynthesis.

The formation of estrogens and/or progestogens can be impaired by ovarian insufficiency caused by an abnormal development (→ p. 278) or by damage (e.g., radiation, chemotherapeutic agents). Inadequate follicular maturation or transformation in the corpus luteum (corpus luteum insufficiency) can cause the deficiency. Lack of estrogen can also be due to an enzyme defect. In the resistant ovary syndrome the ovaries are refractory to the action of gonadotropins. This may be caused by defective receptors or inactivating antibodies. The result is a lack of estrogens despite an increased release of gonadotropins.
A. Release of Female Sex Hormones

- **Stress**
  - Hypothalamus
  - Hypophysis
- **Psyche**
  - Gonadoliberin (GnRH)
- **Androgens, prolactin**
- **Bleeding, ischemia, inflammation, trauma, hypophyseal insufficiency**

**Inflammation, ischemia, tumors, trauma, malnutrition, drugs, genetic defects, norepinephrine, dopamine, serotonin, endorphins, radiation**

1. **Gonadoliberin (GnRH)**
2. **Follitropin (FSH)**
3. **Lutropin (LH)**
4. **Follicle maturation**
   - Granulosa cells
   - Inhibin
   - Activin
   - Androgens
5. **Ovarian insufficiency**
6. **Ovulation inhibitors, tumors**
7. **Estrogens**
8. **Progestogens**
9. **Corpus luteum**

**Graph:**
- **Units/L**
- **ng/mL**
- **Days**

- FSH
- LH
- Progestogens
- Estrogens
Effects of Female Sex Hormones

Estrogens
Estrogens promote the development of the female sex characteristics, i.e., the transformation of the Müller ducts into Fallopian tubes, uterus and vagina, as well as the secondary sexual characteristics (e.g., development of the mammary glands and female fat distribution). They require the cooperation of androgens in order to stimulate axillary and pubic hair growth. Estrogens also influence the psychological development of women. In sexually mature women estrogens and progestogens have partly opposite actions.

Estrogens promote the proliferation of the uterine mucosa. In the cervix and vagina they reduce the viscosity of the cervical mucus and accelerate the exfoliation of the vaginal epithelium, whose glycogen is broken down by the vaginal flora to lactic acid. The resulting fall in pH stops pathogens from penetrating. Estrogens stimulate the formation of ducts in the mammary glands. They promote protein anabolism and increase the cooperation of HDL and VLDL. Conversely, they reduce the concentration of low density lipoproteins (LDL), and thus lower the risk of atherosclerosis. On the other hand, estrogens increase the coagulability of blood. Additionally, they raise electrolyte retention in the kidneys as well as the mineralization of the bones via hydroxylation of vitamin D, and the inhibition of parathyroid hormone (PTH). In children they promote bone growth and maturation and accelerate epiphyseal fusion.

Progestosterone
In the uterus progestosterone promotes the maturation and secretory activity of the uterine mucosa and decreases the contractility of the uterine muscle. When estrogen concentration falls at the end of the menstrual cycle, the mucosa is shed (menstruation). In the cervix and vagina progestogens raise the viscosity of cervical mucosa, narrow the cervical orifice, and inhibit fallopian motility. Furthermore, they inhibit the proliferation and exfoliation of vaginal epithelium. They also promote the formation of alveoli in the mammary glands. Progestogens (progesterone and its analogs) raise the body’s metabolism and temperature, trigger hyperventilation, and reduce sensitivity to insulin in the periphery. Additionally, they have moderate glucocorticoid and antimineralocorticoid (natriuretic) actions. They lower the production of cholesterol and the plasma concentration of HDL and LDL.

Effects of Excess and Deficiency
In excess of female sex hormones (→ A2) gonadotropin release is inhibited, there is no maturation of the follicles, no regular shedding of the uterine mucosa, and the woman will be infertile. An excess of estrogens can cause thrombosis due to a raised clotting tendency. In children high estrogen concentrations lead to premature sexual maturation and accelerate growth. However, premature epiphyseal fusion may eventually result in short stature. Increased progestogen action causes natriuresis, a rise in body temperature and hyperventilation, and via insulin resistance it can promote the development of diabetes mellitus.

A deficiency of female sex hormones (→ A3), like their excess, means that a normal menstrual cycle is not possible. In estrogen deficiency the phase of uterine proliferation is absent and the progestogens are not able to bring about maturation; in progestogen deficiency the uterine mucosa does not mature. In both these cases the woman is infertile and there is no menstrual bleeding (amenorrhea). The lack of estrogens also expresses itself in reduced manifestation of the external sex characteristics, in a tendency toward vaginal infections, in osteoporosis, and in an increased risk of atherosclerosis. In children there will be a delayed epiphyseal fusion that, despite slowed growth, may ultimately lead to tall stature.

The reproductive functions of a woman can also be abnormal independently of the sex hormones, for example, due to malformations or disease of the ovaries, fallopian tubes, or uterus.
A. Effects of Female Sex Hormones

2 Excess

Estrogens

- Gonadotropins↓
- No follicular maturation
- No menstruation

Progestogens↑

- Antimineralocorticoid action
- Basal metabolism, body temperature

In children: accelerated sexual maturation and growth

- Premature epiphyseal fusion
- Clotting tendency↑

Infertility

Thrombosis

Retarded growth

Diabetes mellitus

Hyper-ventilation

3 Deficiency

Estrogens↓

- 25-OH-D₃ formation↓
- Proliferation and desquamation of vaginal epithelium↓

Progestogens↓

- No build-up of mammary gland tubes
- No build-up of uterus mucosa
- No build-up of mammary gland alveoli

- Osteoporosis
- Amenorrhea

- Insulin resistance
- Hyper-ventilation

Vaginal infections

Tall stature

No distinct sexual characteristics

Proliferative phase

Secretory phase

Ovulation

Basal metabolism, body temperature

Amenorrhea

Tall stature

No distinct sexual characteristics

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Intersexuality

The development of the gonadal anlagen to ovaries and testes is fixed by the presence or absence of the testis-determining factor (TDF), which is encoded on the sex determining region of the Y chromosome (SRY) and is responsible for testicular development (→ A1). Ovaries develop if TDF is absent (→ A2). The gonads determine the formation of female and male sexual hormones. Testosterone is formed in the Leydig cells of the testes, while anti-Müller hormones are formed in the Sertoli cells (Müller inhibition factor [MIF]; → A1). However, not only androgens but also progestogens (some of them precursors of testosterone formation) and estradiol (predominantly by peripheral transformation of testosterone) are formed in the male. Progestogens and estrogens and, to a lesser extent, also androgens (mainly androstendion) are produced in the ovaries (→ A2).

The development of the Wolffian ducts to internal male genitals (epididymis and vas deferens) is stimulated by the androgens, while the development of the Müller ducts to form the internal female genitals (fallopian tubes, uterus, vagina) is suppressed by the anti-Müller hormone from the Sertoli cells. The external sexual characteristics are determined, first and foremost, by the concentration of androgens (→ p. 272), whereby the development of the female genitals and some of the sexual characteristics is promoted by estrogens.

The sex of an individual can be defined on the basis of the chromosomal set (XX or XY, respectively), of the gonads (ovary or testis), of the internal organs or of external appearance. Intersexuality occurs when the various sex characteristics have not developed unequivocally or are more or less pronounced.

An abnormal chromosome set occurs, for example, in Klinefelter’s syndrome (XXY), in which the testes are formed in such a way that spermatogenesis is possible, but androgen production is impaired (→ A3). The androgen deficiency then leads to an inadequately male appearance. Only mild clinical symptoms are present in the XXY syndrome. A similar condition prevails in the XX male syndrome, which is probably due to translocation of an SRY-containing Y chromosome fragment onto an X chromosome. In Turner’s syndrome (XO) connective tissue strands are formed in place of normal ovaries and the external features are more likely to be female (→ A4). The condition is characterized by a number of additional malformations (e.g., of the heart and kidneys; dwarfism, webbed neck).

In certain mutations of the SRY gene no functional TDF is formed, despite the presence of a male chromosome set (XY), and ovaries develop (→ A5).

In true hermaphroditism both testes and ovaries are simultaneously formed (→ A6). An XY/XO mosaic can be a cause. Translocation of some parts of the Y chromosome, including of the SRY gene, onto an X chromosome (as in the XX male, see above) can lead to the formation of bisexual gonads and the appearance of intersexual sex characteristics.

In pseudohermaphroditism the gonads correspond to the chromosomal sex, but the sex organs and secondary sex characteristics diverge or are not unequivocal. In male pseudohermaphroditism intersexual or female sex characteristics are present (→ A7). A gonadotropin deficiency may be a cause, for example when gonadotropin release is suppressed due to an increased formation of female sexual hormones by a tumor. Other causes can be defects in the gonadotropin receptor, aplasia of the Leydig cells, enzyme defects of testosterone synthesis (→ p. 264), defective testes, absent conversion of testosterone into dihydrotestosterone (reductase deficiency), or defective androgen receptors (→ p. 272). In rare cases the formation of the female genitals may not be suppressed owing to a defect in the release or action of the anti-Müller hormone. Female pseudohermaphroditism (→ A8) can be the result of iatrogenic administration or increased formation of androgens, for example in an androgen-producing tumor, or can be due to an enzymatic defect in adrenocortical hormone synthesis, or a defect of aromatase, which transforms androstendion or rather testosterone into estrogens (→ p. 264).
A. Intersexuality

1. Genitals | Sexual characteristics | Psyche

2. Genitals | Sexual characteristics | Psyche

3. Klinefelter’s syndrome

4. Turner’s syndrome

5. Mutation of SRY gene

6. True hermaphroditism

7. Male pseudohermaphroditism

8. Female pseudohermaphroditism

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Causes of Hypothyroidism, Hyperthyroidism and Goitre

The hormones thyroxine (T₄) and triiodothyronine (T₃) are formed in the epithelial cells (thyrocytes) that surround the follicles of the thyroid gland. Their synthesis is achieved in several steps, each of which can be disrupted. Iodine is essential for the synthesis of the hormones and has to be supplied in food (→ A1). Iodine is taken from the blood into the follicular epithelial cells by means of a transporter coupled to Na⁺ (→ A2). At the apical membrane of the cells it passes into the follicular lumen by exocytosis and is oxidized there (→ A3).

A tyrosine-rich protein (thyroglobulin, TG) is formed in the epithelial cells (→ A4) and secreted into the follicular lumen, too. Here the tyrosine residues of the globulin are iodized to the residues of diiodotyrosine (DIT) or of monoiiodotyrosine (MIT) (→ A6). The thyroid hormones are stored as thyroglobulin colloid in the follicular lumen. When stimulated to do so by the thyroid-stimulating hormone (TSH; see below), globulin is again taken up into the follicular epithelial cells and thyroxine and to a lesser extent triiodothyronine, is split off from the globulin (→ A7). One iodine is removed from T₄ in the periphery by a deiodinating enzyme (deiodinase) and thus converted into the more active T₃ (→ A8).

Regulation. Formation and release of T₃ and T₄ as well as growth of the thyroid gland are stimulated by thyrotropin (TSH) from the anterior pituitary. Its release is, in turn, stimulated by thyroliberin (TRH) from the hypothalamus. Stress and estrogens increase TSH release, while glucocorticoids, somatostatin, and dopamine inhibit it.

The causes of a lowered release of thyroid hormone (hypothyroidism) are usually found in the thyroid itself. Abnormal synthesis of thyroid hormones can be brought about by any one of the following steps in their synthesis: 1. Decreased iodine intake in food; 2. Impaired iodine uptake in the thyroid cells (genetically defective carrier or inhibition of transport by perchlorate, nitrate, thiocyanate (rhodanate)); 3. Peroxidase deficiency (genetic) or peroxidase inhibition by thiouracil or iodine excess (inhibition of H₂O₂ formation by excessive I⁻); 4. Abnormal breakdown of thyroeglobulin; 5. Defective iodine incorporation (peroxidase is involved in this, too); 6. Defective coupling of two iodinated tyrosine residues; 7. Inability to release thyroxine and triiodothyronine, from thyroglobulin (genetically determined or lithium); 8. Lack of sensitivity of the target organs due to receptor defects or inadequate conversion into the more effective T₃ decreases T₃/T₄ effectiveness even if T₃/T₄ release is normal or even raised.

Furthermore, mutations of the TSH receptors can change the degree to which the thyroid can be stimulated by TSH. However, genetic defects of receptors and enzymes of T₃/T₄ synthesis are rare.

Two very common causes of hypothyroidism are inflammatory damage to the thyroid gland or surgical removal of the gland (due to thyroid cancer). More rarely hypothyroidism is due to a deficiency of TSH (e.g., in pituitary insufficiency) or of TRH (e.g., in damage to the hypothalamus).

The most common cause of an increased release of thyroid hormone (hyperthyroidism) is long-acting thyroid stimulator (LATS) or thyroid-stimulating immunoglobulin (TSI), an IgG that apparently “fits” into the TSH receptor (Graves’ disease). This results, among other effects, in stimulation of hormonal release and thyroid enlargement. TSH release is suppressed by a high T₃/T₄ level. Other causes of hyperthyroidism are orthotopic or ectopic thyroid hormone-producing tumors, inflammation of the thyroid (thyroiditis), increased release of TSH, or excessive supply of thyroid hormones.

Enlargement of the thyroid gland (goitre) is the result of uncontrolled growth (tumor), or of increased stimulation by TSH or TSI. In this situation release of thyroid hormones can either be reduced (e.g., in marked iodine deficiency and the above-mentioned enzyme defects) or increased (e.g., in Graves’ disease).
A. Causes of Hypothyroidism, Hyperthyroidism and Goitre

1. Iodine deficiency
   - Food
   - Iodine excess, rhodanide, etc.

2. Carrier defect
   - Na⁺

3. Peroxidase deficiency

4. Thyroglobulin
   - Cell proliferation
   - Cell damage by tumor, inflammation etc.

5. Thyroglobulin
   - Coupling
   - Proteolysis

6. Coupling
   - Defective conversion

7. Coupling
   - Genetic defect, iodine excess, lithium

8. Coupling
   - Receptor defect

Target organs, e.g. heart

Goitre

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Effects and Symptoms of Hyperthyroidism

In many tissues the thyroid hormones (T₃, T₄) increase enzyme synthesis, Na⁺/K⁺-ATPase activity and oxygen consumption, leading to an increase in basal metabolism and a rise in body temperature. By stimulating glycolysis and gluconeogenesis, the thyroid hormones cause an increase in blood glucose concentration, while on the other hand also increasing glycolysis. They stimulate lipolysis, the breakdown of VLDL and LDL as well the excretion of bile acids in the bile. They stimulate, via increased oxygen consumption, the release of erythropoietin and thus erythropoiesis. The high 2,3-bisphosphoglycerate (DPG) content in newly formed erythrocytes decreases O₂ affinity and thus favors the peripheral release of O₂. Thyroid hormones sensitize the target organs to catecholamines (especially by an increase in β-receptors) and thus increase, for example, cardiac contractility and heart rate. In addition, they raise intestinal motility and stimulate the transport processes in the gut and kidneys. They promote physical (e.g., longitudinal growth) and mental (especially intellectual) development. T₃ and T₄ stimulate the restructuring of bone and muscle, the catabolic effect predominating and increasing neuromuscular excitability. T₃ and T₄ act mainly through enhanced gene expression, which takes several days. Beyond this their prolonged action is due to the long half-life in blood (T₃ = one day; T₄ = seven days). Maternal T₃ and T₄ are largely inactivated in the placenta and thus have only a slight effect on the fetus.

In hyperthyroidism metabolism and heat production are raised (→ A1). Basal metabolism can nearly double. The affected patients prefer cold ambient temperature; in a hot environment they tend to break into a sweat (heat intolerance). The increased O₂ demand requires hyperventilation and stimulates erythropoiesis. The raised lipolysis leads to weight loss, on the one hand, and to hyperlipidacidaemia, on the other (→ A1). At the same time, the concentrations of VLDL, LDL, and cholesterol are diminished (→ A2). The effects on carbohydrate metabolism (→ A3) favor the development of (reversible) diabetes mellitus. When glucose is given (glucose tolerance test), plasma glucose concentration rises more quickly and more markedly than in healthy people; the rise is followed by a rapid fall (abnormal glucose tolerance). Although the thyroid hormones promote protein synthesis, hyperthyroidism increases proteolytic enzymes, and thus causes excess proteolysis with an increase in urea formation and excretion. Muscle mass is reduced (→ A3). Breakdown in bone matrix can lead to osteoporosis, hypercalcemia, and hypercalciuria (→ A4). As a result of the stimulating action on the heart, cardiac output (CO) and systolic blood pressure are raised (→ A5). Atrial fibrillation may occasionally occur. The peripheral vessels are dilated. The glomerular filtration rate (GFR), renal plasma flow (RPF), and tubular transport are increased in the kidneys (→ A6), while in the liver the breakdown of steroid hormones and drugs is accelerated. Stimulation of the intestinal musculature leads to diarrhea; the increase in neuromuscular excitation to hyperreflexia, tremor, muscular weakness, and insomnia (→ A7). In children, accelerated growth may sometimes occur (→ A4). T₃ and T₄ promote the expression of their receptors and thereby sensitize their target organs to their actions, thus increasing the effects of hyperthyroidism.

In immunogenic hyperthyroidism (Graves’ disease; → p. 280) exophthalmous may be added to the increased effects of thyroid hormones (→ A8); protrusion of the eyes with diplopia, excessive tear flow, and increased photophobia also occur. Its cause lies in an immune reaction against retrobulbar antigens that are apparently similar to the TSH receptors. The result is a retrobulbar inflammation with swelling of the eye muscles, lymphocytic infiltration, accumulation of acid mucopolysaccharides, and an increase in retrobulbar connective tissue. Sometimes similar changes can be found in the pretibial region.
A. Effects and Symptoms of Hyperthyroidism

1. Energy metabolism↑
   - O<sub>2</sub> consumption
   - Lipolysis
   - Protein breakdown
   - Weight loss
   - Hyperactivity

2. Accelerated breakdown of VLDL and LDL, stimulation of bile secretion
   - VLDL↓
   - Cholesterol↓

3. Stimulation of glycogenolysis, gluconeogenesis
   - Hyperglycemia

4. Accelerated growth in children
   - Bone metabolism↑

5. Cardiac contractility↑
   - Stroke volume↑
   - Tachycardia
   - Blood pressure amplitude↑
   - Oxygen consumption↑

6. Stimulation of the heart
   - Vasodilation
   - Erythropoiesis
   - Atrial fibrillation

7. Neuromuscular excitability↑
   - Hyperreflexia
   - Tremor
   - Insomnia
   - Muscle weakness

8. In Grave’s disease:
   - Retrobulbar inflammation
   - Exophthalmos
   - Tear flow
   - Light sensitivity
   - Diplopia

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Effects and Symptoms of Hypothyroidism

For a description of the functions of the thyroid hormones, see p. 282. Metabolism and heat production are reduced in hypothyroidism. Basal metabolic rate may fall by half (→ A1), and the patients easily feel cold (cold intolerance). Oxygen consumption, ventilation, and erythropoiesis are diminished. In addition, the development of anemia is encouraged by the impaired absorption in the gut of iron, folic acid, and vitamin B_{12}. Reduced lipolysis promotes weight increase and hyperlipidemia (VLDL, LDL), while the reduced breakdown of cholesterol to bile acids quickly leads to hypercholesterolemia, and thus favors the development of atherosclerosis (→ A2). Impairment of glycogenolysis and gluconeogenesis can result in hypoglycemia (→ A3). Reduced breakdown of glycosaminoglycans (mucopolysaccharides, mucin) causes them to be deposited in various tissues and a dough-like consistency of the skin, which is why the disease has been called myxedema (→ A4). In addition, fibronectin, collagen, and plasma albumin are deposited in the skin. Reduced transformation of carotene into vitamin A causes hyperkeratosis. Also, because of reduced sweat and sebaceous secretion, the skin is dry and the reduced heat production makes it feel cold. The patient often has a hoarse voice.

Reduced stimulation of the heart by thyroid hormones decreases contractility, heart rate, stroke volume, cardiac output and occasionally also the systolic blood pressure (→ A5). In marked thyroid hormone deficiency heart failure can develop. Pleural and pericardial effusions are common. The rate of breathing is slowed and the ventilatory reaction to hypercapnia and hypoxia is impaired.

The glomeruli and tubules in the kidneys are smaller. Glomerular filtration rate, renal plasma flow, and tubular transport capacity are reduced. Decreased renal elimination leads to water and NaCl retention (→ A6). Due to the accumulation of fat, glycosaminoglycans, NaCl, and water, the patient may look somewhat bloated.

In addition, protein synthesis in the liver is impaired and the breakdown of steroid hormones and drugs is delayed.

The reduced stimulation of the intestinal musculature leads to constipation. Impaired function of the esophageal musculature and of the gastroesophageal sphincter may cause gastric reflux and esophagitis.

The activity and effectiveness of the autonomic nervous system is reduced in hypothyroidism (→ A7). Neuromuscular excitability is also reduced, resulting in abnormal sensory functions, hyporeflexia, loss of appetite, loss of memory, depression, and clouding of consciousness progressing even to coma. These defects are reversible in adults. However, a lack of thyroid hormone in fetuses and neonates will produce irreversible brain damage. The thyroid hormones are necessary for the full development of dendrites and axons, the formation of synapses, myelination, and glial formation—all processes that are absolutely essential for brain development in the fetus and up to two years after birth. Intrauterine deficiency of thyroid hormones thus massively impairs this development. If substitution with thyroid hormones after birth is omitted, brain damage occurs that cannot be reversed by later thyroid hormone administration. Affected children are often deaf.

Furthermore, bone growth is delayed in these children (→ A8). Retarded growth and impaired mental capacity lead to the typical feature of cretinism.

The functional effects of thyroid hormone deficiency are accentuated by a reduced expression of T_{3} and T_{4} receptors.

A T_{3}/T_{4} deficiency disinhibits the formation of TRH and TSH (→ p. 280). TSH not only stimulates the formation of TSH, but also of prolatin, and can thus trigger hyperprolactinemia (→ p. 260). TSH also promotes the growth of the thyroid gland, causing goitre (→ p. 280). Lastly, abnormal release of gonadotropins can impair fertility.
Causes of Diabetes Mellitus

Diabetes mellitus is caused by an absolute or relative lack of insulin that, among other consequences, leads to an increase in plasma glucose concentration (see p. 288 for the way in which insulin acts). The disease was given its name because of the glucose excretion in the urine. The disease can be classified into several types, depending on its cause and course. This classification is useful, even though it is greatly simplified.

In type I (insulin-dependent diabetes mellitus [IDDM], previously called juvenile diabetes; → A) there is an absolute lack of insulin, so that the patient needs an external supply of insulin. The condition is caused by a lesion in the beta cells of the pancreas, as a rule produced by an autoimmune mechanism that may, in certain circumstances, have been triggered by a viral infection. The pancreatic islets are infiltrated by T lymphocytes and autoantibodies against islet tissue (islet cell antibodies [ICA]) and insulin (insulin autoantibodies [IAA]) can be detected. ICA may in some cases be detected years before the onset of the disease. After the death of the beta cells, the ICA again disappear. 80% of patients form antibodies against glutamatedecarboxylase expressed in the beta cells. Type I diabetes mellitus occurs more frequently in the carriers of certain HLA antigens (HLA-DR3 and HLA-DR4), i.e., there is a genetic disposition.

Type II (non-insulin-dependent diabetes mellitus [NIDDM], formerly called maturity-onset diabetes; → B) is by far the most common form of diabetes. Here, too, genetic disposition is important. However, there is a relative insulin deficiency: the patients are not necessarily dependent on an exogenous supply of insulin. Insulin release can be normal or even increased, but the target organs have a diminished sensitivity to insulin.

Most of the patients with type II diabetes are overweight. The obesity is the result of a genetic disposition, too large an intake of food, and too little physical activity. The imbalance between energy supply and expenditure increases the concentration of fatty acids in the blood. This in turn reduces glucose utilization in muscle and fatty tissues. The result is a resistance to insulin, forcing an increase of insulin release. The resulting down-regulation of the receptors further raises insulin resistance. Obesity is an important trigger, but not the sole cause of type II diabetes. More important is the already existing genetic disposition to reduced insulin sensitivity. Frequently, insulin release has always been abnormal. Several genes have already been defined that promote the development to obesity and type II diabetes. Among other factors, the genetic defect of a mitochondrial decoupling protein limits substrate consumption. If there is a strong genetic disposition, type II diabetes can already occur at a young age (maturity-onset diabetes of the young [MODY]).

Reduced insulin sensitivity predominantly affects the insulin effect on glucose metabolism, while the effects on fat and protein metabolism are still well maintained. Thus, type II diabetics tend especially toward massive hyperglycemia without corresponding impairment of fat metabolism (ketoadidosis, → p. 288).

Relative insulin deficiency can also be caused by autoantibodies against receptors or insulin as well as by very rare defects in the biosynthesis of insulin, of insulin receptors, or of intracellular transmission (→ C).

Even without any genetic disposition, diabetes can occur in the course of other diseases, such as pancreatitis, with destruction of the beta cells (pancreas-deprived diabetes; → C), or by toxic damage to these cells. The development of diabetes mellitus is promoted by an increased release of antagonistic hormones. Among these are somatostatin (in acromegaly), glucocorticoids (in Cushing’s disease or stress [so-called steroid diabetes]), epinephrine (in stress), progestogens and choriamnomotropin (in pregnancy), ACTH, thyroid hormone, and glucagon. Severe infections increase the release of several of the above hormones and thus the manifestation of diabetes mellitus (→ C). A somatostatinoma can cause diabetes because the somatostatin secreted by it inhibits the release of insulin.
A. Diabetes Mellitus: Type I

- Viral infection ➔ ? ➔ Autoimmune disease
- Genetic disposition ➔ ? ➔ Destruction of beta cells
- Destruction of beta cells ➔ Absolute insulin deficiency
- Absolute insulin deficiency ➔ Hyperglycemia ➔ Protein breakdown ➔ Lipolysis ➔ Hyperglycemia

TYPE I
10% of all diabetics

B. Diabetes Mellitus: Type II

- Familial disposition ➔ Substrate uptake ➔ Substrate consumption
- Obesity ➔ Fatty acids ➔ Ketone bodies
- Lipolysis ➔ Obesity ➔ Insulin insensitivity ➔ Relative insulin deficiency ➔ Hyperglycemia

TYPE II
90% of all diabetics

C. Other Causes of Diabetes Mellitus

- Abnormal insulin release
- Removal of pancreas
- Pancreatic disease
- Unresponsive receptor ➔ Postreceptor defect
- Severe infections
- Antagonistic hormones (e.g., in pregnancy) ➔ Hyperglycemia

Abnormal insulin release
Removal of pancreas
Pancreatic disease
Unresponsive receptor
Postreceptor defect
Severe infections
Antagonistic hormones (e.g., in pregnancy)
Acute Effects of Insulin Deficiency (Diabetes Mellitus)

Insulin acts to create energy reserves. It promotes the uptake of amino acids and glucose, especially in the muscle and fat cells. In hepatic, muscle, and fat cells (among others) insulin stimulates protein synthesis and inhibits protein breakdown; in the liver and muscles it promotes glycogen synthesis, inhibits its breakdown, stimulates glycolysis, and inhibits gluconeogenesis from amino acids. Also in the liver, insulin promotes the formation of triglycerides and lipoproteins as well as the hepatic release of VLDL. At the same time it stimulates lipoprotein lipase and thus accelerates the splitting of triglycerides into lipoproteins in blood (especially chylomicrons). The free fatty acids and glycerol are then taken up by the fat cells and stored again as triglycerides. Insulin stimulates lipogenesis and inhibits lipolysis in the fat cells. Lastly, it promotes cell growth, increases renal tubular absorption of Na\(^+\), and cardiac contractility. Part of insulin action is mediated by cell swelling (especially antiproteinolysis) and intracellular alkalosis (stimulation of glycolysis, increased cardiac contractility). Insulin achieves this effect by activating the Na\(^+\)/H\(^+\) exchanger (cell swelling and alkalinization), the Na\(^+\)-K\(^+\)-2Cl\(^-\) cotransporter (cell swelling), and Na\(^+\)-K\(^+\)-ATPase. This results in K\(^+\) uptake by the cell and hypokalemia. As glucose is coupled to phosphate in the cell, insulin also reduces plasma phosphate concentration. It further stimulates the cellular uptake of Mg\(^2+\). Insulin also paracrinically inhibits the release of glucagon and thus diminishes its stimulating action on glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis.

In acute insulin deficiency the absence of its effect on glucose metabolism results in hyperglycemia (→ A1). The extracellular accumulation of glucose leads to hyperosmolality. The transport maximum of glucose is exceeded in the kidney so that glucose is excreted in the urine (→ A2). This results in an osmotic diuresis with renal loss of water (polyuria), Na\(^+\), and K\(^+\), dehydration, and thirst. Despite the renal loss of K\(^+\), there is no hypokalemia because the cells give up K\(^+\) as a result of reduced activity of Na\(^+\)-K\(^+\)-2Cl\(^-\) cotransport and of Na\(^+\)-K\(^+\)-ATPase. The extracellular K\(^+\) concentration, which is therefore more likely to be high, disguises the negative K\(^+\) balance. Administration of insulin then causes a life-threatening hypokalemia (→ p. 124). Dehydration leads to hypovolemia with corresponding impairment of the circulation. The resulting release of aldosterone increases the K\(^+\) deficiency, while the release of epinephrine and glucocorticoids exacerbates the catabolism. The reduced renal blood flow diminishes the renal excretion of glucose and thus encourages the hyperglycemia.

The cells further lose phosphate (P\(_i\)) and magnesium that are also excreted by the kidney. If there is an insulin deficiency, proteins are broken down to amino acids in muscles and other tissues. This breakdown of muscles will, together with electrolyte abnormalities, lead to muscular weakness. Prevailing lipolysis leads to release of fatty acids into blood (hyperlipidemia). The liver produces acetoacetic acid and \(\beta\)-hydroxybutyric acid from the fatty acids. Accumulation of these acids leads to acidosis, which forces the patient to breathe deeply (Kussmaul breathing: → A3). Some of the acids are broken down to acetone (ketone bodies). In addition, triglycerides are formed in the liver from fatty acids and incorporated into VLDL. As the insulin deficiency delays the breakdown of lipoproteins, the hyperlipidemia is further aggravated. Some of the triglycerides remain in the liver and a fatty liver will develop.

The breakdown of proteins and fat as well as polyuria will result in weight loss. The abnormal metabolism, electrolyte disorders and the changes in cell volume brought about by changed osmolarities can impair neuronal function and cause hyperosmolar or ketoacidotic coma.

The main effects of relative insulin deficiency are hyperglycemia and hyperosmolality, while in absolute insulin deficiency the consequences of increased proteolysis and lipolysis (ketoacidosis) are added to these effects.
A. Acute Effects of Diabetes Mellitus

1. Glucose excess
   - Gluconeogenesis
   - Ketone bodies

2. Kidney
   - Glucosuria
   - Aminoaciduria
   - Polyuria
   - Electrolyte loss
   - Aldosterone

3. Coma
   - Fruity breath
   - Kussmaul breathing

- Acute insulin deficiency
- Lipolysis
- Weight loss
- Fatty liver
- Muscle weakness
- Amino acids↑
- Glucose excess
- Osmolarity↑
- Acidosis
Late Complications of Prolonged Hyperglycemia (Diabetes Mellitus)

The metabolic abnormalities of inadequately treated relative or absolute insulin deficiency (→ p. 286–289) will in the course of years or decades lead to extensive irreversible changes in the organism. Hyperglycemia plays a central role in this.

Glucose is reduced to sorbitol in cells that contain the enzyme aldose reductase. This hexahydric alcohol cannot pass across the cell membrane, as a result of which its cellular concentration increases and the cell swells (→ A1). Due to an accumulation of sorbitol in the lens of the eye, water is incorporated, impairing lenticular transparency (clouding of the lens [cataract]; → A2). Accumulation of sorbitol in the Schwann cells and neurons reduces nerve conduction (polyneuropathy), affecting mainly the autonomic nervous system, reflexes, and sensory functions (→ A3). To avoid swelling, the cells compensate by giving off myoinositol which then, however, will not be available for other functions.

Cells that do not take up glucose in sufficient amounts will shrink as a result of extracellular hyperosmolarity (→ A4). The functions of lymphocytes that have shrunk are impaired (e.g., the formation of superoxides, which are important for immune defense). Diabetics are thus more prone to infection (→ A5), for example, of the skin (boils) or kidney (pyelonephritis). These infections, in turn, increase the demand for insulin, because they lead to an increased release of insulin-antagonistic hormones (→ p. 286).

Hyperglycemia promotes the formation of sugar-containing plasma proteins such as fibrinogen, haptoglobin, α₂-macroglobulin as well as clotting factors V–VIII (→ A6). In this way clotting tendency and blood viscosity may be increased and thus the risk of thrombosis raised.

By binding of glucose to free amino-groups of proteins and a subsequent, not fully understood, irreversible Amadori reaction, advanced glycation end products (AGEs) are formed. They also occur in increasing amounts in the elderly. A protein network can be formed through the formation of pentosin. AGEs bind to respective receptors of the cell membrane and can thus promote the deposition of collagen in the basement membranes of the blood vessels. The formation of connective tissue is in part stimulated via transforming growth factor β (TGF-β). Additionally, however, the collagen fibers can be changed by glycosylation. Both changes produce thickening of the basement membranes with reduced permeability and luminal narrowing (microangiopathy; → A7). Changes occur in the retina, also as a result of microangiopathies, that ultimately may lead to blindness (retinopathy; → A8). In the kidney glomerulosclerosis (Kimmelstiel–Wilson) develops, which can result in proteinuria, reduced glomerular filtration rate due to a loss of glomeruli, hypertension, and renal failure (→ A9). Because of the high amino acid concentration in plasma, hyperfiltration takes place in the remaining intact glomeruli, which as a result are also damaged.

Together with a rise of VLDL in blood (→ p. 288) and the raised clotting tendency of the blood (see above), hypertension promotes the development of a macroangiopathy (→ A10) that can further damage the kidneys and cause myocardial infarction, cerebral infarction, and peripheral vascular disease.

Lastly, glucose can react with hemoglobin (Hb) to form HbA₁c, whose increased concentration in blood points to a hyperglycemia that has been present for some time. HbA₁c has a higher oxygen affinity than HbA and thus releases oxygen in the periphery less readily (→ A11). The persisting insulin deficiency further leads to a reduction in the erythrocytic concentration of 2,3-bisphosphoglycerate (BPG), which, as allosteric regulator of hemoglobin, reduces its oxygen affinity. The BPG deficiency also results in an increased oxygen affinity of HbA.

Diabetic mothers have a statistically higher chance of giving birth to a heavier than normal baby (→ A12). This may be the result of an increased concentration of amino acids in blood, producing an increased release of somatotropin.
A. Late Complications of Diabetes Mellitus

1. Peripheral vascular disease
2. Placental perfusion (in pregnancy)
3. Impaired nerve conduction
4. Persistent glucose excess (hyperglycemia)
5. Hyperosmolarity
6. Microangiopathy
7. Prone to infection
8. Retinopathy
9. Renal failure
10. Macroangiopathy
11. Osmotic swelling
12. Amino acids

Plate 9.18 Diabetes Mellitus: Late Complications

Photo: Hollwich F. Taschenatlas der Augenheilkunde. 3rd ed. Stuttgart: Thieme; 1987

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Hyperinsulinism, Hypoglycemia

Insulin release is, first and foremost, regulated by glucose (→ A1). Glucose is taken up by the beta cells of the pancreas and metabolized in them. The resulting ATP inhibits the ATP-sensitive K+ channels. Subsequent depolarization opens voltage-dependent Ca2+ channels so that Ca2+ enters the cell. The rise in intracellular Ca2+ concentration then triggers insulin release. The sulfonylureas used as oral antidiabetic drugs stimulate the release of insulin by directly inhibiting the ATP-sensitive K+ channels.

Insulin release is stimulated not only by glucose but also by amino acids (→ A2) and a number of gastrointestinal hormones (glucagon, secretin, gastrin, glucose-dependent insulin-releasing peptide [GIP], and cholecystokinin [CCK]) as well as by somatostatin. The action of gastrointestinal hormones is responsible for the fact that oral intake of glucose results in a greater insulin release than the same amount of glucose introduced parenterally.

Insulin excess is usually the result of too high a dose of insulin or of an oral antidiabetic drug during treatment of diabetes mellitus (→ A3). As a rule overdosage becomes manifest when insulin requirement falls on physical activity. Insulin excess also often occurs in newborn babies of diabetic mothers (→ A4). The high glucose and amino acid concentrations in the mother’s blood will lead intracellularly to stimulation and hyperplasia of the child’s beta cells, so that after birth an inappropriately large amount of insulin is released.

In some people insulin release is delayed, so that the hyperglycemia that develops after the intake of a carbohydrate-rich meal is especially marked. This results in an overshoot of insulin release, which after four to five hours causes hypoglycemia. Frequently such patients later develop diabetes.

In rare cases hypoglycemia is caused by insulin-binding autoantibodies. As a result, insulin is released with some delay from its binding to the antibodies. In even rarer cases, stimulating autoantibodies against the insulin receptors can produce hypoglycemia.

In a number of, altogether rare, genetic defects of amino acid breakdown the concentra-
A. Hyperinsulinism

Hyperinsulinism, Hypoglycemia

After birth:
- Increased insulin release
- Beta cell hyperplasia

In fetuses:
- Amino acids
- Glucose

In diabetic mother:
- Amino acids
- Glucose

Exogenous insulin supply
- Tumors

Insulin-antagonistic hormones, e.g., cortisol

Glucose consumption by physical exercise, tumors

Glucose formation by enzyme defects, alcohol, malnutrition

Activation of sympathetic nervous system
- Sweating
- Tremors
- Tachycardia

Voracious appetite

Abnormal supply to the nervous system
- Loss of consciousness
- Seizures
- Irreversible damage

Hypoglycemia

Insulin

Liver failure

Enzyme defect

Ketone bodies

Lipolysis

Oral antidiabetic drugs

Beta cells of pancreas

Gastrointestinal hormones

After gastric resection
Histamine, Bradykinin, and Serotonin

Histamine (\(\rightarrow A\)) is formed by the tissue mast cells and basophils. Its release is stimulated by antigen–antibody (IgE) complexes (type 1 allergy; \(\rightarrow p. 48, 52\)), activated complement (C3 a, C5 a), burns, inflammation, and some drugs. A rare cause of increased histamine release can be a mast cell tumor. Histamine release is inhibited via cAMP by epinephrine, prostaglandin \(E_2\), and histamine itself.

Histamine causes the endothelial release of NO, a dilator of arteries and veins, via \(H_1\) receptors and a rise in endothelial cellular \(Ca^{2+}\) concentration. Via \(H_2\) receptors it also causes the dilation of NO-independent small vessels. This peripheral vascular dilation can lead to a massive fall in blood pressure, despite the histamine-mediated stimulation of cardiac contractility (\(H_2\) receptors), heart rate (\(H_4\) receptors), catecholamine release (\(H_1\) receptors), and contraction of the larger vessels (\(H_1\) receptors). Histamine increases protein permeability in the capillaries. Plasma proteins are thus filtered under the influence of histamine, the oncotic pressure gradient across the capillary wall falls, and edemas are formed. The edema fluid is lost at the expense of the plasma volume, the resulting hypovolemia contributing to the fall in blood pressure. Edemas of the glottis can cause asphyxia by occluding the airway. Histamine, in addition, promotes contraction of smooth muscle in the intestines, uterus, and bronchi. This results, among other consequences, in increased airway resistance (bronchospasm) and abdominal cramps. By stimulating peripheral nerve endings histamine causes itching. Via \(H_2\) receptors histamine stimulates the secretion of HCl in the stomach. \(H_2\) receptor antagonists are effective in the treatment of gastric ulcers (\(\rightarrow p. 144\)). Histamine is largely responsible for the symptoms of type 1 allergy, such as a fall in blood pressure, skin edema (urticaria), rhinitis, and conjunctivitis.

Bradykinin. The enzyme kallikrein is required for bradykinin synthesis (\(\rightarrow A\)). It is formed from kallikreinogen in inflammations, burns, tissue damage (especially pancreatitis; \(\rightarrow p. 158\)), and on activation of blood coagulation (factor XIIa) as well as under the influence of peptidases and some toxins. Kallikrein promotes its own activation via stimulation of factor XIIa (\(\rightarrow p. 60\)). It is broken down very quickly (in < 1 min) in blood by the action of kininases.

The effects of bradykinin resemble those of histamine, namely vasodilation, increased vascular permeability, fall in blood pressure, tachycardia, increased cardiac contractility, raised catecholamine release, and stimulation of bronchial, intestinal, and uterine contraction. In contrast to histamine, however, bradykinin causes pain at nerve endings. In the gut and glands it promotes secretion, while it acts as a diuretic in the kidneys. Bradykinin also plays a role in inflammations (especially pancreatitis), edemas (especially angioneurotic edema), and pain.

Serotonin. In addition to being formed in the central nervous system (\(\rightarrow p. 350\)), serotonin (\(\rightarrow B\)) is formed in the enterochromaffin cells of the gut, in thrombocytes, proximal tubular cells, and the bronchi. Its release is increased especially in tumors of the enterochromaffin cells (carcinoid).

Serotonin leads to contraction of the smooth muscles in the bronchi, small intestine, uterus, and blood vessels either directly, or via the release of other mediators (prostaglandins, catecholamines). The effects of these actions are, among others, diarrhea, bronchospasm, and a rise in blood pressure. Nevertheless, serotonin can also have a vasodilating effect. Its action on blood vessels can cause headache (migraine). Serotonin promotes the aggregation of thrombocytes; it causes pain, can increase the permeability of peripheral capillaries, and can produce edemas. The sudden flushes that occur with tumors of the enterochromaffin cells are probably due to other mediators (especially kinins, histamine). The cause of endocardial fibrosis associated with tumors of the enterochromaffin cells remains undetermined. As serotonin is broken down in the liver, the systemic symptoms of serotonin-producing intestinal tumors (such as bronchospasm) commonly occur only after they have metastasized to the liver.
A. Histamine and Bradykinin

- Antigens
  - Immunoglobulin E
  - Tumor
  - Mast cell
- Drugs
  - Burns, inflammation
  - Complement
- Factor Xlla, plasmin, trypsin, pepsin, toxin
- Epinephrine
  - cAMP
  - PGE₂
- Kallikreinogen
  - Kallikrein
  - Kallidin
  - Kininogen
  - Kinin

1. Histamine
   - HCl secretion ↑
   - Stimulation of peripheral nerve endings
   - Puritis
   - Pain
   - Vascular permeability ↑
   - Cardiac contractility ↑
   - Tachycardia ↑
   - Catecholamine release ↑
   - Bronchospasm
   - Abdominal cramps
   - Drop in blood pressure
   - Diuresis
   - Onset of hypovolemia
   - Edema

2. Bradykinin
   - Secretion
   - Edema
   - Dopamine release
   - Diuresis
   - Hypovolemia
   - Edema

B. Serotonin

- Tumors in the enterochromaffin intestinal cells
- Liver metastases
- Thrombocytes
- Thrombocyte aggregation

- Vascular damage

- Contraction of muscles of:
  - uterus
  - bronchi
  - vessels

- Intestinal motility
  - Diarrhea

- Bronchospasm
  - Endocardial fibrosis

- Blood pressure ↓
- Blood coagulation

- Migraine
- Edema
Eicosanoids

Eicosanoids are a large group of intracellular and intercellular mediators that are formed from arachidonic acid, a polyunsaturated fatty acid. They are rapidly inactivated in the blood and thus act mainly on their immediate environment.

Arachidonic acid is released from phospholipids of the cell membrane under the influence of the enzyme phospholipase A₂ (\( \rightarrow A1 \)). This enzyme is activated by cell swelling and by an increase of intracellular Ca²⁺ concentration. It is stimulated by a number of mediators, such as histamine, serotonin, bradykinin, and norepinephrine (via \( \alpha \)-receptors). Phospholipase A₂ is inhibited by glucocorticoids (via lipocortin) and epinephrine (via \( \beta \)-receptors).

Arachidonic acid can be transformed to leukotrienes via the enzyme lipoygenase and to prostacyclin (prostaglandin G \([PGE_2]\) via the enzyme cyclo-oxygenase. Substances that can be formed from PGG₂ include thromboxan A₂ (TXA₂), and the prostaglandins \( \text{F}_{2\alpha} \) (PGF₂α, E₂ (PGF₂), and I₂ (PGI₂ = prostacyclin) (\( \rightarrow A3 \)). The enzyme cyclo-oxygenase is inhibited by non-steroidal anti-inflammatory drugs (NSAIDs), for example, acetylsalicylic acid (aspirin). Inflammations and tissue damage cause activation of both cyclo-oxygenase and lipoxygenase, and thus increase the formation of eicosanoids.

The leukotrienes (\( \rightarrow A2 \)) cause the contraction of the smooth muscles in the bronchi, blood vessels, gut, and uterus. They are responsible for lasting bronchoconstriction in asthma; their action on the gut can cause diarrhea and their effects on the uterus can bring about abortion of the fetus. Leukotrienes indirectly increase vascular permeability and thus bring about edemas. They also promote adhesions and chemotaxis and stimulate the release of histamine, oxygen radicals, and lysosomal enzymes as well as of insulin.

TXA₂ is formed largely in thromocytes and is essential for blood clotting. An excess of TXA₂ favors the formation of thrombi. Administration of small doses of the cyclo-oxygenase inhibitor acetylsalicylic acid can thus reduce the risk of myocardial infarction because of its effect of reducing thromocyte aggregation.

\( \text{PGF}_{2\alpha} \) stimulates the release of a series of hormones and the contraction of the smooth muscles of blood vessels, gut, bronchi, and uterus.

\( \text{PGE}_2 \) inhibits the release of hormones and lipolysis, stimulates the contraction of smooth muscles of the gut and uterus; however, it inhibits the contraction of the vascular and bronchial muscles. Cyclo-oxygenase inhibitors can thus cause asthma in an atopic individual (so-called analgesic asthma). The vascular effect can cause persistence of the ductus arteriosus. Conversely, the administration of cyclo-oxygenase inhibitors during the last trimester can cause the premature closure of the ductus arteriosus. \( \text{PGE}_2 \) increases glomerular filtration rate. It raises vascular permeability and thus promotes the development of edemas.

\( \text{PGE}_2 \) and \( \text{PGI}_2 \) aid in the demineralization of the bones (osteolysis). They stimulate the renal formation of renin and, by inhibiting the tubular reabsorption of Na⁺ and water, they produce natriuresis and diuresis. They raise the target level of temperature regulation (fever) and cause pain. The effects of the prostaglandins contribute to a large extent to the symptoms of infection.

\( \text{PGE}_2 \) has an essential, protective role in the stomach by inhibiting the secretion of HCl and pepsin while promoting the secretion of HCO₃⁻ and mucus, which has a protective effect. It also causes vascular dilation. A reduction in \( \text{PGE}_2 \) formation by cyclo-oxygenase inhibitors favors the development of gastric ulcers.

\( \text{PGE}_2 \) also has a protective effect on the renal medulla. Via dilation of the vasa recta it improves \( O_2 \) and substrate availability, and decreases the expenditure of energy by inhibiting NaCl reabsorption.

\( \text{PGE}_2 \) is also of great importance in Bartter’s syndrome, which is due to mutations of the Na⁺-K⁺-2Cl⁻ cotransporter, the luminal K⁺ channels, or the basolateral Cl⁻ channels in the loop of Henle. An excessive local formation of \( \text{PGE}_2 \) is the consequence of the resulting transport defect. The inhibitory action of \( \text{PGE}_2 \) on Na⁺ transport in more distal nephron segments adds to NaCl loss and its vasodilator action causes a profound drop in blood pressure. The affected children can be kept alive only with inhibitors of cyclo-oxygenase.

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A. Eicosanoids

- Bradykinin, epinephrine, serotonin, etc.
- Histamine, serotonin
- Glucocorticoids, epinephrine (β)
- Acetylsalicylic acid, etc.
- Ca²⁺

1. Phospholipase A₂
   - Arachidonic acid
   - Lip-oxygenase
   - Cyclooxygenase

2. Leukotrienes
   - Cell swelling
   - Release of: histamine, insulin, lysosomal enzymes

3. Prostaglandin G
   - Hormone release
   - Lipolysis

- TxÁ∞
- Pgf₂α
- Pge₂
- Pgi₂

- Vascular permeability
- Edema
- Osteolysis
- Diuresis

- Gfr
- Fever
- Pain
- Ulcers

- Bartter’s syndrome
- Transport defect

- Chemotaxis, adhesion
- Release of:
  - Histamine
  - Insulin
  - Lysosomal enzymes

- Contraction of smooth muscles
- Persistent ductus arteriosus
- Blood pressure
- Asthma
- Vomiting, diarrhea
- Abortion

- Thrombus formation
- Hormone release
- Lipolysis

- Vessels
- Bronchial
- Gut
- Uterus

- HCl/pepsin secretion

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Overview

The nervous system receives stimuli from the surroundings and its own body, and also directs the body’s functions by influencing muscle activity and autonomic nervous functions (e.g., vascular tone, sweat secretion).

The sensory signals influence motor and autonomic nervous functions in manifold ways by means of reflexes and complex connections. A few of the signals first reach the primary sensory cortex via the thalamus and there become conscious. These perceived signals are then analyzed, interpreted, evaluated (development of emotions), and in certain circumstances stored (memory) by secondary sensory cortical areas.

The emotions, which arise from current perceptions or items of memory, can bring about motor activity. It is the task of associated cortical areas to plan sensible motor responses. The motoneurons that stimulate the muscle fibers are ultimately activated via basal ganglia, cerebellum, thalamus, and the primary motor cortex.

The sensory, motor, and autonomic nervous systems are closely interconnected at every level, and thus the autonomic nervous system is also under the influence of sensory and motor activity and of the emotions.

Disorders of the nervous system can have many different causes, such as genetic defects, degenerative diseases, tumors, mechanical lesions (trauma), bleeding, ischemia, systemic metabolic disorders (hypoglycemia, hyperglycemia, uremia, liver failure, endocrine disorders, etc.), and electrolyte abnormalities. Other possible causes include drugs, toxins (e.g., heavy metals, alcohol), radiation, inflammation, and infection (viruses, bacteria, prions, autoimmune diseases).

The functions of the effectors in the periphery (sensory receptors, muscles, and organs innervated by the autonomic nervous system; \(\rightarrow A1\)), peripheral nerve conduction \(\rightarrow A2\), spinal cord function \(\rightarrow A3\), and/or the supraspinal nervous system \(\rightarrow A4\) can be impaired as a consequence of nervous system disorders.

Damage to the peripheral effectors \(\rightarrow A1\) leads to disturbance of the particular function, which may be localized (e.g., individual muscles) or generalized (e.g., the entire musculature). Such damage can result in overactivity (e.g., involuntary muscle cramps or inadequate activity of sensory receptors with faulty sensory perceptions), or functional deficits (muscle paralysis or sensory deficits). Even when the sensory receptors are intact, sensory perception, especially via the eyes and ears, may be impaired if the transmission apparatus is defective.

An interruption of peripheral nerve conduction \(\rightarrow A2\) impairs the signals that are propagated in this nerve, but different types of fibers (e.g., myelinated and nonmyelinated) may be affected differently. The result of complete disruption of nerve conduction is flaccid paralysis, loss of sensation and of autonomic regulation in the innervation area of the affected nerve. Analogously, lesions of a spinal nerve affect the corresponding dermatome. Diagnosis of nerve lesions thus requires an exact knowledge of the innervation area of individual nerves and dermatomes (cf. anatomy textbooks).

Lesions of the spinal cord \(\rightarrow A3\) can cause loss of sensory perception and/or autonomic functions as well as flaccid or spastic paralysis. Conversely, abnormal stimulation of neurons can lead to inadequate sensations and functions. The affected areas approximately follow the distribution of the dermatomes.

Lesions in supraspinal structures \(\rightarrow A4\) can also result in deficits or abnormal excitations that are circumscribed both as to function and to body region (e.g., in localized lesions in primary sensory cortical areas). However, more commonly they cause complex disorders of the sensory and motor systems and/or autonomic regulation. Additionally, impairment of integrative cerebral functions such as memory, emotions, or cognition may occur in the course of a variety of diseases.
A. Pathophysiology of the Nervous System (Overview)

1. Peripheral effectors
   - Genetic defects
   - Degenerative diseases
   - Tumors
   - Mechanical lesions
   - Bleeding
   - Ischemia
   - Metabolic disorders
   - Electrolyte disturbances
   - Drugs
   - Poisons
   - Radiation
   - Infections
   - Autoimmune diseases

2. Peripheral nerve conduction
   - Supraspinal structures
     - Motor system
     - Sensory system
     - Vegetative system
     - Area of innervation of peripheral nerves

3. Spinal cord
   - Cervical
   - Thoracic
   - Lumbar
   - Sacral

4. Supraspinal structures
   - Thalamus
   - Primary sensory cortex
   - Primary motor cortex
   - Visual cortex
   - Cerebellum

For example:
- Iliohypogastricus n.
- Ventral intercostal n.
- Saphenous n.

Dermatomes

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Pathophysiology of Nerve Cells

In order to fulfill their function, neurons must be able to receive information from other cells and then pass it on to yet other cells. As a rule the information is received via membrane receptors that are activated by neurotransmitters. The activity of ionic channels is influenced directly or via intracellular mechanisms of transmission. Thus, in suitable target cells acetylcholine (ACh) opens nonspecific cation channels that will then allow the passage of Na⁺ and K⁺. This will lead to depolarization of the cell membrane and thus to opening of the voltage-gated Na⁺ and Ca²⁺ channels. Ca²⁺ ions then mediate the release of neurotransmitters by the target cell. In the long term, cell metabolism and gene expression of the target cell, and thus the formation of synapses and the synthesis and storage of neurotransmitters are also regulated.

Abnormalities can interfere with each element of this cascade (→ A). For example, receptor density can be reduced by down-regulation. Also, certain mechanisms of intracellular transmission can be blocked. An example is the blocking of G proteins by, among others, pertussis toxin (→ A1). Ionic channels can be blocked by drugs, or their activity changed by Ca²⁺, Mg²⁺, or H⁺. Furthermore, their effect on the membrane potential can be distorted by a change in ionic gradients, such as an increase or a decrease in the intracellular or, more importantly, extracellular K⁺ concentration. Both occur when Na⁺/K⁺-ATPase is inhibited, for example, due to energy deficiency. Axonal transport as well as formation, storage, release, and inactivation of neurotransmitters (→ A2) can be impaired, for example, by genetic defects or drugs. Functional abnormalities can be reversible once the damage is no longer effective.

Lesions may also lead to irreversible destruction of neurons. In addition to cell death by direct damage to it (necrosis, e.g., due to energy deficiency or mechanical destruction), so-called programmed cell death (apoptosis) may also play a role in this (→ A3 and p. 12). Neurons cannot be renewed in adults. Thus, the destruction of neurons will cause an irreversible impairment of function, even if other neurons can partly take over the function of the dead cell.

Deleterious substances must pass the blood–brain barrier if they are to reach the neurons of the central nervous system (CNS) (→ B). An intact blood–brain barrier impedes the passage of most substances and prevents pathogens and immunocompetent cells entering (→ p. 356). However, some toxins (e.g., pertussis and botulinus toxins) reach neurons in the spinal cord through retrograde axonal transport via peripheral nerves, and thus avoid the blood–brain barrier (→ p. 356). Some viruses also reach the CNS in this way.

If an axon is transected (→ C), the distal parts of the axon die (Waller degeneration). Axons of central neurons as a rule do not grow outward again, rather the affected neuron dies by apoptosis. Causes include absence of the nerve growth factor (NGF), which is normally released by the innervated, postsynaptic cell and, via the axon, keeps the presynaptic cell alive. Interruption of the retrograde axonal transport in an otherwise intact axon also leads to death of the neuron. The proximal stump of the peripheral axon can grow out again (→ C2). The proteins that are necessary for this to happen are formed within the cell body and are transported to the place of injury by axonal transport. A possible reason for survival of the affected cell is that macrophages migrating into the peripheral nerve, via the formation of interleukin 1, stimulate the Schwann cells to produce NGF. Macrophages are not, however, able to enter the CNS.

Transection of an axon not only causes death of the primarily damaged neuron (→ C1), the absence of innervation often leads to death of the target cell (anterograde transneuronal degeneration) and sometimes also of cells that innervate the damaged cell (retrograde transneuronal degeneration).
A. General Functional Disorders

1. Receptor density
   - Receptor blockade
2. Ion channels blocked
3. Extracellular: K⁺
4. G-protein blocked

Functional disorders

- Formation
- Neurotransmitter
- Storage
- Release
- Inactivation

B. Blood-Brain Barrier

- Blood-brain barrier
- Toxins
- Stimuli
- Immune-competent cells, antibodies

Retrograde axonal transport: 1 m/day

C. Axon Transection and Regeneration

1. Effects of axon transection
   - Myelin disintegration
   - Waller degeneration
   - Anterograde transneuronal degeneration
2. Regeneration in peripheral nerve
   - Nerve Growth Factor
   - Interleukin 1

- Thirdly: Schwann cell takes over NGF synthesis
- Secondly: macrophage stimulates Schwann cell
- Firstly: retrograde NGF transport interrupted

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Demyelination

In myelinated nerves, the axon between two nodes of Ranvier (internodal segment) is surrounded by a myelin sheath (→ A). This is a precondition for salutary conduction of the action potentials, i.e., the “jumping” propagation of excitation from one nodal constriction ($R_1$) to the next ($R_2$). The internodal segment itself cannot generate an action potential, i.e., depolarization of the second node ($R_2$) is completely dependent on the current from the first node ($R_1$). However, the current is usually so strong that it can even jump across the nodes.

Nevertheless, on the way along the internodal segment the amplitude of the current will diminish. First of all, the membrane in the internodal segment must change its polarity, i.e., the membrane capacitance must be discharged, for which a current is needed (→ A, green arrow). Secondly, current can also escape through individual ionic channels in the axonal membrane (orange arrow). However, myelination of the internodal segment causes the membrane resistance ($R_m$) to be elevated and the capacity ($C_m$) of the membrane condensor to be reduced (→ A, left).

The resistance of the axonal membrane of the internodal segment is very high because of the low density of ionic channels there. Furthermore, the perimembranous space is insulated by a layer of fat from the free extracellular space. The low capacitance of the condensor is due to the large distance between the interior of the axon and the free extracellular space as well as the low polarity of the fatty material in the space between them.

Demyelination (→ A, right) can be caused by degenerative, toxic, or inflammatory damage to the nerves, or by a deficiency of vitamins $B_6$ or $B_{12}$. If this happens, $R_m$ will be reduced and $C_m$ raised in the internodal segment. As a result, more current will be required to change the polarity of the internodal segment (green arrow) and, through opening up the ionic channels, large losses of current may occur (orange arrow).

If, after the losses in the internodal segment, the current generated at $R_1$ is not adequate to depolarize $R_2$ to the threshold level, excitation is interrupted, even though the axon is completely intact. High frequency of action potentials and low temperature favor interruption of conduction because of decreasing sensitivity of the node $R_2$ (→ A1). Minor lesions of the internodal segment can lead to slowing of conduction, because it can no longer jump across nodes and the next node has to be depolarized to its threshold before the excitation is passed to the afferent nodes (→ A2). The resulting slowing may not be the same in different fibers, so that temporal dispersion of the signal may occur. Lastly, the damaged site may itself trigger action potentials, especially when the axon has concomitantly suffered spontaneous damage or is under mechanical pressure (→ A3); excitation can jump across two neighboring damaged nerve fibers (ephaptic transmission; → A4), or conduction may run retrogradely (→ A5).

Genetic defects of the myelin-sheath protein (e.g., protein $O$ [P$_o$ of peripheral myelin protein 22 (PMP 22)]) or of gap junctions in the Schwann cells (connexin 22) lead to certain hereditary peripheral neuropathies (Charcot–Marie–Tooth syndrome, Dejerine–Sottas syndrome, Pelizaeus–Merzbacher disease).

The most important demyelinating disease is multiple sclerosis (→ B). It is more common in women than men, familial aggregation sometimes occurs, and it has a higher incidence among carriers of HLA3 and HLA7. It is an autoimmune disease that may be triggered by a viral infection and is characterized by demyelinating inflammatory foci (→ B1). The typical feature of multiple sclerosis is the temporally unrelated occurrence of completely different neuronal deficits, caused by lesions in different parts of the brain. Some of the lesions may partly regress when the local inflammatory process has subsided and the nerves (in the case of intact axons) have been remyelinated. The example in B2 illustrates that at first there is a fully reversible loss of vision due to a damaged optic nerve (→ p. 326), followed by a partly reversible sensory loss when the sensory tracts of the spinal cord are affected (→ p. 318). Finally, ataxia sets in when the cerebellum becomes involved (→ p. 316).
A. Development and Effects of Demyelination

![Diagram of Demyelination](image)

- **Stimuli**
- **Action potentials**

1. Myelin sheath
2. Small leakage currents
3. Propagation of action potential
4. Demyelination
5. Large leakage currents

B. Multiple Sclerosis

![Diagram of Multiple Sclerosis](image)

- **Autoimmune disease, possibly caused by viruses**
- **Genetic disposition**
- **Demyelinating foci in spinal cord (after Netter)**
- **Demyelination in CNS**
- **Multiple sclerosis**

1. Periodically recurrent neuronal losses
2. Example of the course of the disease

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Disorders of Neuromuscular Transmission

Neuromuscular transmission is a sequence of events (→ A) that can be interrupted at various levels. The action potential is carried along by activation of the Na\(^+\) channels to the nerve ending, where it depolarizes the cell membrane and thus opens the voltage-gated Ca\(^{2+}\) channels. The Ca\(^{2+}\) ions that enter the nerve ending mediate the fusion of acetylcholine (ACh)-containing vesicles with the presynaptic membrane, whereupon ACh is released into the synaptic cleft. ACh binds to receptors of the subsynaptic membrane and in this way opens nonspecific cation channels. The depolarization of the subsynaptic membrane is transmitted to the postsynaptic membrane where, through opening of voltage-gated Na\(^+\) channels, an action potential is initiated that rapidly spreads over the entire muscle membrane. ACh is broken down by acetylcholinesterase; the choline which has been split off is again taken up into the nerve ending and used again for the synthesis of ACh.

Abnormalities can affect any element of this process. Local anesthetics, for example, inhibit the voltage-gated Na\(^+\) channels of the neuron and thus interrupt nerve transmission to the end-plate. The Ca\(^{2+}\) channels can be blocked by antibodies (see below). Botulinus toxin inactivates synaptobrevin, the protein responsible for binding the ACh-containing vesicles to the plasma membrane and thus for the release of ACh. The ACh receptors can also, like the Ca\(^{2+}\) channels, be blocked by antibodies which furthermore accelerate the internalization and breakdown of the receptors. The receptors can also be blocked by curare that, without itself having an effect, competitively inhibits the binding of ACh to the receptors.

Succinylcholine (suxamethonium chloride) leads to continuous stimulation of the receptors, continuous depolarization of the postsynaptic membrane, and thus to an inactivation of the postsynaptic Na\(^+\) channels. In this way it can, like curare, block neuromuscular transmission. In low concentrations, substances that inhibit acetylcholinesterase (e.g., physostigmine) increase neuromuscular transmission by increasing the availability of ACh in the synaptic cleft. In high doses, however, they inhibit neuromuscular transmission be-

cause high concentrations of ACh, as of succinylcholine, cause continuous depolarization of the subsynaptic membrane and so inactivate the postsynaptic Na\(^+\) channels. The re-uptake of choline into the nerve ending can be inhibited by Mg\(^{2+}\) and hemicholine.

The most important disease affecting the end-plates is myasthenia gravis, a muscle paralysis that results from blockage of neuromuscular transmission (→ B). It is caused by antibodies against the ACh receptors in the subsynaptic membrane which accelerate the breakdown of the receptors (→ B1). This autoimmune disease can be caused by infection with viruses that have an ACh-receptor-like structure. Myasthenia may also occur in patients with a benign tumor of the thymus. The formation of such antibodies is favored in those who express special subtypes (DR3 and DQw2) of the major histocompatibility complex (MHC class II). In patients with myasthenia gravis, repetitive stimulation of a motor nerve will at first cause the production of a normal summated muscle action potential whose amplitude will, however, decrease through progressively increasing “fatigue” of neuromuscular transmission (→ B2).

Another autoimmune disease that impairs neuromuscular transmission is the pseudo-myasthenic syndrome of Lambert and Eaton (→ C). This condition often arises in patients affected by a small-cell carcinoma of the lung. Ca\(^{2+}\) channels in the plasma membrane of the tumor cells sensitize the immune system and stimulate the formation of antibodies that also react with the Ca\(^{2+}\) channels of the end-plate (→ C1). Due to inhibition of the Ca\(^{2+}\) channels, the summated muscle action potential is at first small, but is progressively normalized, because with the repetitive stimulation increasing amounts of Ca\(^{2+}\) are accumulated in the nerve endings (→ C2).
A. Disorders of Neuromuscular Transmission

- Action potential
- Local anesthetics
- Botulinus toxin
- Antibodies
- Suxamethonium
- Phystostigmine
- Curare
- Muscle cell
- Contraction
- Na⁺
- Ca²⁺
- ACh
- ACh-esterase

B. Myasthenia Gravis

- Viral infection
- Genetic disposition
- DR3, DQw2
- Thymoma
- Sensitization against ACh receptor-like structure
- Antibody formation

C. Pseudomyasthenic Syndrome

- Lung carcinoma
- Sensitization against Ca²⁺ channels of the tumor cells
- Antibody formation

1. Repetitive stimulation
2. 1mV
3. 50ms

Myasthenia gravis
Lambert-Eaton myasthenic syndrome
Diseases of the Motor Unit and Muscles

The motor unit consists of the motoneuron (α-motoneuron in the spinal cord or the cranial nerves), the associated axon, and all the muscle fibers innervated by its collaterals. The function of the motor unit can be affected by disease of the motoneuron, by interruption or delay of axonal conduction, or by disease of the muscle (→ A).

The α-motoneurons can be infected by poliovirus and irreversibly destroyed by it. Also in spinal muscular atrophy, a group of degenerative diseases largely of unknown cause, these cells are destroyed. Amyotrophic lateral sclerosis (ALS) may be caused primarily by a disorder, partly genetic, of axonal transport that secondarily leads to the death of spinal α-motoneurons and supraspinal motoneurons (→ A1).

Damage to or death of axons may, among others causes, be due to autoimmune diseases, a deficiency of vitamin B₁ or B₁₂, diabetes mellitus, poisoning (e.g., lead, alcohol), or genetic defects (e.g., Charcot–Marie–Tooth syndrome; → p. 302) (→ A2).

The musculature (→ A3) can also be affected by autoimmune diseases (e.g., dermatomyositis). In addition, genetic defects may involve the musculature, for example, in myotonia or dystrophy (see below).

Lesion of a motor unit causes paralysis of the affected muscles, regardless of whether it is localized in an α-motoneuron, axon, or the muscle itself (→ A). In primary death of an α-motoneuron fasciculations typically occur. They are the result of synchronous stimulation and contraction of the muscle fibers of a motor unit. In ALS the destruction of the supraspinal neurons may result in hyperreflexia and spasticity (→ p. 310), as long as some of the α-motoneurons are still intact. A lesion of a peripheral nerve which has reduced the thickness of the myelin layer will result in a slowing of the nerve’s conduction velocity (→ p. 302). As a rule, sensory parts of the nerve are also affected. This leads to abnormal sensory functions as well as spontaneous action potentials in the damaged nerves, resulting in corresponding sensations (paresthesias). In primary death of muscles fibrillations often occur, i.e., uncoordinated contractions of individual muscle fibers.

Genetic ionic channel defects (→ B) are the cause of a group of functional muscle diseases. Normally (→ B1) depolarization of the muscle cell membrane is triggered on excitation by a voltage-gated Na⁺ channel that causes the opening of a voltage-gated Ca²⁺ channel (→ p. 304) and a Ca²⁺ channel of the sarcoplasmic reticulum. As a result, intracellular Ca²⁺ is increased, mediating muscular contraction. Repolarization is achieved by inactivation of the Na⁺ channels, by Cl⁻ influx, and K⁺ efflux. This causes the inactivation of the Ca²⁺ channels so that the intracellular Ca²⁺ concentration again falls and the muscle relaxes.

Delayed inactivation of the Na⁺ channel due to mutation in the gene for the channel protein can lead to delayed relaxation, increased excitability, and cramps (Na⁺ channel myotonia and congenital paramyotonia; → B2). Cold further slows Na⁺ channel inactivation such that cramps occur, particularly in paramyotonia when the muscle gets cold. An additional defect of the Na⁺ channel or a defective K⁺ channel (?) can cause paralysis when the extracellular concentration of K⁺ is high (hyperkalemic periodic paralysis). A genetic defect of the voltage-gated Ca²⁺ channel also leads to hypokalemic periodic paralysis. If there are defects in the Cl⁻ channels, myotonia occurs. Depending on the severity of the molecular defect, inheritance of the disease is dominant (congenital myotonia, Thomsen’s disease) or recessive (Becker’s myotonia). In certain defects of sarcoplasmic Ca²⁺ channels the volatile halogenated anesthetics may bring about potential-independent activation of these channels with an increase in intracellular Ca²⁺. The resulting massively increased energy metabolism causes hyperthermia (malignant hyperthermia; → p. 22).

In Duchenne’s or Becker’s degenerative muscular dystrophy (→ C; → p. 307) dystrophin, an element of the cytoskeleton, is defective. The responsible gene is on the short arm of the X chromosome. The disease occurs practically only in males, because in females with one defective gene the dystrophin formed from the normal gene is sufficient. In Duchenne’s dystrophy only short, completely functionless dystrophin fragments are formed
A. Diseases of the Motor Unit

- Amyotrophic lateral sclerosis
- Spinal muscular atrophy
- Poliomyelitis
- Autoimmune
- Metabolic (B₁, B₁₂ deficiency, diabetes mellitus)
- Toxic (lead, alcohol)
- Genetic (Charcot-Marie-Tooth syndrome)

1. Death of supraspinal neurons → Hyperreflexia, spasticity
   - Paralysis
2. Death of α-motoneurons → Fasciculation
   - Paralysis
3. Slowing of conduction velocity, disorders of sensory functions (sensory loss, paresthesias)
   - Paralysis

B. Myotonias

1. Action potential
   - Depolarization normal
   - Repolarization normal

2. Action potential
   - Na⁺ channel myotonia, congenital paramyotonia, periodic hyperkalemic paralysis
   - Periodic hypokalemic paralysis
   - Congenital myotonia (Thomsen, Becker)
   - Periodic hyperkalemic paralysis

C. Muscular Dystrophies

1. Xp21 defect
   - Defective dystrophin
   - Disordered gait
   - Becker’s dystrophy
   - Milder course of disease

2. Normal dystrophin molecule
   - Disordered gait
   - Severe muscle dystrophy

- Respiratory muscle
- Respiratory failure, heart failure
- Lordosis
- Calf muscle hypertrophy
- Malignant hyperthermia

- Duchenne’s dystrophy
  - Fatal course within 20 years

(Drawing by Duchenne)
The disease ends in death during the first 20 years of life. Hypertrophied yet weak calf muscles and marked spinal lordosis due to muscular weakness are typical for this form of dystrophy. In Becker’s dystrophy the dystrophin is also defective, but its function is less impaired and the disease therefore less severe (→ C2; → p. 307).

**Diagnosis of Motor Unit Diseases**

A primary myopathy can be distinguished from a neurogenic myopathy by electromyography (→ D).

This is carried out by putting a needle into the muscle and measuring the potential difference from an indifferent electrode on the surface of the skin. As the tip of the intramuscular electrode is largely extracellular, only a fraction of the potential difference across the cell membrane is measured. The amplitude of the recorded changes in potential depends on the number of muscle fibers near the inserted electrode that are depolarized simultaneously.

As all muscle fibers that are innervated by one α-motoneuron are depolarized at the same time, the **amplitude** of the recorded changes in potential is greater, the higher the density of such fibers is near the electrode. Because the various α-motoneurons are not depolarized simultaneously, the **frequency** of the changes in potential is a measure of the **number of α-motoneurons** that innervate the muscle fibers near the electrode.

Normally those muscle fibers in a muscle that are innervated by one α-motoneuron do not lie next to each other, but are distributed over a larger cross-sectional area (→ D1). If muscle fibers are destroyed (myogenic myopathy; → D2), the number of muscle fibers near the electrode decreases. This results in a **decreased amplitude of the deflection**. If an α-motoneuron is destroyed (neurogenic myopathy; → D3), the muscle fibers innervated by it do not atrophy evenly, but some of them are taken over by collaterals of neighboring α-motoneurons. The motor units thus get larger, as does the amplitude of the potential changes. However, the **frequency of the deflections is reduced** because the muscle fibers near the electrode are now innervated by fewer motor units.

An important pointer to the presence and progression of a muscle disease is provided by the concentrations of creatine, creatinine, and creatine kinase in blood (→ E). Creatine is formed in the liver and is eagerly taken up by the intact muscles. Some of the creatine is transformed in the muscles into the anhydride creatinine which, contrary to creatine, easily crosses the cell membrane and is quantitatively excreted by the kidney. The amount of creatinine excreted in the urine per unit of time is thus proportional to the functioning muscle mass. If, as a result of muscular dystrophy, muscle mass is reduced, creatinine excretion decreases (→ E1). In acute cell destruction intracellular creatine kinase and creatine are released and their plasma concentrations rise steeply. If there is no further cell destruction, the plasma concentration of creatine kinase drops to normal, but the concentration of creatine may remain elevated, because the creatine formed in the liver is now taken up by fewer muscles. However, creatine production also falls, as it is inhibited by creatine through a feedback mechanism. As a result, plasma concentration or renal excretion of creatine do not parallel the reduction in muscle mass.
D. Electromyography

- **α-motor neuron**
- **Muscle fiber**
- **Electrode**

1. Normal electromyogram

2. Myogenic myopathy

3. Neurogenic myopathy

Death of individual muscle fibers
Death of individual motoneurons
Reinnervation

E. Creatine Metabolism

- **Liver**
- **Creatine**
- **Creatinine**

Creatine in plasma
Creatinine in urine
Creatine kinase in plasma

Death of muscle cells
Muscle dystrophy

Normal excretion:
Creatine 0 g/day
Creatinine 1.8 g/day
Lesions of the Descending Motor Tracts

Spinal \( \alpha \)-motoneurons are controlled by several supraspinal neuronal tracts (→ A1):
- the pyramidal tract (violet) from the motor cortex;
- the rubrospinal tract from the red nucleus (red);
- the medial reticulospinal tract from the pontine reticular formation (orange);
- the lateral reticulospinal tract from the medullary reticular formation (brown); and
- the vestibulospinal tract (green).

The medial reticulospinal and the vestibulospinal tracts predominantly promote the activity of the so-called antigravity muscles, i.e., the muscles that flex the arms and stretch the legs. The pyramidal, rubrospinal, and lateral reticulospinal tracts, on the other hand, predominantly promote the activity of the flexors of the leg and extensors of the arms.

If the motor cortex or the internal capsule is damaged (e.g., by bleeding or ischemia in the area supplied by the middle cerebral artery), impulse transmission in the immediately adjacent descending cortical tracts is interrupted. These make up the pyramidal tract and other connections of the motor cortex, such as those to the red nucleus and to the medullary reticular formation. The result is a reduced activity not only of the pyramidal tract but also of the rubrospinal and medial reticulospinal tracts. The vestibulospinal and medial reticulospinal tracts are less affected, because they are under stronger noncortical influence, for example, from the cerebellum. An interruption of transmission in the area of the internal capsule thus ultimately results in an excessive activity of the extensors in the legs and the flexors in arms (→ A2).

At first, however, spinal shock will set in due to cessation of supraspinal innervation of \( \alpha \)-motoneurons (→ A3a). The antigravity muscles are also affected, less so than the other muscles though, by the reduced supraspinal activation of the \( \alpha \)-motoneurons. In spinal shock the muscles are flaccid and no reflexes are elicited (areflexia).

However, partial “denervation” of the \( \alpha \)-and \( \gamma \)-motoneurons as well as of interneurons leads to a gradual increase in sensitivity of these neurons. In addition, the endings of supraspinal neurons that are out of action are replaced by synapses with the spinal cord neurons (→ A3b). As a consequence, the reflexes gradually gain a stronger influence on the activity of the \( \alpha \)-motoneurons, and hyperreflexia occurs.

Another consequence is spasticity. After loss of function of the descending tracts, the activity of the \( \alpha \)-motoneurons comes under the increasing influence of the muscle spindles and Golgi tendon organs (→ A4). Stretching the muscle spindles stimulates the \( \alpha \)-motoneurons of the same muscle via a monosynaptic reflex; the increased influence of the muscle spindles results in massive contraction on stretching. Nevertheless, the response of the muscle spindles is mainly phasic, i.e., if they are stretched slowly or continuously their activity slowly decreases. As a result, the influence of the Golgi tendon organs becomes dominant: when the muscle is stretched they inhibit muscle contraction via an inhibiting interneuron. It is also under the influence of the Golgi tendon organs that on slow or continuous stretching the muscle will suddenly become flaccid after initial increase in tone (clasp-knife effect).

The predominance of the stretching muscles leads to extension of the big toe on stroking the sole of the foot (→ A5), instead of its normal plantar flexion. This is called Babinski’s sign or the Babinski reflex. It is taken as evidence for a lesion in the pyramidal tract. In fact the Babinski reflex is the result of a lesion of several descending cortical tracts, including the pyramidal tract. Isolated damage of the pyramidal tract (extremely rare) results in neither spasticity nor the Babinski reflex, but only minor disturbance of fine movement.

If the red nucleus has been destroyed (e.g., due to ischemia of the mid-brain or in Wilson’s disease [→ p. 252]), coarse tremor will result. Neurons of the red nucleus are, among other functions, important for the dampening of oscillations that can occur as a result of a negative feedback in the control of \( \alpha \)-motoneurons. In lesions of the vestibular nucleus abnormalities of balance with vertigo, nystagmus, and nausea predominate (→ p. 330).
A. Lesions of the Descending Tracts

1. Red nucleus
2. Flexor
3. Spinal shock
4. Stretching
5. Babinski's sign

Damage by bleeding, ischemia, etc.

Motor cortex

Pyramidal tract

Midbrain

Reticular formation

Cerebellum

Vestibular nucleus

Reticulospinal tract

Vestibulospinal tract

Medulla

Vestibular nucleus

Reticulospinal tract

Vestibulospinal tract

C6

Extensor

Extensor

Flexor

α-motoneuron

Clasp-knife effect

Normal

Power

Time

Spasticity

Areflexia

Regeneration

Hyperreflexia

Spinal shock

Extensor

Flexor

α-motoneuron

Babinski's sign

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Diseases of the Basal Ganglia

The basal ganglia are made up of:
- the corpus striatum (consisting of the caudate nucleus and the putamen);
- the inner and outer globus pallidus (pallidum, consisting of an internal and an external part);
- the subthalamic nucleus; and
- the substantia nigra (pars reticulata [p.r.] and pars compacta [p.c.]).

Their function is mainly to control movement in conjunction with the cerebellum, motor cortex, corticospinal tracts, and motor nuclei in the brain stem.

Striatal neurons are activated, via glutamate, by neurons of the cortex. The internal interconnections of the basal ganglia (→ A) are mainly provided by the inhibitory transmitter γ-aminobutyric acid (GABA). Ultimately the basal ganglia have an inhibitory effect on the thalamus via GABAergic neurons in the inner pallidum and the substantia nigra (p.r.). These neurons are activated via glutamate from the neurons of the subthalamic nucleus. Finally, the striatal neurons are partly activated and partly inhibited by dopamine from the substantia nigra (p.c.), and also activated via cholinergic neurons. An imbalance between inhibitory and activating influences has a harmful effect on motor functions: too strong an inhibition of the thalamic nuclei has a hypokinetic, too little has a hyperkinetic effect.

Parkinson’s Disease

Parkinson’s disease is a disease of the substantia nigra (p.c.) which via dopaminergic tracts influences GABAergic cells in the corpus striatum. The cause is frequently a hereditary disposition that in middle to old age leads to degeneration of dopaminergic neurons in the substantia nigra (→ B1). Further causes are trauma (e.g., in boxers), inflammation (encephalitis), impaired circulation (atherosclerosis), tumors and poisoning (especially by CO, manganese, and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP], which was once used as a substitute for heroin). The cell destruction probably occurs partly by apoptosis; superoxides are thought to play a causal role. For symptoms to occur, over 70% of neurons in the substantia nigra (p.c.) must have been destroyed.

The loss of cells in the substantia nigra (p.c.) decreases the corresponding dopaminergic innervation of the striatum (→ B1). This leads, first of all, to disinhibition of glutamatergic neurons in the subthalamic nucleus and thus to an increased activation in the internal part of the pallidum and of the pars reticulata of the substantia nigra. Secondly, the dopaminergic activation of the striatal neurons ceases. It normally directly inhibits neurons in the substantia nigra (p.r.) and the internal part of the pallidum. Together these processes ultimately lead to excessive inhibition of the thalamus (GABA transmitter).

Inhibition of the thalamus suppresses voluntary movement (→ B2). Patients have difficulty initiating movement or can do so only as a reaction to external stimuli (hypokinesia). Muscle tone is greatly increased (rigor). In addition, resting tremor (4–8 per second) is common, with alternating movements especially of the hands and fingers (a movement similar to that used when counting money). Hypokinesia typically forces the patient to adopt a moderately bent posture with slightly angulated arms and legs. It also leads to a rather rigid facial expression, micrographia, and soft, monotone, and indistinct speech. Finally, other disturbances occur, for example, increased salivation, depression, and dementia. These are caused by additional lesions (death of neurons in the nucleus of the median raphe, of the locus coeruleus, or of the vagus nerve).

In treating Parkinson’s disease (→ B3) the attempt is made to increase the dopamine formation of the nigrostriatal neurons by administering L-dopa, a precursor of dopamine (which cannot itself pass the blood–brain barrier). Amphetamines can stimulate the release of dopamine as well as inhibit the reuptake of dopamine in the nerve endings. This also increases the synaptic concentration of dopamine. Finally, dopamine breakdown can be delayed by inhibitors of monoaminooxidase (MAO inhibitor) or the effect of dopamine can be imitated by dopamine-like drugs.

In addition to increasing dopamine formation or its effect, transplantation of dopamine-
A. Basal Ganglia

The diagram shows the flow of signals from the cortex to the striatum, globus pallidus, thalamus, and substantia nigra, and further to the brainstem and spinal cord. The diagram highlights the connections between these structures and the neurotransmitters involved.

B. Parkinson's Disease

1. Genetic defect
   - Trauma, inflammation, reduced perfusion, poisoning

2. Cell death in substantia nigra
   - Dopamine deficiency

3. Treatment
   - L-Dopa
   - MAO inhibitor
   - Dopamine agonists

Symptoms of Parkinson's disease include:
- Rigidity
- Tremor at rest (not constantly)
- Hypokinesia
- Facial rigidity
- Salivary flow, sweating
- Depression
- Quiet, monotonous speech
- Bent posture
- Hypokinesia

The diagram illustrates the processes involved in the treatment of Parkinson's disease, focusing on the role of L-Dopa and MAO inhibitors in managing the disease.

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producing cells into the striatum has been tried with the aim of increasing local dopamine concentration. The symptoms of Parkinson’s disease can also be improved by inhibiting cholinergic neurons in the striatum. These neurons stimulate those striatal neurons that are normally inhibited by dopamine.

Glutamate antagonists and lesions of the subthalamic nucleus or the internal part of the pallidum can also cause disinhibition of the thalamus, and thus an improvement in the clinical picture of the disease. Attempts have also been made to delay the apoptotic death of the nigrostriatal neurons by means of antioxidatively-acting drugs and of growth factors.

Hyperkinesias

Chorea is the most common hyperkinetic disease of the basal ganglia. It is largely a disease of the striatum.

The inherited variant of the disease (Huntington’s chorea; →C1) becomes manifest in the fourth or fifth decade of life and leads to an irreversible progressive destruction of striatal neurons. The responsible gene is on the short arm of chromosome 4. It is thought that the genetic defect results in the cellular increase of a protein (huntingtin) that is difficult to break down. Cell death is accelerated by the effect of the excitatory neurotransmitter glutamate, which stimulates neurons by activating calcium-permeable ionic channels. The cell is damaged by excessive entry of Ca²⁺.

In Sydenham’s chorea, contrary to Huntington’s chorea there is largely reversible damage to the striatal neurons (→C2). It is caused by the deposition of immunocomplexes in the course of rheumatic fever, and it occurs mainly in children.

In rare cases the striatal neurons have been damaged by ischemia (atherosclerosis), tumor, or inflammation (encephalitis).

The result of the destruction of striatal neurons is chiefly an increased inhibition of neurons in the subthalamic nucleus that normally activate inhibitory neurons in the substantia nigra (p.r.). This leads to disinhibition of cells in the thalamus, resulting in sudden, erratic, and involuntary movements that are normally suppressed by the basal ganglia.

Hemiballism. After destruction of the subthalamic nucleus (by ischemia or tumor) sudden flinging movements occur. They are thought to be due to decreased stimulation of inhibitory GABAergic neurons in the internal part of the pallidum and substantia nigra (p.r.). It leads to disinhibition of neurons in the thalamus.

Tardive dyskinesia (dystonia) is caused by longer-term treatment with neuroleptics, which displace dopamine from receptors (→D2). These drugs are used as antipsychotics (→p. 352). They cause sensitization of those neurons that express increased numbers of dopamine receptors in the subsynaptic membrane. The activity of the subthalamic nucleus is suppressed via disinhibition of neurons in the external part of the pallidum. Nonactivation of the subthalamic nucleus and increased inhibition by striate neurons decrease the activity of neurons in the internal part of the pallidum and in substantia nigra (p.r.). This results in disinhibition of the thalamus and involuntary movements. In addition to the increased expression of receptors, apoptosis of those neurons that are normally inhibited by dopamine is also important.

Lesions of the striatum and pallidum additionally lead to athetosis, a hyperkinesia marked by excruciatingly slow, screw-like movements. Lesions in the pallidum and thalamus cause dystonia (prolonged torsions and twists; also regarded as proximal athetosis).
C. Chorea

Genetic defect

Glutamate

Glutamate action

Ca^{2+} inflow

Irreversible degeneration

Huntington’s chorea

Sydenham’s chorea

Rheumatic fever

Deposition of immune complexes

Reversible cell damage

Involuntary movements

Chorea

D. Hemiballism and Tardive Dyskinesia

Ischemia, tumor

Flinging movements

Hemiballism

Cell death in the subthalamic nucleus

Thalamus

Pallidum

Substantia nigra

Treatment with neuroleptics

Receptor density

Dopaminergic overstimulation

Involuntary movements

Tardive dyskinesia

Dopamine

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Lesions of the Cerebellum

Lesions of the cerebellum may be caused by poisoning (especially by alcohol, but also DDT, piperazine, 5-fluorouracil, lithium, or diphenylhydantoain), heat stroke, hypothyroidism, malabsorption as well as by genetic defects of enzymes or transport (hexosaminidase, glutamate dehydrogenase, pyruvate dehydrogenase, α-oxydation, DNA repair, transport of neutral amino acids), partially hereditary degenerative processes, inflammation (e.g., multiple sclerosis [p. 302], viruses, prions), cerebellar and extracerebellar tumors (paraneuplasia; p. 16). In hereditary Friedreich’s ataxia, cerebellar function is indirectly affected, for example, by degeneration of the spinocerebellar tracts. The effects of cerebellar lesions depend on their location.

The lateral cerebellar hemispheres (cerebrocerebellum; A, yellow) store programs for voluntary movements (manual dexterity). In voluntary movements, associative cortical areas (A1) activate, via pontine nuclei (A2), neurons in the hemispheres (A3) whose efferent impulses (orange) project, via the dentate nucleus (A4) and thalamus (A5), to the motor cortex (A5). From here spinal motoneurons are activated via the pyramidal tract (violet). Lesions in the hemispheres or in structures connected with them thus impair initiation and planning of movements.

The intermediate part of the hemisphere (spinocerebellum, light blue) is mainly responsible for the control of movement. Via spinocerebellar afferents (blue) it receives information about the state of the motor apparatus. Neurons of the spinocerebellum project to the red nucleus (A9) and thalamus via the nuclei emboliformis and globosus (A8). Spinal motoneurons are influenced by the red nucleus via the rubrospinal tract and by the thalamus via the motor cortex and the pyramidal tract. Disorders of the spinocerebellum impair the execution and control of voluntary movements.

The vestibulocerebellum, comprising flocculus and nodulus and portions of the vermis (bright green), is responsible for control of balance. Neurons in the flocculus receive direct afferents from the vestibular organ (A10). In addition, the flocculus, nodulus, and vermis receive direct afferent signals via spinocerebellar fibers (A7) as well as information on the movements of the eye muscles. The neurons of this part of the cerebellum project directly to the vestibular nucleus (A11) as well as via the nuclei fastigii (A12) to the thalamus, to the reticul formation (A13), and to the contralateral vestibular nucleus (A14). Spinal motoneurons receive impulses via the vestibulospinal and reticulospinal tracts, via the thalamocortical and corticospinal tracts. Lesions in the flocculus, nodulus, and vermis mainly affect balance and body posture as well as the muscles of the trunk and face.

Clinical manifestations of lesions in the cerebellum are delayed onset and stoppage of movements. There are no coordinated movements (dyssynergia) and often the required force, acceleration, speed, and extent of movements is misjudged (dysmetria). The patient cannot immediately withdraw the muscle action when a resistance is suddenly reduced (rebound phenomenon), nor able to perform rapid and consecutive antagonistic movements (dysdiadochokinesia). An intention tremor (3–5 oscillations per second) develops on moving the hand toward an object, the oscillations becoming increasingly marked the nearer the object gets. Movements are discontinuous and divided into separate components (decomposition of movement). Less active resistance is exerted against passive movements (hypotonia). On holding an object the muscle tone cannot be maintained, and patients can only stretch out their arms for a relatively short time (positioning attempt). Muscle stretch reflexes are diminished (hyporeflexia).

Speech is slow, explosive, staccato, and slurred. The control of balance is disturbed; patients stand with their legs apart and walk uncertainly (ataxia). Sitting and standing are also made more difficult by tremors of the trunk muscles (titubation, 2–3 oscillations per second). Abnormal control of the eye muscles causes dysmetria of the eye movements and coarse nystagmus (p. 330) in the direction of the lesion. It increases when patients direct their gaze toward the lesion and decreases when their eyes are closed.
A. Lesions of the Cerebellum

Intoxication (e.g. alcohol), heat stroke, degeneration, tumors, malabsorption, hypothyroidism, inflammations (multiple sclerosis etc.)

Hemisphere
Control of voluntary movements

Medial part
Regulation of movement

Ataxia of distal joint movements, intention tremor, decomposition of movement

Functional areas of the cerebellum

Flocculus, nodulus, vermis
Control of balance

Hypotonia, nystagmus, scanning speech, stumbling gait, standing with legs apart, uncertain gait (ataxia), disturbed balance

Afferent tracts

Efferent tracts

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Abnormalities of the Sensory System

Specialized receptors (sensors) of the skin are stimulated by touch (mainly Meissner bodies), pressure or tension (mainly Ruffini bodies), vibration (mainly Pacini bodies), hair movement (hair follicle receptors), or temperature (cold and heat receptors). Stretch receptors (proprioceptors) in muscles (muscle spindles), tendons (Golgi tendon organs) and joint capsules transmit information about motor activity, while receptors in various internal organs provide information about stretching of hollow organs and concentration of certain substances (CO₂, H⁺, glucose, osmolarity). Pain stimuli are perceived by nociceptors (free nerve endings) in the skin, motor apparatus, internal organs, and vessels (→ p. 320).

Sensory impulses are transmitted to the spinal cord and there influence the activity of motoneurons via reflexes. Via the dorsal column (fine, so-called epicritical mechanoreceptors, muscle spindle afferents, etc) and the anterolateral column (gross mechanoreceptors, temperature, pain) they are transmitted to the medulla oblongata, thalamus, and cortex (postcentral gyrus). Information about movements reach the cerebellum via the spino-cerebellar tracts. The flow of information can be interrupted at various levels.

Receptors that transform different stimuli in the periphery into neuronal activity may cease functioning or may be inadequately stimulated (→ A1). This results in complete or partial absence of sensory perception (anesthesia or hypesthesia), enhanced perception (hyperesthesia), or sensory perception without adequate stimulus (paresthesia, dysesthesia).

Lesions in the peripheral nerves or spinal nerves can also cause anesthesia, hypesthesia, hyperesthesia, paraesthesia or dysesthesia, but also simultaneously influence proprioception and motor functions (→ A2). Because of overlapping innervation areas, lesions of the spinal nerves merely cause hypesthesia (or hyperesthesia) but not anesthesia of the affected dermatome.

Spinal cord. Hemisection of the spinal cord (Brown–Squard’s syndrome; → A3), will result in ipsilateral loss of proprioception and of epicritical surface sensations and contralateral loss of gross mechanoreceptor function, temperature and pain sensation (dissociated disorder of sensation). Additionally, there will be ipsilateral loss of the descending motor functions (lower motoneuron paralysis; → p. 310).

An interruption in the dorsal column (→ A4) stops adequate vibratory sensation and diminishes the ability to precisely define mechanical stimuli in space and time, and accurately to determine their intensity. Proprioception is also affected, which means that it is mainly information from the muscle spindles which is impaired, and thus the control of muscular activity. One of the effects is ataxia. In a lesion within the dorsal tracts their topographical arrangement is of importance. The cervical tracts lie most posterior, the sacral ones medial.

A lesion in the anterolateral tract (→ A5) especially impairs pressure, pain, and temperature sensation. Anesthesia, hypesthesia, hyperesthesia, paraesthesia and dysesthesia may occur. Movements of the vertebral column can, by stimulating the damaged afferent nerves, cause corresponding sensations (Lhermitte’s sign: sudden, electric shock-like, paresthesia in upper limbs and trunk on forward neck flexion).

Lesions in the somatosensory cortex (→ A6) impair the ability to separate sensations in time and space; the sense of position and movement have been lost, as has the ability to judge the intensity of a stimulus.

Lesions in the association tracts or cortical areas (→ A7) lead to abnormal processing of sensory perception. This results, for example, in the inability to recognize objects by feeling or touching them (astereognosis) and topognosis (inability to identify the exact spot where a sensation is felt). Abnormalities of body image and position may also occur. Another function that may be lost is the ability to discriminate between two simultaneously presented stimuli (deletion phenomenon). Hemineglect (ignoring the contralateral half of the body and its environment) may also result from such a lesion.
A. Disorders of the Sensory System

1. Receptor abnormalities
   - Anesthesia, hypesthesia, dysesthesia, hyperesthesia, paresthesia

2. Peripheral nerve
   - All modalities

3. Hemisection of spinal cord
   - Dissociated disorders of sensory perception
   - Loss of and abnormal excitation: pressure, temperature, pain

4. Posterior column
   - Lesion in the associative cortex
   - Abnormal processing of sensory perceptions

5. Anterior column
   - Lesion in the somatosensory cortex
   - Abnormal functions relating to discrimination and further sensory processing

6. Spinal cord
   - Proprioception and surface sensibility
   - Pain, pressure, temperature
   - Posterior spinocerebellar tract
   - Anterior spinocerebellar tract

7. Internal organs
   - Posterior column
   - Anterior column

Skin
Muscle
Internal organs
Spinal cord
Cerebellum
Reticular formation
Medulla oblongata
Thalamus

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Pain

Pain stimuli are received by nociceptors in the skin and the viscera which are excited by high-intensity, non-noxious stimuli (distension, temperature) as well as by tissue lesions (→ A). Necrotic cells release K⁺ and intracellular proteins. An increase in extracellular K⁺ concentration depolarizes the nociceptors, while the proteins and, in some circumstances, infiltrating microorganisms may cause an inflammation. As a result, pain-producing mediators are released (→ p. 294 ff.). Leukotrienes, prostaglandin E₂, and histamine sensitize the nociceptors so that even otherwise subthreshold noxious and harmless stimuli can produce pain (hyperalgesia or allodynia). Tissue lesions also activate blood clotting and thus the release of bradykinin and serotonin (→ p. 294). If there is vascular occlusion, ischemia occurs and the resulting extracellular accumulation of K⁺ and H⁺ further activates the sensitized nociceptors. The mediators histamine, bradykinin, and prostaglandin E₂ have a vasodilator effect and increase vascular permeability. This results in local edemas; the tissue pressure rises and this also stimulates the nociceptors. Their stimulation releases the peptide substance P (SP) and the calcitonin gene-related peptide (CGRP), which promote the inflammatory response and also produce vasodilatation and increase vascular permeability.

Vasoconstriction (by serotonin), followed by vasodilatation, is probably also responsible for migraine attacks (recurring severe headache, often unilateral and associated with neurological dysfunctions due, in part at least, to cerebral vasomotor abnormalities).

Afferents from organs and the surface of the skin are intertwined in parts of the spinal cord, i.e., the afferent nerves converge upon the same neurons in the spinal cord (→ B). Excitation of the nociceptors in an organ then triggers pain sensations in those areas of the skin whose afferents make connections in the same spinal cord segment (referred pain; → B1). In myocardial infarction, for example, pain radiates into the left shoulder and left arm (Head’s zones).

Projected pain is produced by stimulation of a nerve (e.g., of the ulnar nerve in the ulnar sulcus; → B2). The perception of pain is projected to the innervation area of the nerve. A special form of projected pain is phantom pain of an amputated limb or part thereof. In neuralgia, continued abnormal stimulation of a nerve or posterior root results in chronic pain in the area of innervation.

The impulses along the afferent nerves synapse in the spinal cord and pass via the anterolateral tracts to the thalamus and from there to, among others, the somatosensory cortex, the cingular gyrus, and the insular cortex (→ C). Appropriate connections produce various components of pain sensation: sensory (e.g., perception of localization and intensity), affective (ailment), motor (protective reflex, muscle tone, mimicry), and autonomic (changes in blood pressure, tachycardia, pupillary dilatation, sweating, nausea). The connections in the thalamus and spinal cord are inhibited by the descending tracts from the cortex, midbrain periaqueductal gray matter, and raphe nucleus; these tracts employ norepinephrine, serotonin, and especially endorphines. Lesions of the thalamus, for example, can produce pain through an absence of these inhibitions (thalamus syndrome).

To counteract pain, the activation of pain receptors can be inhibited, for example, by cooling of the damaged area and by prostaglandin synthesis inhibitors (→ C1). The transmission of pain can be inhibited by cooling and by Na⁺ channel blockers (local anesthetics; → C2). Transmission in the thalamus can be inhibited by anesthesia and alcohol (→ C5). Attempts have now and again been made to interrupt pain transmission by means of surgical nerve transaction (→ C6). Electroacupuncture and transcutaneous nerve stimulation act via activation of the descending, pain-inhibiting tracts (→ C3). The endorphine receptors are activated by morphine and related drugs (→ C4). Endogenous pain-inhibiting mechanisms can be aided by psychological methods of treatment.

An absence of pain brought about by pharmacological means or the very rare congenital condition of congenital analgesia interrupt these warning functions. If the cause of the pain is not removed, the consequences can be life-threatening.
A. Peripheral Mechanisms of Pain

Injury → Pathogen → Inflammation → Blood clotting → Necrosis → Ischemia → Proteins → Proteins

Histamine → Bradykinin → Serotonin → Leukotrienes → Serotonin

PGE₂ → Vasodilation, vascular permeability → Edema formation → Tissue pressure → Nociceptors → Pain

Leukotrienes → Sensitization → CGRP, SP

B. Referred Pain

Converging neurons → Pain sensation

1 Referred pain

Infarction

2 Projected pain

Contusion

3 Phantom pain

C. Pain Relief

Perception → Suffering

Anesthesia, alcohol → Thalamus

Morphine → Central grey matter

Electroacupuncture, transcutaneous nerve stimulation → Raphe nuclei

Cooling, Na⁺ channel blocker → Associated autonomic reaction, motor response

Cooling, PGE synthesis inhibitor → Anterior column

Inhibitory pain tract → Tissue pressure → Edema formation → Tissue pressure → Nociceptors → Pain

CGRP, SP → CGRP, SP
Diseases of the Optical Apparatus of the Eye

The optical apparatus of the eye serves to project a sharp image of outer objects onto the retina. The most common abnormalities of the image-projecting apparatus are inadequate refraction, abnormal regulation of the internal pressure of the eye (in glaucoma), and lack of transparency of the light-refracting system (especially in cataract).

Abnormalities of refraction (→ A). Viewed objects are not focussed onto the retina.

- In myopia the bulb of the eye is usually too long for refraction (axial myopia). Less frequently refraction is too strong (refractive myopia). As a result, the light that originates from distant objects does not converge onto the retina, and thus distant objects do not produce sharp images on the retina. The anomaly can be corrected by means of a concave lens.

- In hyperopia the bulb is either too short (axial hyperopia) or the refraction too low (refractive hyperopia). As a result, light that originates from a near object can no longer converge on the retina and near objects are not seen clearly. The abnormality can be corrected by means of a convex lens.

- The plasticity of the lens deteriorates with age and thus also its maximal curvature on near accommodation. This results in presbyopia, the inability to see near objects clearly. A convex lens is necessary for viewing near objects, although it has to be removed when looking at distant ones.

Astigmatism (→ B). The surface of the eye is not perfectly spherical. In regular astigmatism the curvature’s radiuses in the horizontal and vertical axes are different; and an upright square is imaged as a rectangle. This abnormality can be corrected by means of a cylindrical lens. A minor form (< 0.5 diopter) of regular astigmatism, with increased refraction in the vertical direction, is normal. In oblique astigmatism the normally horizontal and vertical axes are oblique to one another. In irregular astigmatism the corneal surface is irregular, for example, due to a corneal scar, which can be corrected by a contact lens (more recently by laser treatment).

Glaucosa. The pressure within the eyeball (ca. 10 – 20 mmHg) results from the equilibrium between the secretion of fluid into the anterior chamber (ca. 4 µl/min) within the ciliary body and its outflow from the chamber via the trabecular network at the edge of the chamber (the iridocorneal angle) into Schlemm’s canal (→ C). An increase in the intraocular pressure (high pressure glaucoma) can be due to impaired outflow of aqueous humor (the usual cause) or (more rarely) increased production of aqueous humor. Among the causes of an impaired outflow are thickening of the trabecular network or narrowing of the chamber angle. The latter is often narrowed if the bulb is shallow (marked axial hyperopia) or by an increase in lens thickness with age. Widening of the pupil further narrows the angle when the base of the iris is broadened, as happens in the dark and through sympathetic nervous stimulation.

The high intraocular pressure gradually but irreversibly damages the optic nerve, leading to visual field defects that start around (Marianne’s) blind spot and in the nasal periphery (→ C2). Attempts at treating the defects involve lowering the intraocular pressure by narrowing the pupil (parasympathetic drugs) and reducing aqueous production. Aqueous humor secretion, like the reabsorption of HCO₃⁻ in the kidney’s proximal tubules (→ p. 96 ff.), requires the action of carbonic anhydrase and can be reduced by carbonic anhydrase inhibitors. Even without a rise in pressure, damage to the optic nerve typical of glaucoma can occur (low-pressure glaucoma), probably due to reduced blood perfusion.

Cataract. The transparency of the lens is, among other factors, dependent on a strictly regulated water content. In diabetes mellitus a high glucose concentration brings about glycosylation of proteins (advanced glycation end-products [AGE]) (→ C3). Similar products also accumulate with age. In diabetes mellitus there is also an accumulation of sorbitol in the lens (→ p. 290). Irregular hydration and a change in connective tissue proteins bring about clouding or opacification of the lens (cataract; → C3).
A. Refraction Abnormalities

<table>
<thead>
<tr>
<th>Proximity</th>
<th>Distance</th>
<th>Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal 24.4 mm</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Short-sightedness (myopia)
- Long-sightedness (hyperopia)
- Long-sightedness of the elderly (presbyopia)

B. Astigmatism

- Regular
- Oblique
- Irregular

C. Glaucom and Cataract

- Increased production:
  - Aqueous humor
  - Intraocular pressure

- Damage to optic nerve
- Clouding of the lens

- Visual field defects

- Increased production:
  - Aqueous humor
  - Sympathetic nerve stimulation

- Diabetes mellitus
  - Sorbitol
  - AGE

- Galactosemia
Diseases of the Retina

The receptors of the retina (→ A 1 b) are rods (Rs) and three different types of cones (Cs). The latter mediate the color sense (red, green, blue; see below) and are particularly numerous at the site of sharpest vision (fovea centralis). The rods mediate black and white vision and particularly predominate in the retinal periphery. The light-sensitive outer segments of the photoreceptors are renewed regularly, while the residues of the pigment epithelial cells are phagocytized. The photoreceptors transmit their excitation via bipolar cells (Bps) to the ganglion cells (Gs). Amacrine cells (Ams) and horizontal cells (Hcs) form cros-connections between photoreceptors, bipolar cells and ganglion cells (→ A 1 a).

If phagocytosis of the pigment epithelial cells is impaired, metabolic products accumulate and the photoreceptors degenerate (retinitis pigmentosa; → A 2). Macular degeneration that occurs in childhood (Stargardt’s disease) is due to a genetic defect of an ATP-binding transport protein (ABCR) that is normally expressed in the outer segment of the photoreceptors. A defect of this transporter can disturb the normal turnover of the outer segments. Heterozygote carriers of the genetic defect suffer from increasing macular degeneration as they grow older.

Electroretinogram (ERG). When light falls on the retina, potential differences can be recorded between the cornea and an indifferent electrode on the ear (→ A 3). Sudden exposure to light at first generates an a-wave, the summation of potential changes at the receptors. It is followed by a b-wave due to potential changes in the bipolar cells and glial cells, and a c-wave due to potential changes in the pigment epithelium. When the light is turned off, a d-wave is registered (off-effect), the sum of the potential changes in the photoreceptor and bipolar cell membranes (reversed potential).

Occlusion of the central artery causes death of the amacrine cells, bipolar cells and ganglion cells and thus blindness. However, the receptors and pigment epithelium survive because they are supplied with adequate oxygen by the choroid vessels. In the ERG the b-wave is thus absent, but the a-wave and c-wave are preserved. In retinal detachment from the pigment epithelium no deflections are registered in the ERG. If the retina is completely detached, the patient is totally blind.

Diabetic retinopathy (→ B) is the most common disease of the retina. The cells around the thin retinal blood vessels (pericytes) produce sorbitol from the increased supply of glucose (→ p. 290), swell up, and thus narrow the vessels. Additionally, the vessel walls are thickened by glycosylation (AGE; → p. 290). This results in ischemia of the tissues, formation of angiotrophic mediators, increase in vascular permeability, formation of new vessels, and hemorrhages. This bleeding opacifies the vitreous body, the ischemia destroys the retina and may ultimately lead to blindness.

Night blindness. The visual pigment consists of 11-cis-retinol, a metabolite of vitamin A and a protein that is different in the rods and the three types of cones (→ C 1). In vitamin A deficiency the formation of visual pigment in rods and cones is impaired, resulting in reduced light perception especially at low light intensity.

The function of the cones is to provide color vision. The pigments of the red, green, and blue cones each have different spectral sensitivities. Mutations of the genes for the respective pigments impair color vision. Partial or complete loss of the particular pigment (→ C 2) leads to weak red color vision or red color blindness (protanomaly or protanopia, respectively), green color weakness or blindness (deuteranomaly or deuteranopia), or blue color weakness or blindness (tritanomaly or tritanopia). As the genes for the red and green pigments are located on the X chromosome, many more men than women suffer from red or green color blindness.

If there are no cones, not only is there no color vision, but visual acuity is also greatly reduced, because the person can see only with much fewer rods in the fovea (rod monochromasia).

Color vision can be tested e.g. with tables in which the numbers can be correctly recognized only by means of the corresponding cones (→ C 3).
**A. Diseases of the Retina**

- Retinitis pigmentosa
- Macular degeneration
- Retinal detachment
- Phagocytosis
- Degeneration of the photoreceptor cells
- Cell death
- Blinding

**B. Diabetic Retinopathy**

- Diabetes mellitus
- Capillary
- Glucose
- Sorbitol
- AGE
- Thickening of capillary wall
- Vessel narrowing
- Ischemia
- Vessel proliferation
- Bleeding

**C. Night Blindness and Color Blindness**

- Vitamin A deficiency
- all-trans-vitamin A
- 11-cis-vitamin A
- Meta-rhodopsin
- 11-cis-retinal
- Rhodopsin
- Light perception
- Night blindness

**Visual pigment deficiency**

**Red blindness** (protanopia)

**Green blindness** (deuteranopia)

**Test charts**

- Protanopia: no number
- Deuteranopia: no number

**Plate 10.14 Diseases of the Retina**

Photo: Hollwich F. Taschenatlas der Augenheilkunde. 3rd ed. Stuttgart: Thieme; 1987

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Visual Pathway and Processing of Visual Information

The information from both eyes is transmitted to the visual cortex via the visual pathway (→A). On each side the visual tracts cross over in the optic chiasm from the nasal half of the retina, while the nerves from the temporal sides pass on without crossing over. After synapsing in the lateral geniculate body of the thalamus, the information reaches the primary visual cortex in the occipital lobe. A lesion in the temporal part of the retina of the left eye causes a deficit in the nasal half of this eye’s visual field (→A1). If the optic nerve of the left eye is interrupted, the entire visual field of this eye is lost (amaurosis; →A2). Interruption of the pathway in the optic chiasm especially affects the crossing fibers, the consequence being that the lateral portion of the visual field is lost in both eyes (bitemporal hemianopsia, “blinker blindness”; →A3). Complete lesion of the optic tract on the left results in loss of the right half of the visual field in both eyes (homonymous hemianopsia; →A4). Homonymous anopsia also results from destruction of the lateral geniculate body. Interruptions in the optical radiation (e.g., upper and lower quadrant anopsia; →A5, 6) and in the primary visual cortex (→A7; see below) lead to further characteristic visual field deficits, depending on their localization.

Pupillary reflex. The afferent fibers from the retina serve not only the flow of visual information to the visual cortex, but also to promote the contraction of the pupillary sphincter via the pretemporal area of the mid-brain and the oculomotor nerve (acetylcholine). Conversely, the pupils are widened by contraction of the pupillary dilator muscles stimulated by sympathetic fibers (→B1). When light is shone into one eye, not only is the pupil of this eye constricted (direct reaction), but also that of the other eye (consensual reaction; →B2). If one eye is blind, both pupils remain dilated when light is shone into the blind eye (→B3b). However, when light is shone into the healthy eye, the pupil of the blind eye constricts consensually (→B3b). If the patient has a unilateral lesion of the oculomotor nerve (→B4a), the pupil of the diseased eye remains dilated to light, but there is consensual contraction of the pupil of the healthy eye (→B4b). Yet if there is a loss of sympathetic stimulation, the pupil is also constricted in the dark (→B5); under massive sympathetic stimulation it is dilated even under the influence of light (→B6). If the lesion is in the region of the pretemporal area, the pupils remain dilated even under the influence of light, but they are constricted by near-response (light-near dissociation; →B7a,b).

Loss of the primary visual cortex (→C) results in an inability consciously to perceive visual stimuli, even though the retina, thalamus, and subcortical visual centers are intact and, for example, pupillary reflexes are maintained (cortical blindness). The phenomenon of blindsight is caused by lesions in the visual cortex: the person can point at the source of the localized light flash without being conscious of the flash of light. The ability depends on connections between the subcortical visual centers and the somatomotor areas.

If there are lesions in the occipitotemporal association fields, neither objects (object agnosia), faces and facial expressions (prosopagnosia), nor colors (achromatopsia) can be recognized.

Lesions in the occipitotemporal association fields can, in addition, lead to hemineglect, a condition in which perceptions from one half of a room or the body are ignored. It is more marked with lesions of the right hemisphere (ignoring objects on the left hand side) than those of the left hemisphere, because the right hemisphere is dominant in spatial orientation. In addition, such patients are often incapable of perceiving the movement of objects (akinetopsia).

With lesions in the visual association fields, faulty spatial and three-dimensional perception also often occurs, objects being perceived as distorted (dysmorphopsia, metamorphopsia), as too small (microopsia), or too large (macropsia). Other lesions cause asynesthesia (inability to combine different properties of one object).

If the connection from the visual cortex to area 39 is interrupted (→p. 345), the patient is no longer able to read (alexia).
A. Visual Field Defects

B. Pupillary Reactions

C. Abnormalities of Visual Processing
Hearing Impairment

Sound waves are transmitted from the ear-drum (tympanum) via the ossicles to the fenestra vestibuli (vestibular window) (→A). The transmitting apparatus in the middle ear acts as an impedance converter. Without it 98% of sound energy would be reflected away because of the markedly different resistances to the sound waves in the air and in the fluid of the inner ear. Invagination of the fenestra vestibuli results in simultaneous evagination of the fenestra cochleae (cochlear window). The eardrum normally protects the latter against external sound waves and conducts the sound energy specifically toward the fenestra vestibuli. Sound waves can also be transmitted to the bones of the skull and can thus stimulate the inner ear. However, this requires a much greater energy of sound.

The oscillation of the fenestra vestibuli produces traveling waves in the inner ear, at first spreading along the scala vestibuli. The stereocilia of the outer and inner hair cells are bent by evagination of the cochlear septum with the basilar membrane and the organ of Corti at a frequency-dependent location (→B1). This leads to the opening of K⁺ channels in the cell membrane. The endolymph in which the stereocilia of the hair cells are suspended (→B2) has a very high K⁺ concentration (ca. 150 mmol/L). K⁺ is secreted by the epithelial cells of the stria vascularis, by Na⁺–K⁺–2 Cl⁻ cotransport and by Na⁺/K⁺-ATPase in the antiluminal membrane, as well as by a luminal K⁺ channel (→B3). When the K⁺ channels in the membrane of the hair cells are opened, K⁺ enters the cells and depolarizes them. This depolarization then triggers the release of the transmitter, especially in the inner hair cells. By contracting, the outer hair cells increase the local traveling wave and thus the amount of stimulation of the hair cells.

Causes of deafness. A tear in the eardrum, a lesion in the ossicles, or immobilization of the conduction apparatus, for example, caused by a purulent middle ear infection, dampen transmission to the fenestra vestibuli. Furthermore, if there is a hole in the drum, the fenestra cochleae is no longer protected. This results in middle ear hearing loss. While conduction through the air is impaired, bone conduction remains normal (→A).

The hair cells can be damaged by sound stress (i.e., impingement of too loud a sound for too long) and ischemia. But thanks to its high glycogen content they can survive short periods of ischemia by anaerobic glycolysis. Hair cells can also be damaged by certain drugs—such as amino-glycoside antibiotics and the chemotherapeutic agent cisplatin—that, via the stria vascularis, are accumulated in the endolymph. This results in inner ear hearing loss that affects air and bone conduction equally (→B4). Both the hearing threshold and the active component of basilar membrane displacement are affected, so that discrimination of different higher-frequency tones is impaired (→B5). Lastly, inadequate depolarization of the inner hair cells can produce an unusual and disturbing sound sensation (subjective tinnitus). This can also be caused by inadequate excitation of neurons in the auditory pathway or the auditory cortex.

Stiffening of the basilar membrane disturbs the micromechanics and thus probably contributes to hearing loss in the elderly (→B1).

Inner ear deafness can also be the result of abnormal endolymph secretion. Thus loop diuretics at high dosage not only inhibit renal but also auditory Na⁺–K⁺–2 Cl⁻ cotransport. In addition, there is a known (but rare) genetic defect of the luminal K⁺ channel. The channel, which consists of two subunits (IsK/KvLQT1), is also expressed in the heart (as well as other organs), where it participates in repolarization. A defect of KvLQT1 or IsK results not only in deafness but also in delayed myocardial repolarization (long QT interval [Jervell, Lange-Nielsen syndrome]). Abnormal absorption of endolymph can also cause deafness. The endolymph space becomes evacu-ated, distorting the relationship between hair cells and tectorial membrane (endolymph edema; →B6). Finally, increased permeability between the endolymph and perilymph spaces may be responsible for Ménière’s disease, which is characterized by attacks of deafness and vertigo (→B7).
A. Conductive Hearing Loss

- Purulent middle ear infection
- Lesion of the ossicles
- Tear in eardrum

B. Inner Ear Hearing Loss

- Sound, ischemia, toxins
- Age
- Basilar membrane stiffness
- Loop diuretics
- Disorder of endolymph secretion
- Genetic defect of K⁺ channel
- Disorder of endolymph absorption
- Endolymph edema
- Increased permeability

Hearing loss

Level of sound pressure (dB SPL)

Frequency (kHz)

Normal

Bone conduction

Air conduction

Menière’s disease

Deafness

Vertigo

Disorder of endolymph absorption

Endolymph edema

Increased permeability
Vestibular System, Nystagmus

In order to maintain positional equilibrium the organism requires information about the movement of the endolymph in the semicircular canals, the position of the statoliths in the inner ear (in relation to gravity), the position and tension of the body’s musculature as well as the retinal image in relation to the activity of the eye muscles (→ A). On turning the head the eye muscles normally move in such a way that a stable picture is transiently maintained on the retina (→ A1). As soon as maximal displacement of the head is obtained, the eye is returned in jolt-like movements of restoration and a new point in the environment is fixed (optokinetic nystagmus). All this information is processed in the vestibular nucleus and the cerebellum, and in turn such information influences the eye muscles via the oculomotor and abducens nerves. An abnormality of the sense of balance can occur in damage to the semicircular canals and the maculae of the membranous labyrinth (ischemia, trauma, inner ear infection, Ménière’s disease [→ p. 328]), the cerebellum (intoxication, genetic defects, degenerative disease, inflammation [→ p. 316]), the thalamus (ischemia), and the cerebral cortex (ischemia, epilepsy [→ p. 338]). False information leads to inadequate movement of the eye muscles (nystagmus), and thus to roving of the surrounding objects on the retina (the room spins). Dizziness occurs and, via connections with autonomic neurons, nausea and vomiting. However, these disturbances are usually quickly compensated if there is prolonged loss of one of the organs in the vestibular system.

Olfaction

Sensory cells in the olfactory mucosa transmit different qualities of odor, namely flowery, ethereal, musky, camphoric, foul, sweaty, and stinging. Their axons pass through openings in the cribiform plate to the olfactory bulb (→ B). From there the information reaches the olfactory cortex via the olfactory tract and is then transmitted to the hypothalamus, the amygdaloid bodies, and, via the thalamus, to the cortex (frontal lobe and insular cortex). The olfactory sense may be lost in circulatory disorders, for example, in a nasal cold, nasal malformation, foreign body, tumor, hematoma, or abscess (conductive hyposmia). The sensitivity of the sensory cells is increased by estrogens and decreases in the elderly. It is reduced by genetic defects, some drugs (e.g., cocaine, morphine), and toxins (e.g., cement dust, lead, cadmium, cyanide, chlorine compounds). The axons of the sensory cells can be torn by fracture in the region of the cribiform plate. The central processing of olfactory sensations is impaired by neurodegenerative disease (Alzheimer’s disease [→ p. 348], Parkinson’s disease [→ p. 312 ff.],) inflammation, tumors, alcohol, epilepsy (→ p. 338) and schizophrenia (→ p. 352). This results in reduced (hyposmia) or absent (anosmia) sense of smell, or increased (hyperosmia), inadequate (parosmia), or unpleasant (cacosmia) olfactory sensation.

 Taste

Taste receptors in the tongue, palate, and throat transmit the modalities sweet, sour, salty, and bitter. The information is transmitted to the solitarius nucleus via the facial (VII), glossopharyngeal (IX), and vagus (X) nerves (→ C). After connecting with second-order neurons, the afferent fibers pass via the thalamus to the primary taste cortex in the region of the insula. Taste receptors may be genetically defective or damaged by radiation or some drugs (e.g., local anesthetics, cocaine, penicillamine, streptomycin). Their sensitivity is reduced in hyperthyroidism. Patients with diabetes mellitus suffer from a reduction in the ability to sense sweet tastes; those with an aldosterone deficiency cannot sense salty tastes. The chorda tympani of the facial nerve may be damaged by a skull fracture or inflammation as well as damage to or operation on the ear, while the glossopharyngeal nerve may be damaged during tonsillectomy. Central conduction and processing can be affected by tumors, ischemia, and epilepsy, causing a reduction or loss of gustatory sense (hyposgeusia or ageusia, respectively). The sense of taste may also be increased (hypergeusia), inadequate (parageusia), or unpleasant (dyseusia).
A. Disturbance of Balance, Nystagmus

- Vertigo
- Nystagmus
- Nausea
- Eye movement

Genetic defects, degeneration, inflammation
Menière’s disease, ischemia, trauma, ear infection, temperature changes
Epilepsy
Ischemia

B. Abnormalities of the Sense of Smell (Olfaction)

- Trauma
- Neurodegeneration, inflammation, epilepsy, tumors, alcohol, schizophrenia
- Genetic receptor defects, drugs, toxins
- Conductive hyposmia
- Sex hormones, age

C. Abnormalities of the Sense of Taste

- Nerve lesions
- Genetic defects, radiation, drugs, diabetes, aldosterone deficiency
- Ischemia, epilepsy
- Tumors

Parageusia, dysgeusia, hypogeusia, ageusia, hypergeusia
Disorders of the Autonomic Nervous System

The sympathetic and parasympathetic nervous systems are complementary regulators of manifold autonomic functions. Both systems can become overactive or inactive as a result of disease of the autonomic nervous system.

The sympathetic nervous system can be activated by emotions, fall in blood pressure (e.g., in hypovolemic shock), and hypoglycemia. Furthermore, a tumor of the cells in the adrenal medulla (pheochromocytoma) can form and release epinephrine. Lastly, some drugs can trigger sympathetic nerve activity. When pain occurs (→ p. 320), activation of sympathetic nerves may produce autonomic side effects.

Activation of the sympathetic nervous system (→A) will, via β₁-receptors, increase the excitability of the heart (bathmotropism), cardiac contractility (inotropism), heart rate (chronotropism) as well as the conduction velocity of the action potential (dromotropism). Blood vessels in the skin, lung, kidney, gut, and sex organs are constricted via α₁-receptors, while those in the heart, muscle, and liver are dilated by β₂-receptors. The circulatory effects of the sympathetic nerves are to raise the blood pressure, the skin becomes pale through vasoconstriction.

The sympathetic nerves stimulate sweat (cholinergic) and salivary (β) secretion, hair becomes erect (arrectores pilorum muscle [α]), eyelids are raised (levator palpebrae muscle [α]), and the pupils dilated (dilator pupillae muscle [α]). In addition, bronchial and uterine musculature is dilated (β₂), the activity of the intestinal musculature is inhibited, and the intestinal and bladder sphincters contracted. Contraction of the seminal vesicle and the ductus deferens triggers ejaculation. Sympathetic nerves also promote muscular tremor, stimulate the breakdown of glycogen in the liver and muscles (β₂), lipolysis (β₂) as well as the release of, among others, glucagon, corticotropin, somatotropin, and renin. They also inhibit insulin and histamine release. Finally, they aid in mobilizing leukocytes and in aggregating platelets.

Sympathetic stimulation may cease partly or completely (a rare event) because of degeneration of the autonomic nerves (autonomic failure or idiopathic orthostatic hypotension). Additionally, some drugs block sympathetic action, causing effects that are a mirror image of the consequences of excessive sympathetic stimulation. The main effect is a drop in blood pressure, dysfunction of the sex organs, and abnormal thermoregulation due to the absence of sweat secretion. The airway may be narrowed in those who are susceptible to this occurring. Loss of sympathetic innervation of the eye causes Horner’s syndrome, which is characterized by constricted pupils (miosis) and lid droop (ptosis) as well as eyeball retraction (enophthalmos).

Loss of parasympathetic stimulation (e.g., as a result of cholinergic receptor blockers) leads to tachycardia and dilated pupils. Furthermore, bronchial, intestinal, and bladder muscles, erection (in the male), vasocoagulation (in the female), and tear, salivary, bronchial, and gastrointestinal secretions are inhibited. If there is an anticholinergic action, sweat secretion is also inhibited.

Section of the spinal cord (→C) causes the loss of autonomic nervous system regulation. At first, as described with respect to somatomotor functions (→ p. 310), spinal shock occurs. Below the level of the lesion in the spinal cord the cutaneous blood vessels are dilated and autonomic functions, for example, defecation and micturition, are lost. Normally the wall tension of the bladder is measured by tension receptors (→C). If the tension reaches a certain threshold, bladder emptying is initiated via a pontine “micturition center”. In spinal shock micturition ceases. If bladder emptying is not ensured by catheterization, an “overflow bladder” results, along with urinary congestion and infection. However, autonomic nervous function recovers in one to six months because new synapses are formed in the spinal cord below the lesion, and the deprived cells are sensitized. A bladder-emptying reflex can be established (“automatic bladder”) by tapping on the abdominal wall above the bladder. Nevertheless, supraspinal control of bladder emptying is no longer possible.
A. Sympathetic Nerve Activation

- Eye opening
- Pupil dilation↑
- Salivary secretion↑
- Bronchial dilation
- Heart:
  - Contraction↑
  - Rate↑
  - Stroke volume↑
  - Conduction velocity↑
- Vasodilation:
  - Heart, liver, muscles
- Vasoconstriction:
  - Skin, lung, kidney, gut, sex organs
- Drugs
- Fall in blood pressure
- Blood pressure↑
- Hypoglycemia
- Sweat secretion↑
- Skin pallor
- Lipolysis↑
- Glucagon↑
- Corticotropin↑
- Somatotropin↑
- Renin↑
- Insulin, histamine↓
- Pheochromocytoma
- Endocrine etc.
- Uterus contraction↑
- Intestinal motility↓
- Muscle tremor
- Ejaculation
- Leukocyte mobilization, thrombocyte aggregation
- Sphincter contraction↑

B. Loss of Parasympathetic Stimulation

- Pupil dilation
- Inhibition of sweating
- Tachycardia
- Decreased motility:
  - Bronchi, gut, bladder
  - (but not sphincters)
- Decreased secretion:
  - Tears, saliva, bronchi, gastrointestinal

- Anticholinergic drugs

- No erection♂
- No vasocongestion♀

C. Paraplegia
Lesions of the Hypothalamus

The hypothalamus integrates the body’s autonomic, endocrine, and somatomotor functions. Neurons in the hypothalamus are responsible for regulating various homeostatic functions such as food intake, electrolyte and water metabolism, temperature regulation, and circadian rhythm. In addition, the functions are adapted in the hypothalamus to the required behavioral patterns, such as the fight and flight reaction, nutritive or sexual behavior. The programs required for the particular behavioral patterns are stored in the hypothalamus and are called up as needed, in particular by the neurons of the limbic system.

Circumscribed lesions in the hypothalamus can occur as the result of tumors, trauma, or inflammation, and they can produce profound disorders of autonomic regulation (→ A1).

A lesion in the anterior hypothalamus (including the preoptic region) leads to disturbances of temperature regulation and circadian rhythm (destruction of the suprachiasmal nucleus). It expresses itself, for example, in insomnia. Also, as a result of lesions in the supraventricular nuclei, the antidiuretic hormone (ADH) and oxytocin (see below) are no longer formed, and there is no sense of thirst.

A lesion in the medial hypothalamus also results in disorders of temperature control and the sense of thirst. At the same time there may be marked impairment of food intake. A lesion in the lateral part of the medial hypothalamus stops the sensation of hunger. Such patients no longer have the urge to eat (aphagia), their food intake is inadequate, and they lose weight (anorexia). Conversely, lesions of the medial hypothalamus cause a craving for food (hyperphagia) and, because of the intake of hypercaloric food, lead to obesity. However, obesity or anorexia are only rarely due to a hypothalamic lesion, but rather have psychological causes (→ p. 26). Damage to the medial hypothalamus also brings about disorders of memory acquisition and emotions.

Lesions in the posterior hypothalamus lead to poikilothermia, narcolepsy and memory gaps, along with other complex autonomic and emotional disorders.

Abnormal release of hypophyseal hormones occurs with lesions in different parts of the hypothalamus. As a result, the peripheral functions regulated by the hormones are affected (→ A2). When ADH is not released diabetes insipidus develops in which the kidney can no longer produce concentrated urine and may excrete as much as 20 l of urine daily (→ p. 260).

Abnormal release of gonadotropin can cause hyperfunction or hypofunction of the peripheral hormonal glands. Increased release of sex hormones can result in premature sexual maturation (precocious puberty), while reduced release brings about delayed sexual maturity and infertility (→ p. 272 ff.).

Longitudinal growth is promoted by the sex hormones, somatotropin (→ p. 262 ff.), and the thyrotropin-regulated thyroid hormones (→ p. 280 ff.). A reduced concentration of these hormones delays growth, reduced release of the sex hormones retarding the fusion of the epiphysial plates which may eventually cause gigantism, despite the slower growth. Corticotropin inhibits longitudinal growth via the action of cortisol.

The main hormones that affect metabolism are somatotropin, thyroid hormones, and the adrenocortical hormones (→ p. 268 ff.) which are regulated by corticotropin. Abnormal release of the latter hormones can have massive metabolic effects. Thyroid and adrenocortical hormones also have a profound effect on the circulation. The adrenocortical hormones also have an influence on the blood cells. They cause an increase in erythrocytes, thrombocytes and neutrophils, while decreasing the number of lymphocytes, plasma cells, and eosinophils. They thus affect O2 transport in blood, blood clotting, and immune defenses (→ p. 268 ff.).
A. Hypothalamic Lesions

1. Insomnia
2. Hyperthermia
3. Hypothermia
4. Lack of thirst

Hormonal disorders

ADH
Gonadotropins
Oxytocin
Prolactin
Somatotropin
Thyrotropin
Corticotropin
Melanotropin

Renal water re-absorption
Growth, maturation
Circulation
Metabolism
Skin pigmentation

Tumors
Inflammation
Trauma
Narcolepsy
Poikilothermia
Abnormal sympathetic nervous system adaptation
Loss of emotional control
Memory disturbances
Hyperphagia (medial h.)
Aphagia (lateral h.)
The Electroencephalogram (EEG)

The neurons of the cerebral cortex, when their membrane potential is changed, generate varying electrical fields on the surface of the skull that can be recorded with suitable leads. The EEG can provide valuable clues to neuronal functions and as a result has gained great clinical importance. Like the electrocardiogram (ECG) \( \rightarrow p.184 \), the EEG registers the summated activity of the cells that, projected onto the area of the recording lead, generates similarly directed dipoles.

The potential changes on the cortical surface largely depend on the post synaptic potentials at dendrites of the pyramidal cells \( \rightarrow A \). Although the postsynaptic potentials have a lower amplitude than the action potentials, they last significantly longer. Because the pyramidal cells are positioned at right angles to the cortical surface, their local activity generates dipoles in the direction of the surface much more easily than other cells in the cortex. They thus have a much greater impact on the surface potential than other neurons. Furthermore, they are all orientated in parallel to one another, so that equidirectional potential changes of neighboring pyramidal cells are summated. EEG deflections are to be expected only if (around the lead electrode) several pyramidal cells are simultaneously depolarized, i.e., there is a synchronized event.

During an excitatory postsynaptic potential, \( \text{Na}^+ \) enters the cell and thus leaves behind a local negative extracellular potential \( \rightarrow A1 \). The depolarization promotes an efflux of \( \text{K}^+ \) ions along the remaining cell membrane, this efflux in turn generating a local positive extracellular potential. If an excitatory synapse at the apical end of a dendrite is activated, the extracellular space in the area is relatively negative, but relatively positive at the base of the dendrite \( \rightarrow A1 \); to simplify matters the \( \text{K}^+ \) efflux has been entered at only one site). As a result a dipole is generated that creates a negative potential at the surface. Commissural fibers from the other cortical hemisphere and nonspecific parts of the thalamus form excitatory synapses mainly at the surface; excitation via these fibers thus leads to a negative potential at the surface electrode \( \rightarrow A1 \). Conversely, activation of specific thalamocortical fibers are more likely to lead to positive potentials at the surface \( \rightarrow A2 \) because they act near the cell body, i.e., deep in the cerebral cortex. Inhibition in the area of the cell body theoretically results in a negative potential at the surface, but it is not strong enough to be registered at the surface of the scalp \( \rightarrow A3 \).

The neurons in the thalamus that excite the cortical pyramidal cells undergo a rhythmical activity due to negative feedback \( \rightarrow A4 \). This rhythm is transmitted by the thalamocortical tracts to the pyramidal cells, with one thalamic neuron simultaneously exciting several pyramidal cells. Because of this, subcortical lesions are better registered in the EEG than small cortical ones.

The frequency of the recorded waves (deflections) is a diagnostically significant criterion when analysing the EEG \( \rightarrow B1 \). In adults who are awake with their eyes open it is predominantly \( \beta \)-waves (14–30 Hz) that are registered. With their eyes closed the somewhat slower \( \alpha \)-waves (8–3 Hz) dominate. Yet slower waves such as the \( \delta \)-waves (4–7 Hz) and the \( \theta \)-waves (0.5–3 Hz) are not normally recorded in waking adults but only in children and adolescents. However, in adults the latter slow waves are recorded during the phases of deep sleep \( \rightarrow p.340 \). Some diseases of the brain can result in slowing (sleeping-drug overdose, dementia, schizophrenia) or acceleration (alcoholism, manic-depressive illness) of the recorded frequency.

The EEG is of particular importance when diagnosing epilepsy, which is characterized by massive synchronized excitation of cortical neurons \( \rightarrow p.338 \). It causes "spike" activity ("seizure spikes" \( \rightarrow B2 \)) or "spike and wave" complexes \( \rightarrow B3 \).

In destruction of the cerebral cortex (brain death) all electrical activity will have ceased and the EEG tracing will therefore be isoelectric ("flat"), i.e., there will be no deflections.
A. Genesis of the EEG

1. Activation by contralateral cortex and nonspecific parts of thalamus
2. Activation by specific parts of thalamus
3. Inhibition by basket cells
4. Normal EEG frequencies

B. Wave Frequency Pattern of EEG

1. Normal EEG frequencies
2. Onset of an epileptic attack
3. Rhythmic spike-wave complexes in absences

\[
\begin{align*}
\alpha & \quad 8\text{–}13\text{Hz} \\
\beta & \quad 14\text{–}30\text{Hz} \\
\theta & \quad 4\text{–}7\text{Hz} \\
\delta & \quad 0.5\text{–}3\text{Hz}
\end{align*}
\]
Epilepsy

An epileptic seizure (epileptic attack, epileptic fit) is triggered by a spontaneous, synchronized, massive excitation of a large number of neurons, resulting in localized or generalized activation of motor (fits or seizures), sensory (sensory impressions), autonomic (e.g., salivation), or complex (cognitive, emotional) functions (→A).

The epileptic seizures can occur locally, for example, in the left precentral gyrus in the area of those neurons that control the right foot (partial seizure). They can spread from there to the entire precentral gyrus (Jacksonian epilepsy). Clonic cramps may spread, as in this example, from the right foot to the entire right half of the body (“Jacksonian motor march”), the patient not necessarily losing consciousness. However, should the seizures spread to the other side of the body, the patient will lose consciousness (partial seizure with secondary generalization). Primary generalized seizures are always associated with loss of consciousness. Certain seizures (“absences”) can also lead to isolated loss of consciousness.

The triggering phenomenon is paroxysmal depolarization of individual neurons (paroxysmal depolarization shift [PDS]). This is caused by activation of Ca2+ channels (→A1). The entering Ca2+ first of all opens nonspecific cation channels and thus causes massive depolarization, which is terminated by opening of the Ca2+-activated K+ and Cl– channels. An epileptic seizure occurs when a sufficient number of neurons has been excited. Causes or factors which favor epilepsy are, for example, genetic defects (of K+ channels and others), malformation of the brain, trauma to the brain (glial scars), tumor, bleeding, or abscesses. Seizures may also be provoked or promoted by poisoning (e.g., alcohol), inflammation, fever, cell swelling or (less likely) shrinkage, hypoglycemia, hypomagnesemia, hypocalcemia, lack of sleep, ischemia or hypoxia, and repetitive stimuli (e.g., a flickering light). Hyperventilation can lead to cerebral hypoxia, via hypocapnia and cerebral vasoconstriction, and may thus promote the onset of a seizure. Epileptic seizures have a higher incidence among pregnant women.

Neuronal excitation or the spread of excitation to neighboring neurons is promoted by a number of cellular mechanisms:

The dendrites of the pyramidal cells contain voltage-gated Ca2+ channels that open on depolarization and thus increase depolarization. In lesions of neurons more of these Ca2+ channels are expressed. They are inhibited by Mg2+, while hypomagnesemia promotes the activity of these channels (→A2). An increased extracellular concentration of K+ reduces K+ efflux through the K+ channels, i.e., it has a depolarizing effect and thus at the same time promotes the activation of Ca2+ channels.

The dendrites of pyramidal cells are also depolarized by glutamate from excitatory synapses (→A3). Glutamate acts on a cation channel that is impermeable to Ca2+ (AMPA channel) and one that is permeable to Ca2+ (NMDA channel). The NMDA channel is normally blocked by Mg2+. However, the depolarization that is triggered by activation of the AMPA channel abolishes the Mg2+ block (co-operation of the two channels). Mg2+ deficiency and depolarization thus favor activation of the NMDA channel.

The membrane potential of the neurons is normally maintained by the K+ channels. A precondition for this is an adequate K+ gradient across the cell membrane. This gradient is created by Na+/K+-ATPase (→A4). A lack of available energy (e.g., due to O2 deficiency or hypoglycemia) impairs Na+/K+-ATPase and thus promotes depolarization of the cell.

Normally depolarizations are reduced by inhibitory neurons that activate K+ and/or Cl– channels via GABA, among others (→A5). GABA is formed by glutamate decarboxylase (GD), an enzyme that needs pyridoxine (vitamin B6) as co-factor. Vitamin B6 deficiency or a reduced affinity of the enzyme for vitamin B6 (genetic defect) favors the occurrence of epilepsy. Hyperpolarization of thalamic neurons can increase the readiness of T-type Ca2+ channels to be activated, thereby promoting the onset of absences.
A. Epilepsy

Fever
Injuries (scars)
Genetic defects
Tumors, bleeding, abscess
Poisoning (alcohol), inflammation
Cell swelling

Paroxysmal activation of Ca\textsuperscript{2+} channels

1. ECS
2. Mg\textsuperscript{2+}
3. Depolarization
4. ATP
5. Glutamate

Glutamate
NMDA
AMPA

Inhibitory basket cell
Pyramidal cell

Localized seizures (e.g. Jacksonian epilepsy)

Motor (fits)
Sensory (hallucinations)

Autonomic (salivation)
Cognitive (‘déjà vu’)
Emotional (rage, laughter)

Generalized seizures
Unconsciousness

Hyperactivity
Sleep Disorders

Normal sleep requires the interplay of several cerebral structures, among them the loci ceruleus and subceruleus (norepinephrine being the transmitter), the raphe nucleus (serotonin as transmitter), tractus solitarius nucleus, and neurons in the hypothalamus. A lesion in the **subceruleus nucleus** results in rapid eye movement (REM) insomnia (see below); lesions in the **raphe nuclei** or the **anterior hypothalamus** lead to (transient) insomnia; lesions in the **posterior hypothalamus** cause narcolepsy. Excitation of the tractus solitarius nucleus (e.g., by gastric distension) causes fatigue. Sleep is also very dependent on the circadian rhythm, in that destruction of the central rhythm generator, the **suprachiasmatic nucleus (SCN)** leads to irregular periods of falling asleep and of difficulty in awakening. The latter is mediated by the **ascending reticular activating system (ARAS)**, a connection between the reticular formation via intralaminar nuclei of the thalamus to large areas of the brain (→ A). Destruction of the **intralaminar thalamic nuclei** (e.g., by ischemia) leads to somnolence. Desynchronization between subcortical activity and cortical sleep may be the cause of **sleepwalking** (somnambulism).

Disorders of the regulation of breathing during sleep have been held responsible for the **sudden infant death syndrome (SIDS)** and **sleep apnea** in adults. Metabolic alkalosis is thought to favor sleep apnea. In addition, decreased muscle tone during sleep promotes the collapse of the airways, apnea, and hypoxia.

Normally one passes through several phases of varying depth during sleep (→ B). During one night there are typically about 5 phases of **REM sleep** (→ B, marked in red), during which bursts of excitation from the brain stem produce twitches in the otherwise hypotonic musculature. Several phases of **non-REM (NREM)** sleep must be passed through before REM sleep is reached, whereby increasing depth of sleep correlates with decreasing frequency of the EEG waves. Chronic use of **sleeping pills** leads to lighter NREM sleep and only occasional REM phases.

During the awake phases endogenous **sleep factors** accumulate, such as the sleep-inducing peptides that are broken down again during sleep. It is possible that serotonin stimulates the formation of sleep factors, because inhibiting serotonin formation, release or action (e.g., by the antihypertensive drug reserpine) causes insomnia.

The sleep-inducing peptides cause **“sleep pressure”** (NREM sleep pressure or slow wave sleep [SWS]; → C 1). The net sleep pressure is the difference between sleep pressure (violet) and the reciprocal of the REM sleep pressure (green) that follows a circadian rhythm essentially in parallel to body temperature and similar bodily parameters, such as “readiness for activity and effort”. The ability to fall asleep is a function of this net sleep pressure.

When experiencing a change of time zone (jet lag; → C 2) or when doing **shift work**, the circadian rhythm at first continues to oscillate in the original phase. When the day is shortened, it is impossible to go to sleep at the local time because of the low net sleep pressure. When the day gets longer, the sleep pressure is increased by the longer waking period and falling asleep at the local time is no problem. The subsequent circadian rhythm, however, causes early awakening.

Falling asleep is also disturbed by **delayed sleep phase insomnia** (→ C 3), caused by an inflexible circadian rhythm that cannot be shortened. When going to sleep too early the net sleep pressure is too low. During chronotherapy a lengthened daily rhythm (27 hours) is forced upon the patient until the desired circadian periodicity has been obtained.

**Depression** (→ C 4) possibly reduces the formation of sleep-inducing peptides through a lack of serotonin (→ p. 350). This results in a decrease in net sleep pressure (red line) and difficulty in falling asleep. The sleep pressure can be increased by sleep deprivation the next day, and thus normal sleep can be achieved.

**A raised level of excitement** makes falling asleep more difficult and reduces the duration of sleep (→ C 5). Anxiety about insomnia raises this level and is thus counterproductive.
A. Disorders of Sleep Regulation

- Lesions, ischemia
- Asynchronous
- Insomnia, hypersomnia
- Metabolic alkalosis
- Abnormal regulation
- Muscle tone
- Stridor
- Sleep apnea

B. Sleep Phases

1. Normal sleep phases
2. "Normal" onset of night
3. Jet lag
4. Delayed sleep phase insomnia
5. Depression
6. Excitement

C. Sleep Factors

- Normal sleep phases
- 1/REM sleep pressure
- Net sleep pressure
- Depth of sleep
- "Normal" onset of night
- Jet lag
- Delayed sleep phase insomnia
- Depression
- Excitement
- Serotonin deficiency (?)
Consciousness

We become conscious of only a fraction of the information reaching our brain. The conscious contents are stored in associative cortical areas that specialize in this task (→ p. 346). Conscious awareness requires not only that the specific afferents have been transmitted to the cerebral cortex, but also nonspecific activation by the ARAS through which neurons from the reticular formation activate wide areas of the cerebral cortex via intralaminar neurons of the thalamus (→ A).

Damage to large areas of the cortex and/or breakdown of the ARAS brings about loss of consciousness. In addition, there may be primary causes influencing neuronal excitability in the above-mentioned neuronal structures. Ischemia (e.g., atherosclerotic vascular occlusion) or hypoxia (e.g., suffocation) (→ A1) impair excitability directly or by cell swelling. Swelling of glial cells impairs, among other functions, their capacity to take up K+ and thus to keep down the concentration of extracellular K+. This has an indirect effect on neuronal excitability. Part of the effect of tumors, abscesses, or bleeding is also exerted via ischemia or hypoxia (→ A1) in that they raise the cerebral pressure and thus impair cerebral perfusion by narrowing the blood vessels. Hypoglycemia also modifies excitability, partly via cellular swelling (→ A2). Hyponatremia and ammonia (NH₄⁺) also act via this mechanism. The rise in NH₄⁺ in hepatic encephalopathy (→ p. 174) causes the formation of glutamine from α-ketoglutarate and glutamate in glial cells; the accumulation of glutamine causes them to swell. At first this swelling is counteracted by the removal of osmolytes, seen in magnetic resonance imaging as a decrease in the cerebral concentration of inositol. When this compensatory mechanism is exhausted, consciousness is lost.

The excitability of neurons is also affected by epilepsy (→ p. 338), hyperosmolality (hypernatremia, hyperglycemia; → A3) as well as by disorders of electrolyte (Ca²⁺, Mg²⁺, HPO₄²⁻) and acid-base metabolism (→ A4). Uremia (in renal failure) and diabetes mellitus act partly via changes in extracellular osmolarity and electrolyte composition. Numerous substances can impair the excitability of the ARAS (→ A5), such as NMDA receptor antagonists, alcohol, narcotics, hypnotics, psychoactive drugs, anticonvulsives, Na⁺/K⁺-ATPase inhibitors (cardiac glycosides), heavy metals. Extreme excess or lack of hormones (e.g. T₃, T₄, parathyroid hormone, adrenocorticoid hormones, pheochromocytoma) as well as massive neuronal excitation, for example, caused by pain or psychogenic disease (schizophrenia), can lead to loss of consciousness (→ A6). Lastly, neuronal excitability can also be so severely impaired by hyperthyroidism, hypothermia, inflammatory (e.g., meningitis) or mechanical damage, and neurodegenerative disease that it could lead to loss of consciousness (→ A7).

Loss of consciousness can be divided into several stages (→ A): in a state of drowsiness the patient can still be roused and will respond; in a stupor (profound sleep) patients can be awakened by vigorous stimuli; when in a coma this is no longer possible. In so-called “coma dépassé” vital functions will also have ceased (e.g., respiratory arrest).

The split brain represents a special abnormality of consciousness (→ B). Uniform consciousness presupposes communication between the two cerebral hemispheres. This takes place along large commissural fiber bundles through the corpus callosum and the anterior commissure. In treating uncontrollable epilepsy the commissural fibers have been transected in some patients, stopping this communication between the two hemispheres. The two hemispheres now produce two distinct kinds of consciousness: if an object (e.g., a saucepan) is placed into the right hand or placed in the right visual field, the patient can correctly name the object. But if the object is placed into the left hand or projected into the left visual field, the patient is able to recognize the object and, for example, find the appropriate saucepan cover with the left hand, but will not be able to name it.
A. Unconsciousness

1. Conditions leading to unconsciousness:
   - Infection
   - Tumor
   - Trauma
   - Vascular occlusion
   - Asphyxiation
   - Ischemia
   - Hypoxia

2. Hypoglycemia, hyponatremia, NH₄⁺

3. Electrolyte disorders, abnormal H⁺

4. Hypernatremia, hyperglycemia

5. Alcohol, narcotics, toxins

6. Excessive hormonal disorder

7. Temperature, inflammation, neurodegeneration

8. Neuronal excitability in cortex

B. ‘Split brain’

- Corpus callosum transected
- Left hemisphere
- Right hemisphere

- ‘Sauce-pan’
- ‘coma dépassé’

- Sensory system
- Motor system

Plate 10.23 Consciousness

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Aphasias

Speech and language comprehension are tasks that engage a large part of the cerebral cortex. For this reason, lesions in various parts of the cortex may lead to an impairment of speech and of language comprehension.

Simply put, spoken language is first perceived in the primary auditory cortex (→A; marked in violet) and then in the sensory speech center (Wernicke’s area, marked in light blue). Written words are transmitted via the primary (gray-blue) and secondary (dark blue) visual cortex to area 39, where acoustic, optical, and sensory perceptions are integrated. When writing, the premotor cortex is activated via the arcuate fasciculus of the pre-motor cortex that, in turn, activates the motor cortex via the basal ganglia and the thalamus. In right-handed people the structures involved are predominantly localized in the left hemisphere, and speech disorders (aphasia) are almost always the result of lesions in the left hemisphere.

Each of the above-mentioned structures can cease functioning, for example, due to traumatic or ischemic damage. Depending on which cerebral area is affected, abnormalities characteristic for each will develop.

Broca’s aphasia is caused by a lesion of the motor speech center in area 44 and the neighboring areas 9, 46, and 47. Spontaneous speech (verbal output) is grammatically incorrect and the patient typically communicates by using single words and is incapable of repeating someone else’s words (impaired repetition ability). Language comprehension is not, or less markedly, impaired. As a rule patients cannot write normally. However, if the lesion is limited to area 44, the ability to write is preserved (a rare disorder, called aphemia).

Wernicke’s aphasia results from a lesion in the sensory speech region, i.e., in the posterior portion of the temporal gyrus of the auditory association cortex (area 22) and/or the supramarginal gyrus (area 40). Language comprehension is impaired in these patients. At the same time they also lose the ability to repeat words spoken by somebody else. Spontaneous speech is fluent; sometimes patients speak all the time (logorrhea). However, in doing so they may make occasional phonetic (“spill” instead of “spin”) or semantic errors (“mother” instead of “woman” [paraphasia]) or create new words (neologisms).

In conductive aphasia the connection between sensory and motor speech center (arcuate fasciculus) is interrupted. Speech is fluent (although sometimes paraphasic) and comprehension is good. However, their repetition ability is greatly impaired. They are also unable to read aloud, even though they understand the text they read.

In global aphasia (damage to both the sensory and the motor centers, e.g., by occlusion of the medial cerebral artery) both spontaneous speech and comprehension are impaired.

Anomic aphasia is the result of a lesion in the temporal lobe in the region of the medial and inferior gyri. Patients’ speech is largely normal but it is difficult for them to find the right word for certain objects. In achromatic aphasia (lesion at the left inferior temporal lobe close to temporal-occipital border) the person cannot name a color (even though it is correctly recognized and objects can normally be sorted by color).

Transcortical motor aphasia is caused by a lesion in the anterior inferior frontal lobe near the Broca speech center. Spontaneous speech is markedly impaired, while repetition and comprehension are normal.

Transcortical sensory aphasia occurs after a lesion in the parietal–temporal association cortex near the Wernicke speech center or area 39. The patient can speak fluently and repetition is normal. However, there is a problem understanding words and finding the right word; reading and writing are impossible.

Subcortical aphasia is due to lesions in the region of the basal ganglia (especially the caudate nucleus) and the thalamus. There are transient disorders of comprehension and finding of words.
### A. Aphasias

**Word which is heard**
- Primary auditory cortex
  - Secondary auditory cortex (Wernicke’s area)
  - Premotor cortex (Broca’s area)
  - Basal ganglia, cerebellum
  - Thalamus

**Word which is read**
- Primary visual cortex
  - Secondary visual cortex
  - Area 39
  - Anterior superior frontal lobe
  - Premotor cortex (Broca’s area)

**Spoken word**
- Motor cortex
- Thalamus

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<table>
<thead>
<tr>
<th>Type</th>
<th>Spontaneous speech</th>
<th>Repetition of words</th>
<th>Language comprehension</th>
<th>Finding words</th>
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<tr>
<td>Broca’s aphasia</td>
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<td>abnormal</td>
<td>normal</td>
<td>impaired</td>
</tr>
<tr>
<td>Wernicke’s aphasia</td>
<td>fluent</td>
<td>abnormal</td>
<td>impaired</td>
<td>impaired</td>
</tr>
<tr>
<td>Conduction aphasia</td>
<td>fluent, but paraphasic</td>
<td>markedly impaired</td>
<td>normal</td>
<td>abnormal, paraphasic</td>
</tr>
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<td>Global aphasia</td>
<td>abnormal</td>
<td>abnormal</td>
<td>abnormal</td>
<td>abnormal</td>
</tr>
<tr>
<td>Anomic aphasia</td>
<td>fluent</td>
<td>normal, but anomic</td>
<td>normal</td>
<td>impaired</td>
</tr>
<tr>
<td>Achromatic aphasia</td>
<td>fluent</td>
<td>normal, but anomic</td>
<td>normal</td>
<td>impaired</td>
</tr>
<tr>
<td>Motor transcortical aphasia</td>
<td>abnormal</td>
<td>normal</td>
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<td>fluent</td>
<td>normal</td>
<td>abnormal (transient)</td>
<td>abnormal (transient)</td>
</tr>
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</table>
Disorders of Memory

Two forms of memory are distinguished: Declarative, explicit memory (semantic or episodic) stores memory that can only be recalled consciously (→ A). It is needed, for example, in order to be able to recognize certain things (apples, animals, faces). Procedural, implicit memory (→ A3) does not require conscious activation for storage and recall. It is required, e.g. for learning to play the piano.

To form declarative memory (→ A1) the information first of all reaches the corresponding association cortex (e.g., the secondary visual cortex) via the particular primary sensory cortical area (e.g., the primary visual cortex). From here, via the entorhinal cortex (area 28), the information reaches the hippocampus, which is essential for long-term storage of declarative memory. With mediation from structures in the diencephalon, basal forebrain, and prefrontal cortex the item is again stored in the association cortex. In this way the information is first taken up, via the sensory memory, by the short-term memory, which can hold on to the content for only a few seconds to minutes. The information can be transferred to the long-term memory, for example, through being rehearsed (→ A2). Such rehearsal is not an essential precondition for the formation of long-term memory, however.

It is particularly the transfer into long-term memory that is impaired in lesions of the above-named structures in neurodegenerative diseases (e.g., Alzheimer’s disease; → p. 348), trauma, ischemia, alcohol, carbon monoxide, and inflammation. In addition, memory formation can be temporarily stopped by electric shock. The most important transmitter in the hippocampus is glutamate (NMDA receptors). Memory formation is promoted by norepinephrine and acetylcholine (nicotinicergic receptors).

Lesions in the hippocampus or its connections result in anterograde amnesia (→ A2). The affected patients will from that moment on no longer be able to form any new declarative memory. They will remember events prior to the lesion but none subsequent to it.

Retrograde amnesia (→ A2), i.e., the loss of already stored information, occurs in disorders in the relevant associative cortical fields. Depending on the extent and localization of the disorder, the loss can be reversible or irreversible. In the former case the patient will lose items of memory, but they can be retrieved. In irreversible loss the particular items are permanently lost.

Transitory bilateral functional disturbance of the hippocampus can cause anterograde and retrograde (days to years) amnesia (transient global amnesia). In Korsakoff’s syndrome (frequent in chronic alcoholics) both anterograde and retrograde amnesia can occur. Patients thus affected often try to cover up gaps in memory by means of confabulations.

The procedural (implicit) memory (→ A3) is not impaired in lesions of the hippocampus. It allows imprinting, learning of skills, sensitization, habituation, and conditioning. Depending on the task, cerebellum, basal ganglia, amygdala and cortical areas are involved. Both the cerebellum and basal ganglia play an important role when learning skills. Relevant afferent impulses reach the cerebellum via olivary and pontine nuclei. The storage capacity of the cerebellum can be lost by, for example, toxic damage, degenerative diseases, and trauma. Dopaminergic projections of the substantia nigra also play a part in the formation of procedural memory.

The amygdala is important in conditioning anxiety reactions. It receives its information from the cortex and thalamus and influences motor and autonomic functions (e.g., muscle tone, palpitations [awareness of tachycardias], goose-pimples) via the reticular formation and hypothalamus. Removal of the amygdala (e.g., by trauma or opiates) cancels conditioned anxiety reactions. Bilateral removal of the amygdala with portions of the hippocampus and temporal lobe results in amnesia and disinhibited behavior (Klüver–Bucy syndrome).
A. Disorders of Memory

1 Declarative memory

- Sensory perception
- Hippocampus

2 Model of cognitive learning

- Short-term memory
- Rehearsal
- Long-term memory
- Sensory cortex
- Trauma, tumors, inflammation, ischemia
- Degeneration, alcohol, CO, electric shock, epilepsy
- Anterograde amnesia
- Retrograde amnesia

3 Procedural learning

- Sensory perception
- Basal ganglia
- Hypothalamus
- Basal prosencephalon
- Diencephalon
- Association cortex
- Prefrontal cortex

Glutamate (NMDA), acetylcholine, nicotine, norepinephrine

Imprinting, skills, sensitization, habituation, conditioning

Trauma, opiates

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Alzheimer’s Disease

The occurrence of Alzheimer’s disease, the most common cause of (senile) dementia (about 70%), is favored by a genetic disposition. However, the disease is not genetically uniform. An especially severe form of the disease has an autosomal dominant inheritance. Defects on chromosomes 1, 12, 14, 19, or 21 were found in families with Alzheimer’s disease. The defective gene on chromosome 19, for example, codes for apolipoprotein E (ApoE 4), the relevant gene on chromosome 21 for a protein (β-amyloid precursor) that can be broken down to small amyloid peptides. These can on their own bunch themselves together into protein fibrils 7–10 nm long (→ A1). These amyloid fibrils can then form aggregates, 10 μm to several hundred μm in diameter (senile plaques), that are frequently found in the brain of patients with Alzheimer’s disease (→ A2). In addition to extracellular amyloid, these plaques contain distorted dendrites and axons with abnormal intracellular neurofibrils. The formation of these atypical elements of the cytoskeleton apparently precedes the death of the neurons (see below).

Certain mutations of the β-amyloid precursor gene promote the formation of senile plaques. Amyloid deposits can also occur under the influence of other genetic or external factors. It is thought, for example, that toxins can penetrate the brain via the olfactory nerves and cause the disease. Amyloid deposits also occur in trisomy 21 (Down’s syndrome) that also leads to dementia.

β-amyloid fibrils can react with receptors at the cell surface, such as the receptor for advanced glycation end products (RAGE), and a scavenger receptor (RA). Oxygen radicals formed as a result may increase the neuronal intracellular concentration of Ca²⁺ (→ A3), possibly via depolarization of the cell membrane and activation of NMDA receptors. The O₂ radicals and Ca²⁺ promote cell death. In microglial cells (→ A4) the activation of RAGE and RA stimulates the formation or release, respectively, of NO, prostaglandins, excitotoxins, cytokines, tumor necrosis factor (TNF-α), tumor growth factor (TGF-β1), and fibroblast growth factor (b-FGF). This results in inflammation that also impairs neurons. Increased concentration of the osmolyte inositol points to a disorder of cell volume regulation.

The death of neurons is accelerated by a lack of NGF or of NGF receptors and can be delayed by NGF.

Cholinergic neurons in the basal nucleus of Meynert, in the hippocampus (especially CA1, the subiculum) and in the entorhinal cortex (→ B1) are particularly affected by cell death, but neurons also die in other cerebral areas, such as the frontal lobes, anterior temporal lobes, parietal lobes, olfactory cortex, hypothalamus, locus ceruleus, and raphe nuclei.

Neuronal death is accompanied by decreased formation and concentration of neurotransmitters in the brain. Acetylcholine is markedly affected: in the cerebral cortex and the hippocampus there is an up to 90% decrease in the concentration of choline-acetyl transferase, the enzyme that is necessary for the formation of acetylcholine. The concentration of other neurotransmitters is also reduced, for example, norepinephrine, serotonin, somatotropin, neuropeptide Y, substance P, and corticotropin-releasing hormone ([CRH] corticosterin).

A consequence of the degenerative changes is an increased loss of cerebral functions (→ B2). The disease typically begins insidiously with subtle deficits of memory, neglect of appearance and body hygiene, phases of confusion, and taking wrong decisions. As the disease progresses, anterograde amnesia (→ p. 346) will be followed by impairment of past memories as well as procedural memory. Lesions in the limbic system express themselves alternately through restlessness and lethargy. Motor deficits (speech disorders, abnormal muscle tone, ataxia, hyperkinesia, myoclonus) occur relatively late.

Creutzfeldt–Jakob disease, possibly caused by prions (proteinaceous infectious particles), is a neurodegenerative disease that, in addition to motor (e.g., ataxia) and psychogenic disorders, also leads to dementia.
A. Causes of Alzheimer's Disease

- Normal protein
- Defective β-amyloid precursor
- Other genetic factors
- Environmental factors
- Toxins

Long arm of chromosome 21

NO, exitotoxins, TNFα, TGFβ, bFGF

1. Amyloid
2. Senile plaques
3. Abnormal neurofibrils
4. Glial cell

Inflammation

RA RAGE

NMDA receptor

Cell death

B. Effects of Alzheimer's Disease

- Neuronal death
- Acetylcholine
- Somatostatin
- Neuropeptides
- Substance P
- Norepinephrine
- Serotonin
- CRF
- Somatostatin

Hippocampus

CA1
Subiculum
Entorhinal cortex

Basal nucleus of Meynert

Complete loss of mental control
Motor seizures
Lethargy
Global amnesia
Anterograde amnesia
Forgetfulness

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Depression

Depression is a disease with an increased familial incidence. It can alternate with manic phases (bipolar disorder) or can occur in isolation (unipolar disorder).

Pathophysiology, depression is thought to be connected with decreased (relative or absolute) availability of norepinephrine and/or serotonin in the brain.

Norepinephrine is formed in neurons of the locus ceruleus and the tegmentum (→ A). Axons from the tegmentum predominantly connect with the hypothalamus, anterior pituitary, brain stem, and spinal cord. Fibers from the locus ceruleus project to spinal cord, hypothalamus, thalamus, limbic system, and cortex.

The release and action of norepinephrine at the nerve endings can be reduced by a number of substances, leading to depression (→ A1):
- The synthesis of norepinephrine from tyrosine via DOPA can be reduced by enzyme inhibitors (e.g., methylyrosine).
- The uptake of norepinephrine in presynaptic stores can be inhibited (e.g., by reserpine).
- Norepinephrine can be replaced at the postsynaptic receptors (e.g., phenoxybenzamine, phentolamine).

The synaptic norepinephrine concentration and action can, however, also be increased, an effect which is in part utilized in the drug treatment of depression (→ A2):
- Inhibitors of monoamine oxidase A (MAO-A), which is specific to norepinephrine (and serotonin) (e.g., tranylcypromine, moclobemide), can delay the breakdown of norepinephrine in the presynaptic endings and thus increase its availability.
- Inhibitory substances of catechol-orthomethyl-transferase ([COMT]) e.g., tropoline) delay the breakdown of norepinephrine.
- Amphetamines increase synaptic concentration of norepinephrine, dopamine, and serotonin by inhibiting transport of the transmitter.
- Desipramine inhibits re-uptake, and thus similarly increases the synaptic norepinephrine concentration.
- The receptors can be stimulated by agonists (e.g., clonidine).

Serotonin (5-hydroxytryptamine [5-HT]) is formed in neurons of the raphe nuclei that project to the spinal cord, cerebellum, thalamus, hypothalamus, basal ganglia, the limbic system, and cerebral cortex (→ B).

A reduced availability or action of serotonin (→ B1) favors development of depression, for example
- by inhibiting synthesis from tryptophan (e.g., chlorophenylalanine);
- by inhibiting uptake in presynaptic stores (e.g., reserpine);
- due to increased consumption of serotonin through formation of inactive melatonin (when dark, in the pineal gland).

An antidepressive effect has been observed when serotonin action or stimulation of the serotonin receptors has been increased (→ B2):
- Availability of tryptophan can be increased by administering glucose. Glucose promotes insulin release, and the antiproteolytic and protein synthesis-stimulating effect of insulin leads to a reduction of amino acid concentration in blood. Some amino acids competitively inhibit tryptophan uptake across the blood–brain barrier. Loss of this inhibition would raise tryptophan uptake in the brain.
- Tricyclic antidepressants (e.g., imipramine, fluoxetine) inhibit the re-uptake of serotonin in presynaptic stores and in this manner also increase its synaptic concentration.
- MAO-A inhibitors (see above) raise the availability of serotonin by inhibiting its breakdown.
- Exposure to light inhibits the conversion of serotonin to melatonin. Because of the short and relatively dark days, depression is particularly frequent in northern countries during the winter months. Conversely, depression can sometimes be successfully treated by exposing patients to bright light (phototherapy).
- Agonists (e.g., lysergic acid diethylamide [LSD]) can directly stimulate serotonin receptors.
- Lithium probably exerts its antidepressive effect by influencing intracellular signal transmission (→ p. 6).
Schizophrenia

Schizophrenia is a disease with an increased familial incidence. It is characterized by delusions, hallucinations, socially unacceptable behavior and/or inadequate associations (so-called positive symptoms). Lack of motivation and of emotion also frequently occur (so-called negative symptoms). In some patients the positive symptoms predominate (type I), in others the negative ones (type II).

In schizophrenia there is reduced blood flow and glucose uptake especially in the prefrontal cortex and, in type II patients, also a decrease in the number of neurons (reduction in the amount of gray matter). In addition, abnormal migration of neurons during brain development is of pathophysiological significance (→A2).

Atrophy of the spiny dendrites of pyramidal cells has been found in the prefrontal cortex and the cingulate gyrus. The spiny dendrites contain glutamatergic synapses; their glutamatergic transmission is thus disturbed (→A1). In addition, in the affected areas the formation of GABA and/or the number of GABAergic neurons seems to be reduced, so that inhibition of pyramidal cells is reduced.

Special pathophysiological significance is ascribed to dopamine: excessive availability of dopamine or dopamine agonists can produce symptoms of schizophrenia, and inhibitors of 

D_{1} dopamine receptors have been successfully used in the treatment of schizophrenia (see below). On the other hand, a reduction in D_{2} receptors has been found in the prefrontal cortex (→A1), and a reduction of D_{1} and D_{2} receptors correlates with negative symptoms of schizophrenia, such as lack of emotions. It is possible that the reduction in dopamine receptors is the result of an increased dopamine release and in itself has no pathogenetic effect.

Dopamine serves as a transmitter in several pathways (→B):

- Dopaminergic pathways to the limbic (mesolimbic) system; and
- to the cortex (mesocortical system) are probably essential in the development of schizophrenia.
- In the tubuloinfundibular system dopamine controls the release of hypophyseal hormones (especially inhibition of prolactin release; →p.260 ff.).

- It controls motor activity in the nigrostriatal system (→ p. 312 ff.).

Release and action of dopamine are increased by several substances that promote the development of schizophrenia (→A3, left). Thus, the dopaminergic treatment of Parkinson’s disease can lead to symptoms of schizophrenia, which in turn can limit the treatment of Parkinson’s disease:

- L-dopa leads to an increased formation and release of dopamine.
- Monoamine oxidase inhibitors (MAO inhibitors) inhibit the breakdown of dopamine and thus increase its availability for release in the synaptic cleft.
- Cocaine stimulates dopamine release in the synaptic cleft, too.
- Amphetamine inhibits dopamine uptake in presynaptic nerve endings and thus at the same time raises the transmitter concentration in the synaptic cleft.

Conversely, antidopaminergic substances can improve schizophrenia (→A3, right):

- Some substances (e.g., phenothiazines, haloperidol) displace dopamine from receptors and thus have an antidopaminergic action.
- Inhibition of the uptake of dopamine in the synaptic vesicle, for example, by reserpine, ultimately impairs the release of the transmitter in the synaptic cleft. However, reserpine is at present not used therapeutically.

The long-term use of dopamine antagonists in a patient with schizophrenia can lead to “tardive dyskinesia” as a result of their action on the striatum (→ p. 314). This complication can limit the treatment of schizophrenia.

It is possible that serotonin also plays a role in producing schizophrenic symptoms. Excessive serotonin action can cause hallucinations, and many antipsychotic drugs block 5-HT_{2A} receptors (→A1).
A. Schizophrenia

Genetic and other factors

Negative symptoms:
- lack of motivation,
- lack of emotion

Positive symptoms:
- delusions, hallucinations, socially unacceptable behavior, inadequate associations

Dopamine receptors (D$_1$)
- Hallucinogens
- 5-HT$_2A$ receptors
- GABAergic neurons
- Reduced inhibition

Limbic system

Prefrontal cortex

Number of neurons
- Abnormal neuron migration

Circulation

Symptoms increased by:
- L-Dopa
- Synthesis
- MAO inhibitors
- Breakdown
- Amphetamine
- Re-uptake
- Cocaine
- Release
- D$_2$ receptors

Symptoms reduced by:
- Reserpine
- Storage
- Phenothiazine, haloperidol
- Free receptors

Glutamate effect

Dendrites
- Spines

Pyramidal cells

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Dependence, Addiction

Dependence or rather addiction is an acquired compulsion that dictates the behavior of those who are dependent or addicted. In drug dependence there is a great craving for the particular drug. For the dependent person, obtaining and supply of the drug become priorities over all other kinds of behavior. Among the most important of such drugs are nicotine, alcohol, opiates, and cocaine. There are, however, also many other drugs (especially sleeping pills [hypnotics] and analgesics) that can lead to dependence.

It is not only the supply of the particular drug that is important in the development of addiction, as only some of those who take a drug become dependent. Of great significance for the development of addictive behavior is a genetic disposition (→ A). It has been shown that in those dependent on alcohol or cocaine, certain polymorphisms of the gene for the dopamine transporter (DAT-1) are especially common. Genetic defects of alcohol dehydrogenase (ADH) or acetaldehyde dehydrogenase (ALDH) impair the breakdown of alcohol and thus increase its toxic effect. These enzyme defects therefore protect against alcohol dependence. The attempt has been made to achieve pharmacological inhibition of ALDH (with desulfiram) in order to force an increase in acetaldehyde and thus stop addictive behavior through the toxic effect of acetaldehyde (nausea, vomiting, hypotension). Because of the high risk and relatively limited success this approach has now been abandoned.

Another important factor in dependence is the social context (→ A). Thus, a change in social environment can make it easier to give up drugs. Most of the soldiers, for example, who took drugs during the Vietnam War were not addicted after their return to the USA.

Frequently addicts develop a tolerance to the substance and the initial effect gradually weakens if drug intake continues (→ A, B). If intake is suddenly discontinued, there is a reversal of effect (→ B). Chronic intake weakens the effect of the drug and increases the reversal effect on discontinuance. If the addict wants to attain the same effect, the dosage has to be increased. When the drug is discontinued, withdrawal symptoms develop that get worse the longer the drug addiction had lasted. Withdrawal symptoms lead to physical dependence in the addict. Psychological dependence is the result of the need for the positive effects of the drug and/or the fear of the neurobiological or psychological withdrawal symptoms (→ A). The desire for the positive effects remains after the withdrawal symptoms have abated. Stress, among other factors, favors relapse.

Mesolimbic and mesocortical dopaminergic pathways (→ A; see also p. 352) apparently play an important role in the development of dependence or addiction. By activating these pathways, for example, with alcohol or opiates, the addict tries to produce a feeling of wellbeing or euphoria or, conversely, to prevent dysphoria. It is possible that on withdrawing the substance the activity of the dopaminergic system is reduced or the target cells are less sensitive. Withdrawal symptoms can be attenuated by activating endorphinergic, GABAergic, dopaminergic, or serotoninergic receptors.

The cellular mechanisms of tolerance have been in part elucidated for opiates. Stimulation of the receptors leads to phosphorylation via G protein receptor kinases and thus to the inactivation of the receptor (→ C). The receptors are also internalized. The effectiveness of receptor stimulation can also be reduced by influencing cellular signal transmission. The opiate receptor acts partly via inhibition of adenylyl cyclase (AC), a decrease of cyclic adenosine monophosphate (cAMP) and reduced activation of protein kinase A (→ D). Taking opiates thus at first diminishes cAMP formation (→ E2). Chronic intake, however, raises the expression of adenylyl cyclase by influencing cAMP-responsive element-binding protein ([CREB] → p. 6 ff.). As a result, even in the presence of opiates, cAMP is still formed (→ E3). Subsequent withdrawal of opiates will, for example, via a massive increase in cAMP (→ E4), lead to withdrawal symptoms.
A. Drug Usage

- Stress
- Genetic disposition (DAT-1, ADH)
- Social context (e.g. war)

Mesolimbic dopaminergic system

- Dependence
- Addiction

Endorphins, dopamine, serotonin, GABA

Positive effects:
- e.g. Euphoria
- Feeling of omnipotence
- Relaxation

Withdrawal symptoms:
- Depression
- Anxiety
- Nervousness

B. Reversal of Drug Effect

Primary intake
- Sudden withdrawal

Effect reversal
- Withdrawal symptoms

Renewed intake

C. Receptor Inactivation

Opiates

- Receptor
- P
- G

Internalization

G protein receptor kinase

Phosphorylation

Cellular effects

D. Signal Transduction

Opiates

- G protein
- Adenylylcyclase
- Protein kinase A
- CREB

E. Adaptation of Signal Transduction

1. Normal
- AC-activating receptor
- cAMP

2. Primary intake
- Opiate receptor

3. Chronic intake
- AC
- cAMP

4. Withdrawal
- AC
- cAMP
Cerebrospinal Fluid, Blood–Brain Barrier

Cerebrospinal fluid (CSF) flow (→A). CSF is formed mainly in the choroid plexus of the lateral ventricles. It flows via the interventricular foramina (→A1) into the third ventricle and from there into the fourth ventricle via the aqueduct (→A2). It then circulates via the foramina of Luschka and Magendi (→A3) into the subarachnoid space and the arachnoid villi of the sinuses of the dura mater (Pacchionian bodies) and from there into the venous sinuses (→A4).

CSF flow may be slowed or interrupted at each of the named structures. This results in CSF backward congestion (hydrocephalus) with raised pressure. Depending on the site of the obstruction, one distinguishes a communicating hydrocephalus, in which CSF flow between the ventricles is uninterrupted, from a non-communicating hydrocephalus, where the connections between the ventricles are obstructed.

Obstruction of the CSF channels, especially the aqueduct, can be the result of malformations, scars (as after an infection or bleeding), or tumors. The absorption of CSF in the arachnoid villi is impaired if drainage in the sinuses is obstructed (e.g., in thrombosis) or the systemic venous pressure is raised (e.g., in heart failure). Drainage can also be reduced after subarachnoid hemorrhage or meningitis as well as by a high protein concentration in CSF (tumors or infection), because the arachnoid villi can be obstructed by proteins. Lastly, absorption may be reduced for no obvious external reasons. An increase of the CSF space caused by primary cerebral atrophy is termed hydrocephalus e vacuo.

In congenital hydrocephalus the cranial bones may be separated because their sutures have not yet fused, resulting in an enlarged cranium ("water on the brain", the literal meaning of the term hydrocephalus) (→A5). Once the bony sutures have fused, an excess of CSF causes an increased CSF pressure (→p. 358).

Composition of CSF (→B). The normal composition of CSF is approximately the same as that of serum. However, it has lower protein and protein-bound Ca²⁺ concentrations. The K⁺ concentration is also lower (about 1 mmol/l). Changes in the composition of CSF are of great diagnostic significance in certain brain diseases:

CSF is normally as clear as water and does not contain any erythrocytes and only very few leukocytes (<4 per μL, largely lymphocytes). However, in infections (e.g., meningitis) leukocytes may pass into the CSF (→cloudy CSF), and after hemorrhage (e.g., a brain tumor) erythrocytes may be found in CSF (→reddish discoloration). A yellowish CSF may indicate the presence of blood pigments or bilirubin-binding plasma proteins.

The protein concentration in CSF is increased if there is no CSF absorption in the arachnoid villi or in infection (especially formation by immune competent cells).

The glucose concentration in CSF is decreased by tumors, acute bacterial infections, tuberculosis, fungal infections of the brain as well as defective glucose transport in rare cases.

Blood–brain barrier (→C). The endothelial cells of the blood capillaries in the brain (except for the posterior pituitary, area postrema, choroid plexus, and circumventricular organs) under the influence of astrocytes form dense tight junctions that prevent the passage of substances dissolved in blood (electrolytes, proteins) or of cells. In this way the extracellular milieu of the brain is separated from the blood, thus preventing nerve cells being exposed to electrolyte changes, transmitters, hormones, growth factors, and immune reactions. Under abnormal circumstances the tight junctions can be opened. This happens, for example, in brain tumors that contain no functional astrocytes. The blood–brain barrier may also be breached in hyperosmolarity (brought about by infusion of hypertonic mannitol solutions) or in bacterial meningitis.

The blood–brain barrier is not yet closed in newborns. As a result, in hyperbilirubinemia of the newborn bilirubin can reach the brain and damage nuclei ("Kerne") in the brain stem (hence kernicterus). Damage to the basal ganglia may, for example, cause hyperkinesias (→p. 134).
A. Cerebrospinal Fluid (CSF) Flow

1. Normal cerebral capillary
2. Abnormal

B. CSF Composition

<table>
<thead>
<tr>
<th>Electrolytes</th>
<th>Protein</th>
<th>Leukocytes, proteins</th>
<th>Erythrocytes</th>
<th>Blood pigments, plasma proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum normal</td>
<td>CSF normal</td>
<td>Abnormal CSF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proteins g/L</td>
<td>70</td>
<td>0.2</td>
<td>Infections, CSF obstruction</td>
<td></td>
</tr>
<tr>
<td>Glucose mmol/L</td>
<td>5</td>
<td>3</td>
<td>Tumors, infection</td>
<td></td>
</tr>
<tr>
<td>Na⁺ mmol/L</td>
<td>145</td>
<td>150</td>
<td>Infections, CSF obstruction</td>
<td></td>
</tr>
<tr>
<td>K⁺ mmol/L</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ca²⁺ mmol/L</td>
<td>2.5</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mg²⁺ mmol/L</td>
<td>0.8</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osm</td>
<td>295</td>
<td>295</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C. Blood-Brain-Barrier

- Astrocytes
  - Lipid-soluble substances
  - Electrolytes, proteins, cells
  - Closed tight junctions
  - Selective carrier

- Tumors
- Bacterial meningitis
- Infusions
- Defective astrocytes
- Open tight junctions
- Osmolarity ↑↑
After the the cranial bone sutures have fused, the brain is confined within a rigid casing. Its volume cannot expand and any intracranial compartments can get larger only at the expense of other compartments (→ A1).

The cerebrospinal fluid (CSF) space of the brain is open to the CSF space of the spinal cord via the foramen magnum. The intravascular space is momentarily increased with each systolic pulse wave, and synchronously with the pulse a small volume of CSF escapes through the foramen magnum into the spinal CSF space, i.e., the intravascular space is increased at the expense of the CSF space (→ A2).

Similarly, an increase in interstitial or intracellular volume at first occurs at the expense of the CSF space. Once this reserve is used up and the CSF space has collapsed, CSF pressure quickly rises and there is a marked decrease in cerebral perfusion (→ A3).

Several forms of cerebral edema are distinguished (→ B):

- **Cytotoxic edemas** enlarge the intracellular space as a result of cell swelling (→ B1). Among causes are energy deficiency (e.g., due to hypoxia or ischemia). Impairment of Na+/K⁺-ATPase raises the intracellular Na⁺ concentration and decreases intracellular K⁺ concentration. Subsequent depolarization leads to Cl⁻ entry and cell swelling (→ p. 10).

- Reduction of extracellular osmolality can also cause cell swelling, for example, in hypotonic hyperhydration (→ p. 122).

- Treatment of prolonged hypernatremia demands caution. The glial cells and neurons compensate for the extracellular hyperosmolality by intracellular accumulation of osmoles (e.g., inositol), a process that takes days. If the hypernatremia is corrected too quickly, the osmoles are not removed quickly enough and the cells swell.

- **Cerebral edemas of vascular origin** occur when there is increased permeability of the cerebral capillaries. The resulting capillary filtration of proteins with osmotically obliged water (→ B2) thus increases the interstitial space. Among causes of increased permeability are tumors, infections, abscesses, infarcts, bleeding, or poisoning (lead).

Water can also accumulate in the interstitial space when the blood–brain barrier is intact but the osmolarity of the interstitial space is higher than that of blood, for example, if there is a rapid fall in the concentration of blood sugar (during treatment of diabetes mellitus), of urea (dialysis), or of Na⁺ (interstitial cerebral edema; → B3). In those conditions the increase of interstitial space may be accompanied by cell swelling.

**CSF congestion** also increases cerebral pressure (→ p. 356). An acute disorder of CSF drainage causes a rise in pressure that, via narrowing of the vessel lumen, impairs cerebral perfusion (→ A4). Chronic drainage abnormality, by bringing about the death of neurons, i.e., a decrease in intracellular space, will ultimately result in a decrease in cerebral mass (→ B5).

**Tumors and bleeding** (→ A3) take up intracranial volume at the expense of other compartments, especially the CSF space.

**Symptoms of increased CSF pressure.** Due to the increased cerebral pressure, lymph from the back of the eye can no longer flow toward the intracranial space via the lymphatic canal at the center of the optic nerve. Lymph thus collects at the exit of the optic nerve and causes bulging of the papilla (papilledema; → C1). Other consequences of increased CSF pressure are **headache, nausea, vomiting, dizziness, impaired consciousness** (e.g., due to decreased perfusion), bradycardia and arterial hypertension (through pressure on the brain stem), **squinting** (compression of the abducens nerve), and **dilated pupils which are unresponsive to light** (compression of the oculomotor nerve) (→ C2). The pressure gradients bear an increasing risk of herniation of parts of the brain through the cerebellar tentorium (→ C3a) or the foramen magnum (→ C3b). The herniated parts compress the brain stem causing immediate death. If the increase in CSF pressure is unilateral, the cingulate gyrus may herniate under the falx cerebri (→ C3), causing compression of the anterior cerebral vessels with corresponding deficits in cerebral function (→ p. 360).
A. Volume Changes of Brain Compartments

1 Cranial volumes

- Skull
- Intracellular (~80%)
- Interstitial (<10%)
- CSF (~10%)
- Intravascular (~1-3%)

Exchange of metabolites

1. Volume Changes of Brain Compartments

- Cell swelling
- Outflow obstruction
- Cerebral perfusion

2. Pulse-synchronous vessel dilation

3. Cell swelling

4. Acute CSF obstruction

5. Chronic CSF obstruction

B. Cerebral Edema

1. Cytotoxic cerebral edema

- Energy deficiency
- Depolarization
- Cell swelling
- H₂O entry

2. Of vascular origin

- Blood
- H₂O
- Interstitial space
- Na⁺
- Cl⁻

3. Interstitial

- Osm
- H₂O

C. Effects of Increased Intracranial Pressure

1. Papilledema

2. Additional effects

- Headache
- Nausea
- Vomiting
- Coma
- Bradycardia
- Hypertension
- Squint
- Fixed pupils

3. Herniation

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Disorders of Cerebral Blood Flow, Stroke

Complete cessation of cerebral blood flow causes **loss of consciousness** within 15–20 seconds (→ p. 342) and **irreversible brain damage** after seven to 10 minutes (→ A1). Occlusion of individual arteries results in deficits in circumscribed regions of the brain (stroke). The basic mechanism of damage is always **energy deficiency** caused by ischemia (e.g., atherosclerosis, embolism). **Bleeding** (due to trauma, vascular aneurysm, hypertension; → p. 208) also causes ischemia by compressing neighboring vessels.

By inhibiting Na⁺/K⁺-ATPase, energy deficiency causes the cellular accumulation of Na⁺ and Ca²⁺ as well as an increased extracellular concentration of K⁺, and thus depolarization. This results in the cellular accumulation of Cl⁻, cell swelling, and **cell death** (→ A; see also p.10). It also promotes the release of glutamate, which accelerates cell death via the entry of Na⁺ and Ca²⁺.

Cell swelling, release of vasoconstrictor mediators, and occlusion of vessel lumina by granulocytes sometimes prevent **reperfusion**, despite the fact that the primary cause has been removed. Cell death leads to inflammation that also damages cells at the edge of the ischemic area (penumbra).

The **symptoms** are determined by the site of the impaired perfusion, i.e., the area supplied by the vessel (→ B).

The frequent occlusion of the **middle cerebral artery** causes contralateral muscle weakness and spasticity as well as sensory deficits (hemianesthesia) by damage to the precentral and postcentral lateral gyri. Further consequences are **ocular deviation** (“déviation conjuguée” due to damage of the visual motor area), **hemianopsia** (optic radiation), motor and sensory **speech disorders** (Broca and Wernicke speech areas of the dominant hemisphere), abnormalities of spatial perception, apraxia, and hemineglect (parietal lobe).

Occlusion of the **anterior cerebral artery** causes **contralateral hemiparesis and sensory deficits** (due to loss of the medial portion of the precentral and postcentral gyri), **speech difficulties** (due to damage of the supplementary motor area) as well as **apraxia of the left arm**, when the anterior corpus callosum, and thus the connection from the dominant hemisphere to the right motor cortex, is impaired. Bilateral occlusion of the anterior cerebral artery leads to **apathy** as a result of damage to the limbic system.

Occlusion of the **posterior cerebral artery** leads to partial **contralateral hemianopsia** (primary visual cortex) and **blindness** in bilateral occlusion. In addition, there will be **memory losses** (lower temporal lobe).

Occlusion of the **carotid** or **basilar artery** can cause deficits in the supply area of the anterior and middle cerebral arteries. When the **anterior choroid artery** is occluded, the basal ganglia (hypokinesia), the internal capsule (hemiparesis), and optic tract (hemianopsia) are affected. Occlusion of the branches of the **posterior communicating artery** to the thalamus primarily causes sensory deficits.

Complete occlusion of the **basilar artery** causes paralysis of all limbs (tetraplegia) and of the ocular muscles as well as coma (→ p. 342). Occlusion of the branches of the **basilar artery** can cause infarctions in the cerebellum, mesencephalon, pons, and medulla oblongata. The effects depend on the site of damage:

- **Dizziness, nystagmus, hemiataxia** (cerebellum and its afferent pathways, vestibular nerve).
- **Parkinson’s disease** (substantia nigra), **contralateral hemiplegia** and tetraplegia (pyramidal tract).
- **Loss of pain and temperature sensation** (hypesthesia or anesthesia) in the ipsilateral half of the face and the contralateral limbs (trigeminal nerve [V] and spinotalamic tract).
- **Hypacusis** (auditory hypesthesia; cochlear nerve), **ageusia** (salivary tract nerve), **singuilatus** (reticular formation).
- Ipsilateral ptosis, miosis, and facial anhidrosis (Horner’s syndrome, in loss of sympathetic innervation).
- **Paralysis of the soft palate and tachycardia** (vagal nerve [X]). **Tongue muscle paralysis** (hypoglossal nerve [XII]), **drooping mouth** (facial nerve [VII]), **squinting** (oculomotor nerve [III], abducens nerve [VI]).
- **Pseudobulbar paralysis** with global muscular paralysis (but consciousness maintained).
A. Effects of Abnormal Cerebral Perfusion

- Ischemia
- Bleeding
- Oxygen (O2) reduction
- Increased ATP
- Increased Na
- Increased Ca
- Glutamate
- H2O
- Nerve cell
- Cell swelling
- Depolarization
- Necrosis
- Brain tissue
- Intracranial pressure
- Lesion of cells at margin of ischemic region
- Inflammation
- Thromboxan
- Vasoconstriction

B. Vascular Occlusion as Cause of Ischemia

- Anterior cerebral a.
- Medial cerebral a.
- Posterior cerebral a.
- Basilar a.
- Posterior communicating a.
- Internal carotis a.
- Branches of basilar a.
- Mid-brain
- Pons
- Medulla oblongata
- Basilar a.
- Basilar a.
- Internal carotis a.
- Posterior communicating a.
- Anterior choroid a.
- Basal ganglia
- Internal capsule
- Optic tract
- Thalamus

- Hemiparesis
- Hemianesthesia
- Apraxia
- Apathy
- Hemianesthesia
- Hemiparesis
- Conjugate deviation
- Visual field defect
- Aphasia
- Apathy
- Hemineglect
- Hypokinesia
- Hemiparesis

- Hemianopsia
- III, VII, XII, Parkinson’s dis., hemiparesis
- V, VI, VII, hypacusis, ataxia, nystagmus, Horner’s syndrome
- Tetraplegia, pseudobulbar paralysis
- V, X, nystagmus, Horner’s syndrome, hemiataxia, hiccough, hemianästhesia, ageusis, hypakusis
- XII, hemiparesis, Hemihypesthesia

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Further Reading

**General Physiology**

West JB. Physiological Basis of Medical Practice. 12th ed. Baltimore: Williams & Wilkins; 1990

**General Pathophysiology**

McCance KL, Huether SE. Pathophysiology. The Biologic Basis for Disease in Adults and Children. 2nd ed. St. Louis: Mosby-Year Book; 1994

**Single Topics of Pathophysiology and Physiology**

**Cell Physiology**


**Blood and Immunology**

Kuby J. Immunology. 2nd ed. New York: Freeman and Company; 1994

**Respiration and Acid–Base Balance**

West JB. Respiratory Physiology: The Essentials. 5th ed. Baltimore: Williams & Wilkins; 1995

**Kidney and Electrolytes**


**Stomach, Intestine, Liver**

Medical Dictionaries

Journals
Annual Review of Physiology. Annual Review Inc. Palo Alto, California/USA
NIPS (News in Physiological Sciences). Schultz SG, ed. Houston, Texas/USA
Physiological Reviews. The American Physiological Society, Bethesda, Maryland/USA
Science. American Association for the Advancement of Science, New York/USA
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