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Color Atlas of Pathophysiology

Stefan Silbernagl
Florian Lang

2nd edition

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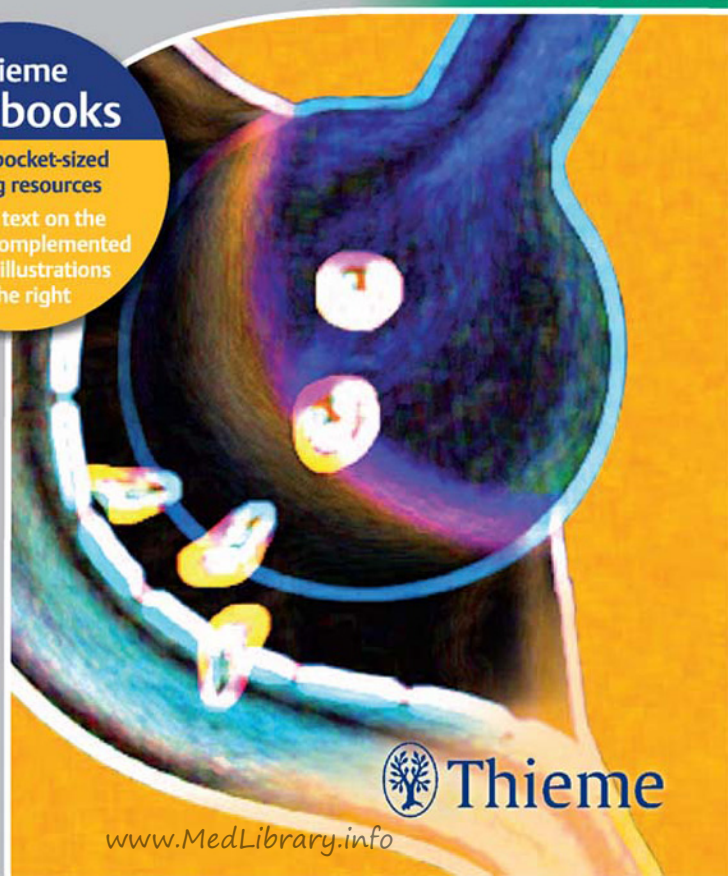

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At a Glance

Color Atlas of Pathophysiology

2nd edition

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Preface to the Second Edition

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.

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 endocrinal abnormalities, diseases of skeletal muscle, 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 book has met the interest of numerous readers and thus a second edition has become necessary. The new edition provided us with the opportunity to critically review the former edition and to include new knowledge. We continue to appreciate any critical comments and ideas communicated to us from the readership.

The second edition of the *Atlas* would again have been inconceivable without the great commitment, amazing creativity and outstanding expertise of the graphic designers, Ms. Astried Rothenburger and Mr. Rüdiger Gay. We would like to extend our warmest gratitude to them for their renewed productive co-operation. Our thanks also go to our publishers, in particular Ms. Rachel Swift und Ms. Elisabeth Kurz for their exceptional skill and enthusiasm in editing and producing the 2nd edition of the *Atlas*. Ms. Katharina Völker did a great job during the updating of the subject index, Ms. Tanja Loch during proofreading.

We hope that readers continue to find in this *Atlas* what they are looking for, that they find the text and pictures understandable, and that they enjoy using this book throughout their studies and their working life.

Würzburg and Tübingen, Germany
September 2009

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For Jakob

Stefan Silbernagl

For Viktoria and
Undine, Karl, Philipp, Lisa

Florian Lang

Cell Growth and Cell Adaptation

In the middle of the 19th century 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.

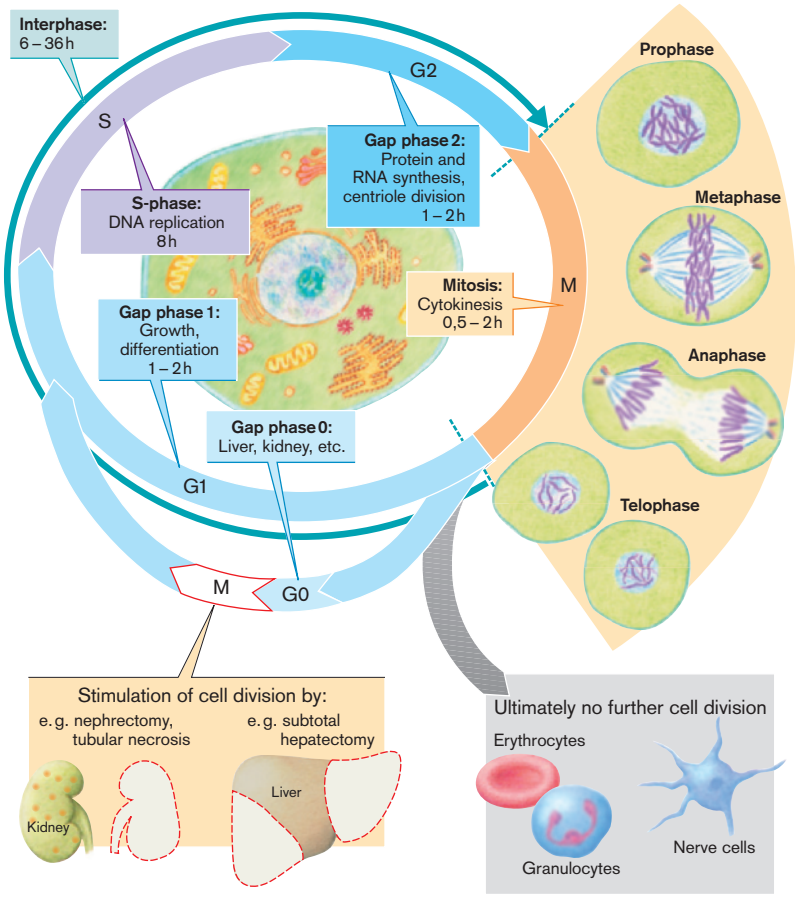
With the exception of the germ cells, whose chromosome set is halved during meiotic division (*meiosis*), most cells divide after the chromosome set has first been replicated, i.e., after mitosis (so-called indirect division of the nucleus) followed by division of the cell (*cytokinesis*). In this process 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 $p34^{cdc2}$, 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_1 phase* (**g**ap 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 **s**ynthesis). After the subsequent *G_2 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* (chromosome 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_1 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. 32 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*.

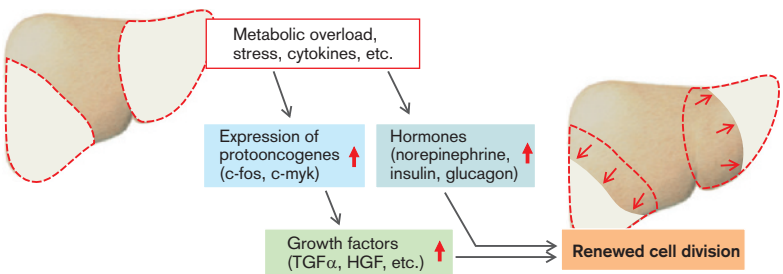
The cells of some organs and tissues do not normally proliferate (see below). Such **stable** or **resting cells** enter a resting phase, the *G_0 phase*, after mitosis. Examples of such cells are the parenchymal cells of the liver, kidneys, and pancreas as well as connective tissue and mesenchymal cells (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_1 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_0 phase to the G_1 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**). The GF re-

A. Cell Cycle



B. Compensatory Hyperplasia



ceptors are activated (usually tyrosine kinase activity; → p. 7 f., 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. 16).

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. 16) 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.

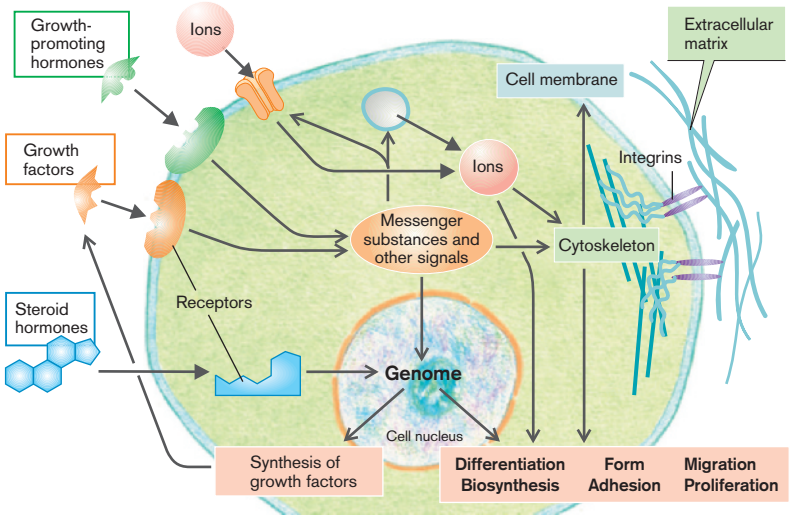
The regeneration of labile and stable cells does not necessarily mean that the original tissue structure is reconstituted. For this to happen the **extracellular matrix** must be intact, as it serves as the guiding system for the shape, growth, migration, and differentiation of the cell (→ **C**). The extracellular matrix consists of fibrous structural proteins (collagen I, II and 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. 156 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 can hardly 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. 234).

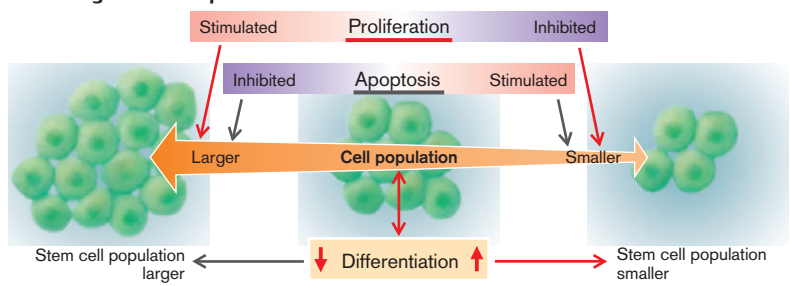
Adaptation to changed physiological or unphysiological demands can be achieved through an increase or decrease in the **number of cells** (*hyperplasia* or *aplasia*; → **D**, **E**). This can be triggered by *hormones* (e.g., development of secondary sex characteristics and growth of mammary epithelium 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 (body-building) 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. 222 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. 14), 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. 148 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. 16).

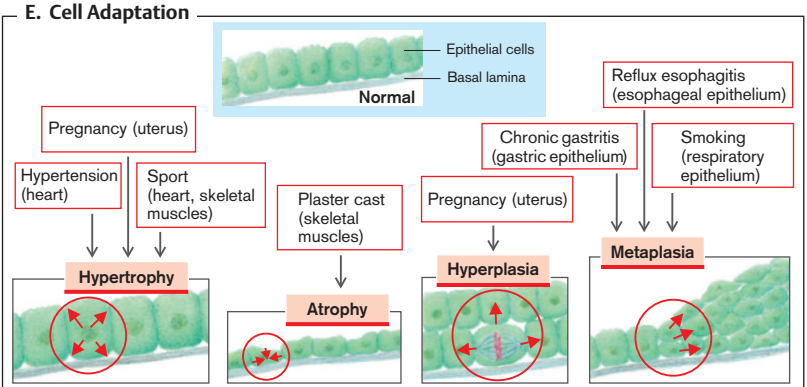
C. Regulation of Cell Proliferation, Motility and Differentiation



D. Changes in Cell Population



E. Cell Adaptation



Abnormalities of Intracellular Signal Transmission

Most hormones bind to **receptors of the cell membrane** (→ **A 1 – 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 stimulates the formation of different intracellular second messengers. **Abnormalities** can occur if, for example, the *number of receptors* is reduced (e.g., down-regulation at 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 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** activate via a *stimulating G protein* (G_s) an *adenylyl cyclase* (AC), which forms cyclic adenosine monophosphate (**cAMP**) (→ **A1**). cAMP activates *protein kinase A* (PKA), which phosphorylates and thus influences, 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] V_2 receptors), gastrin, secretin, vasoactive intestinal peptide (VIP), oxytocin, adenosine (A_2 receptor), serotonin (S_2 receptor), dopamine (D_1 receptor), histamine (H_2 receptor) and prostaglandins.

Some peptide hormones and neurotransmitters, for example, somatostatin, adenosine (A_1 receptor), dopamine (D_2 receptor), serotonin ($S_{1\alpha}$), angiotensin II, and acetylcholine (M_2 receptor), act by inhibiting AC and thus **reducing the intracellular cAMP concentration**, via an *inhibiting G protein* (G_i) (→ **A 2**). Some hormones can, by binding to different receptors, either increase the cAMP concentration (epinephrine: β-receptor; dopamine: D_1 receptor), or reduce it (epinephrine: α_2-receptor; dopamine: D_2 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 α_s 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. 162). *Pertussis toxin* from Hemophilus pertussis, the bacillus that causes whooping-cough (pertussis), blocks the G_i protein and thus raises, among others, the cAMP concentration (disinhibition of AC). *Forskolin* directly stimulates AC, while *xanthine derivatives*, for example, theophylline or caffeine, inhibit phosphodiesterase and thus the breakdown of cAMP (→ **A 4**). The xanthine derivatives are, however, mainly effective by inhibiting purinergic receptors.

In addition to cAMP, cyclic guanosine monophosphate (**cGMP**) serves as an intracellular messenger (→ **A 5**). 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 (IP_3), 1,3,4,5-inositol tetrakisphosphate (IP_4), and diacylglycerol (DAG). A membrane-bound phospholipase C (PLC) splits phosphatidylinositol diphosphate (PIP_2) into IP_3 and DAG after being activated by a G_0 protein. This reaction is triggered by, among others, epinephrine (α_1), acetylcholine (M_1 receptor), histamine (H_1 receptor), ADH (V_1 receptor), pancreozymin (CCK), angiotensin II, thyrotropin-releasing hormone (TRH), substance P, and serotonin (S_1 receptor). **IP_3** releases **Ca^{2+}** from intracellular stores. Emptying of the stores

opens Ca^{2+} channels of the cell membrane (→ **A 6**). Ca^{2+} can also enter the cell through ligand-gated Ca^{2+} channels. Ca^{2+}, 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** and Ca^{2+} stimulate protein kinase C (PKC), which in turn regulates other kinases, transcription factors (see below) and the cytoskeleton. PKC also activates the Na^+/H^+ exchanger leading to cytosolic alkalization and an increase in cell volume. Numerous cell functions are influenced in this way, among them metabolism, K^+ channel activities, and cell division. PKC is activated by **phorbol esters** (→ **A 8**).

Ca^{2+} activates an endothelial NO synthase, which releases NO from arginine. NO stimulates, e.g., in smooth muscle cells, a protein kinase G, which fosters the Ca^{2+} extrusion, decreases cytosolic Ca^{2+} concentration and thus leads to vasodilation. NO is further effective through nitrosylation of proteins.

Insulin and growth factors activate **tyrosine kinases** (→ **A 8**), which can themselves be part of the receptor or associate with the receptor upon stimulation. Kinases are frequently effective through phosphorylation of further kinases and thereby trigger a *kinase cascade*. Tyrosine kinases, for instance, activate with the involvement of the small G-protein Ras the protein kinase Raf, which triggers via a MAP-kinase-kinase the MAP (mitogen activated) kinase. 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. Through phosphorylation of the transcription factor Stat the tyrosine kinase Jak1 mediates effects of interferons, growth hormones, and prolactin. Activin, anti-Müllerian hormone and the transforming growth factor TGF-β similarly regulate the Smad transcription factors via a serine/threonine kinase.

Phosphorylated proteins are dephosphorylated by **phosphatases**, which thus terminate the action of the kinases. The Ca^{2+}-activated phosphatase calcineurin activates, among others, the transcription factor NFAT, which fosters, among others, hypertrophy of vascular smooth muscle cells and activation of T-lymphocytes.

Transcription factors (→ **A 9**) regulate the synthesis of new proteins. They travel into the nucleus and bind to the appropriate DNA sequences, thus controlling gene expression. Transcription factors may be regulated by phosphorylation (see above).

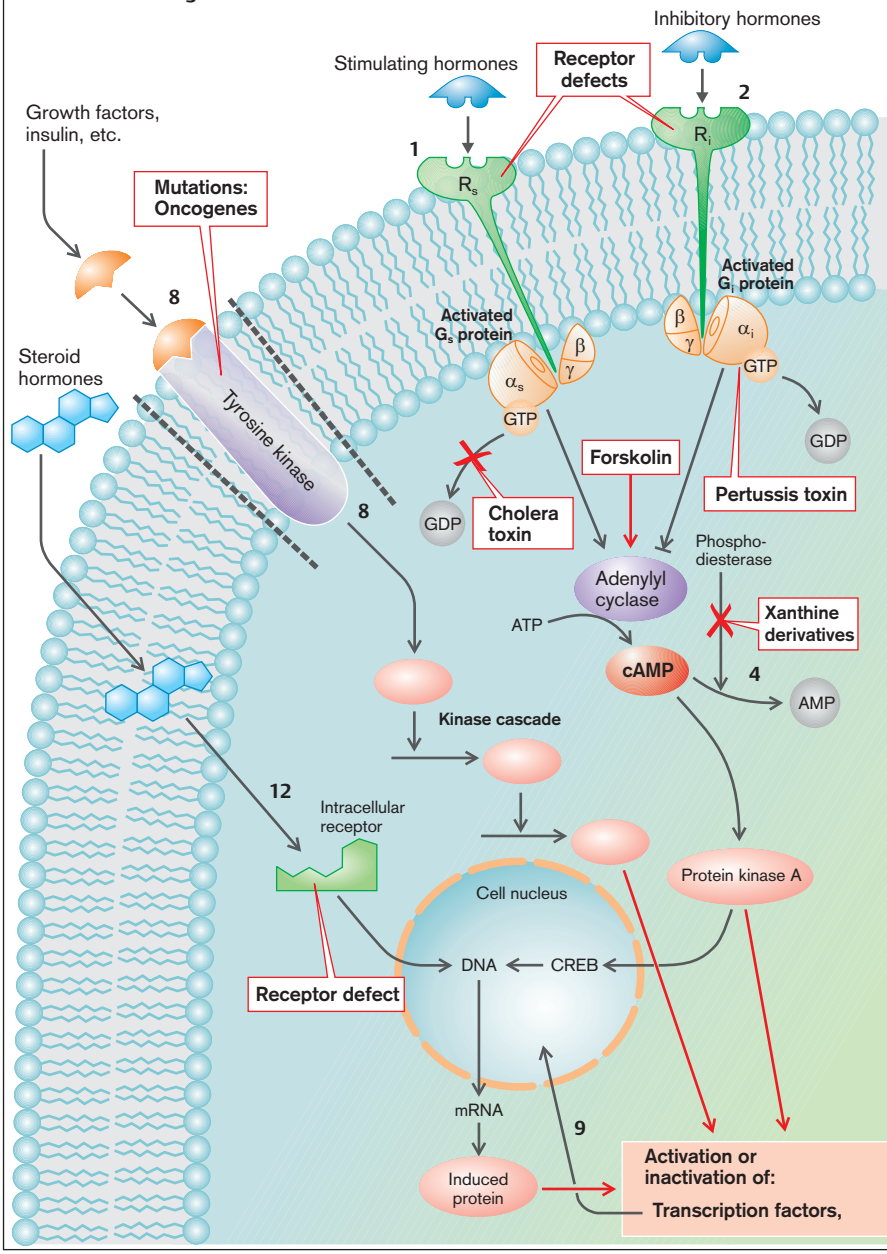
The degradation of proteins is similarly under tight regulation. **Ubiquitin ligases** attach the signal peptide ubiquitin at the respective proteins. Ubiquitinylated proteins are degraded through the proteasome pathway. Regulation of ubiquitin ligases includes phosphorylation.

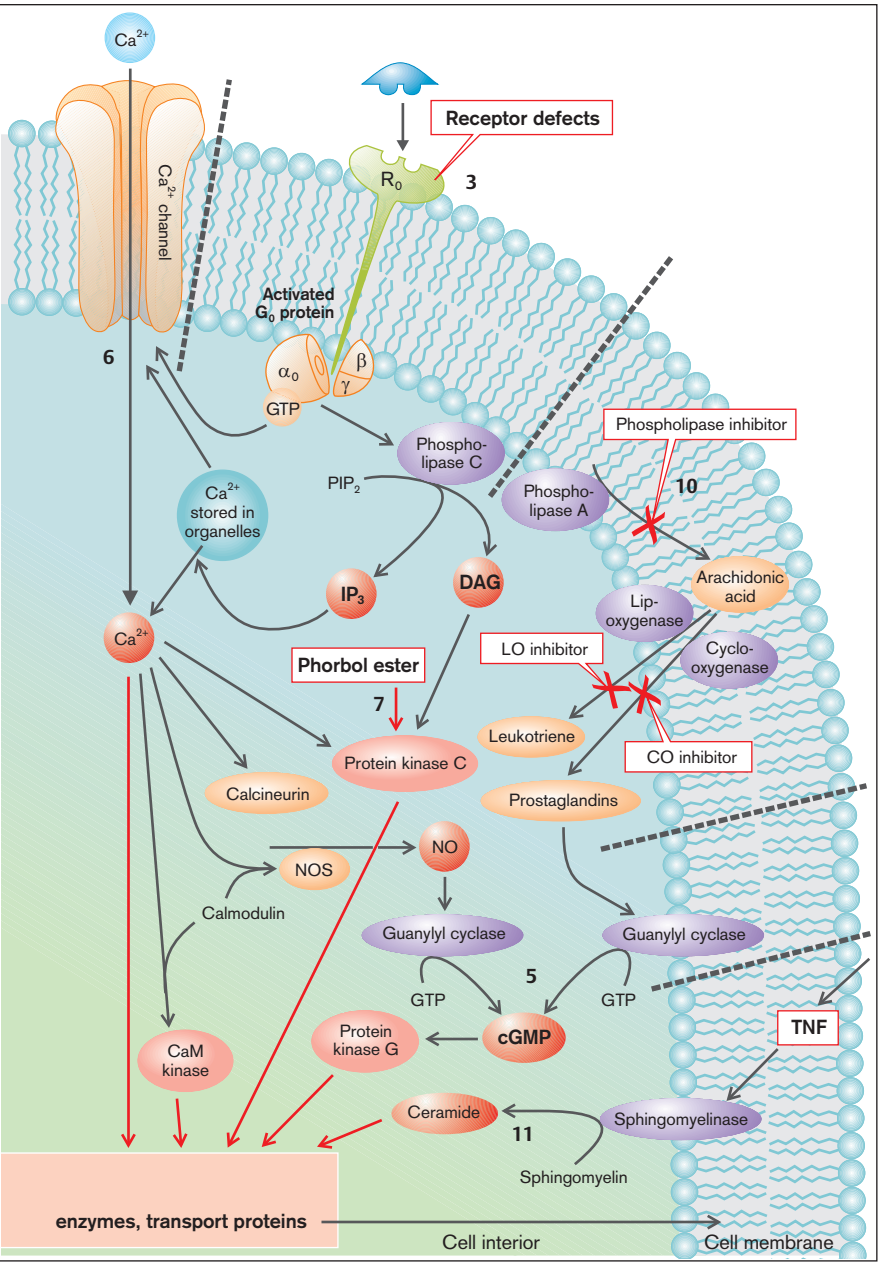
Arachidonic acid, a polyunsaturated fatty acid, can be split from membrane lipids, including DAG, by *phospholipase A* (→ **A 10**). Arachidonic acid itself has some cellular effects (e.g., on ion channels), but through the action of **cyclo-oxygenase** can also be converted to *prostaglandins* and *thromboxan*, which exert their effects partly by activating adenylyl cyclase and guanylyl cyclase. Arachidonic acid can also be converted to *leukotrienes* by **lipoxygenase**. Prostaglandins and leukotrienes are especially important during inflammation (→ p. 52 ff.) and not only serve as intracellular messengers, but also as extracellular mediators (→ p. 318). **Lipoxygenase inhibitors** and **cyclo-oxygenase inhibitors**, frequently used therapeutically (e.g., as inhibitors of inflammation and platelet aggregation), inhibit the formation of leukotrienes and prostaglandins.

Some mediators (e.g., the tumor necrosis factor [TNF] and CD95 [Fas/Apo1] ligand) activate acid **sphingomyelinase**, which forms *ceramide* from sphingomyelin (→ **A 11**). Ceramide triggers a series of cellular effects, such as activation of small G proteins (e.g., Ras), of kinases, phosphatases, and caspases, 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. 14).

Steroid hormones (glucocorticoids, aldosterone, sex hormones), thyroid hormones (TR), calcitriol (VDR), retinoids (RAR), and lipids (PPAR) bind to *intracellular (cytosolic or nuclear) receptor proteins* (→ **A 12**). 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





The **phosphatidylinositol-3-kinase** (PI3-kinase) is bound to phosphorylated tyrosine residues and associated IRS1 (insulin receptor substrate 1) of activated growth factor- and insulin-receptors (→ **A1**). The PI3-kinase generates $PI_{3,4,5}P_3$ (phosphatidylinositol-3,4,5-trisphosphate), which is anchored in the cell membrane. $PI_{3,4,5}P_3$ binds to PDK1 (phosphoinositide-dependent kinase 1) and the protein kinase B (PKB/Akt). In the following PDK1 phosphorylates and thus activates PKB/Akt (→ **A2**).

PKB/Akt stimulates several transport processes, such as the *glucose carrier GLUT4* (→ **A3**). It phosphorylates and thus inactivates the antiproliferative and proapoptotic *forkhead transcription factor FKHRL1* (FoxO1) and thus fosters cell proliferation and counteracts apoptosis (→ **A4**). PKB/Akt further phosphorylates and thereby activates MDM2, which inhibits the proapoptotic transcription factor p53 (→ **A5**).

PDK1 and PKB/Akt regulate gene expression further via the *transcription factor NFκB* (→ **A6**). NFκB is bound to the inhibitory protein IκB and is thereby retained in the cytosol. IκB is phosphorylated by the IκB kinase (IKK) leading to its ubiquitinylation and degradation. In the absence of IκB, NFκB travels into the nucleus and stimulates gene expression. NFκB stimulates, among others, the synthesis of extracellular matrix proteins and thereby favors the development of fibrosis. PKB/Akt phosphorylates and thereby activates IKK leading to activation of NFκB. The IKK is further activated by TNF-α and interleukin 1.

PKB/Akt phosphorylates *Bad* (→ **A7**), a protein stimulating the release of cytochrome *c* from mitochondria and thereby triggering apoptosis (→ p. 14). Phosphorylated Bad is bound to the protein 14-3-3 and is thus prevented from interacting with mitochondria. PKB/Akt phosphorylates and thereby inactivates caspase 9, a protease similarly involved in the signaling cascade leading to apoptosis (→ p. 14). Accordingly, PKB/Akt inhibits apoptosis.

PKB/Akt phosphorylates and thereby activates NO synthase. NO may similarly inhibit apoptosis. PKB/Akt activates $p47^{Phox}$ and thus stimulates the formation of reactive oxygen species (ROS) (→ **A8**).

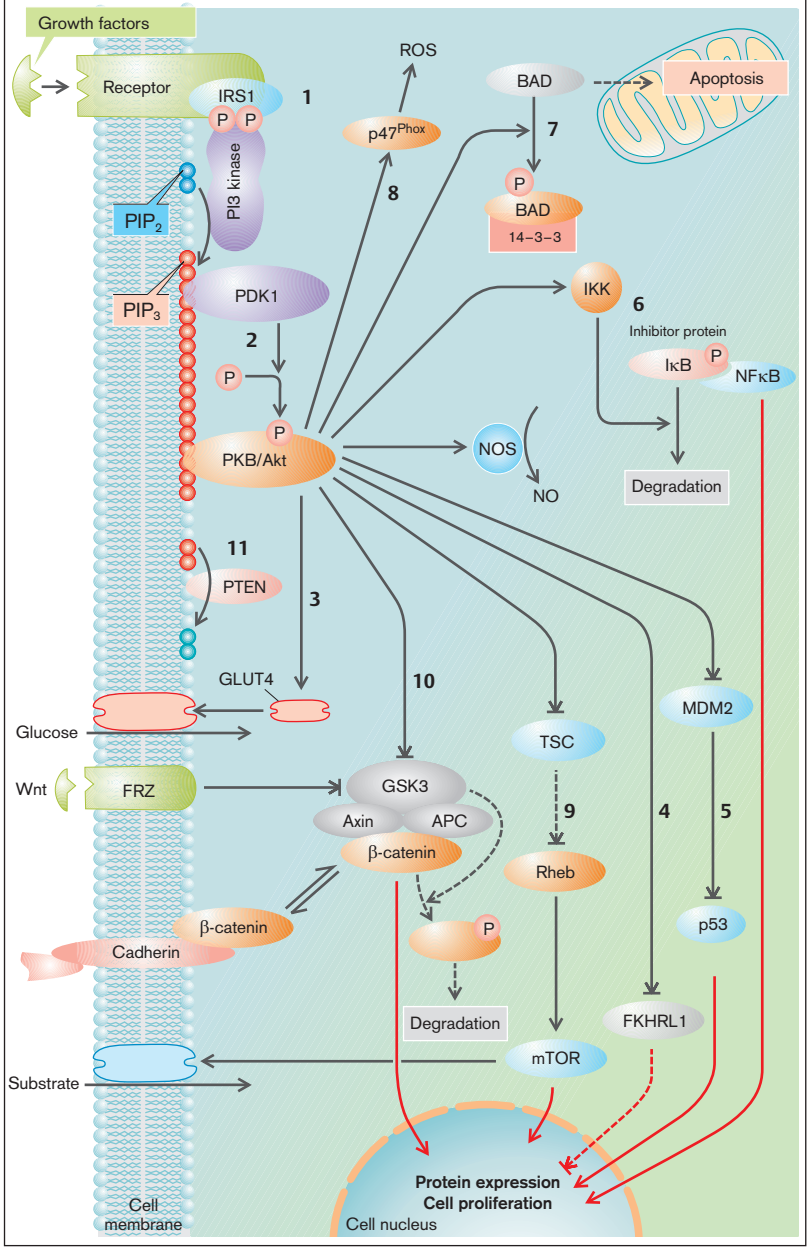
PKB/Akt phosphorylates and thereby inactivates *tuberin*, which forms a complex with Hammartin (tuberin sclerosis complex TSC). The TSC inactivates the small G-protein Rheb (→ **A9**). Activated Rheb stimulates the kinase mTOR (mammalian target of rapamycin), a protein stimulating cellular substrate uptake, protein synthesis, and cell proliferation. The inhibition of tuberin by PKB/Akt stimulates mTOR. The TSC is further stimulated and thus mTOR inhibited by the AMP-activated kinase (AMPK). Energy depletion increases the cellular AMP concentration and thus activates AMPK and inhibits mTOR.

PKB/Akt phosphorylates, and thereby inactivates, the *glycogen synthase kinase 3* (GSK3α and GSK3β) (→ **A10**). The GSK3 is further inhibited by the growth factor Wnt, an effect involving the receptor frizzled and the protein dishevelled. GSK3 binds to a protein complex consisting of Axin, von Hippel–Lindau protein (vHL), and adenomatous polyposis coli (APC). The complex binds the multifunctional protein *β-catenin*. GSK3 phosphorylates β-catenin, thus triggering its degradation. β-Catenin may bind to E-cadherin, which establishes a contact to neighboring cells. Free β-catenin travels into the nucleus, interacts with the TCF/Lef transcription complex and thus stimulates the expression of several genes important for cell proliferation. Wnt and activated PKB/Akt foster cell proliferation in part through inhibition of GSK3 and subsequent stimulation of β-catenin-dependent gene expression.

PDK1 phosphorylates and thereby activates the **serum- and glucocorticoid-inducible kinase** (SGK1). The expression of SGK1 is stimulated by glucocorticoids, aldosterone, TGF-β, ischemia, and hyperosmolarity. SGK1 stimulates a variety of carriers, channels, and the Na^+/K^+ ATPase. The kinase shares several target proteins with PKB/Akt. Following stimulation of its expression, it may play a leading part in PI3K-dependend signaling.

The **phosphatase PTEN** dephosphorylates $PI_{3,4,5}P_3$ and thereby terminates $PI_{3,4,5}P_3$-dependent signal transduction (→ **A11**). Accordingly, PTEN inhibits cell proliferation. Oxidative stress (→ p. 92) inactivates PTEN and thus increases the activity of Akt/PKB and SGK.

A. PI3 Kinase-Dependent Signal Transduction



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 (→ **A 1**), 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^+ (→ **A 2**). Normally the cell membrane is only slightly permeable for Na^+ (→ **A 3**), but highly permeable for K^+, so that K^+ diffuses out again (→ **A 4**). This K^+-efflux creates an inside negative potential (→ **A 5**) which drives Cl^- out of the cell (→ **A 6**). 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 the 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* (→ **A 9**) eliminates one H^+ for one Na^+, while the *3 Na^+/Ca^{2+} exchanger* (→ **A 8**) eliminates one Ca^{2+} for 3 Na^+. Na^+-bound transport processes also allow the (secondarily) active uptake of amino acids, glucose, phosphate, etc. into the cell (→ **A 7**). Lastly, depolarization achieved by opening the Na^+ channels (→ **A 10**) 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 the Na^+/K^+-ATPase. This intracellular Na^+ homeostasis may be **disrupted** if the activity of the 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 **Ca^{2+}** via the activation of the respective channels (→ **B**).

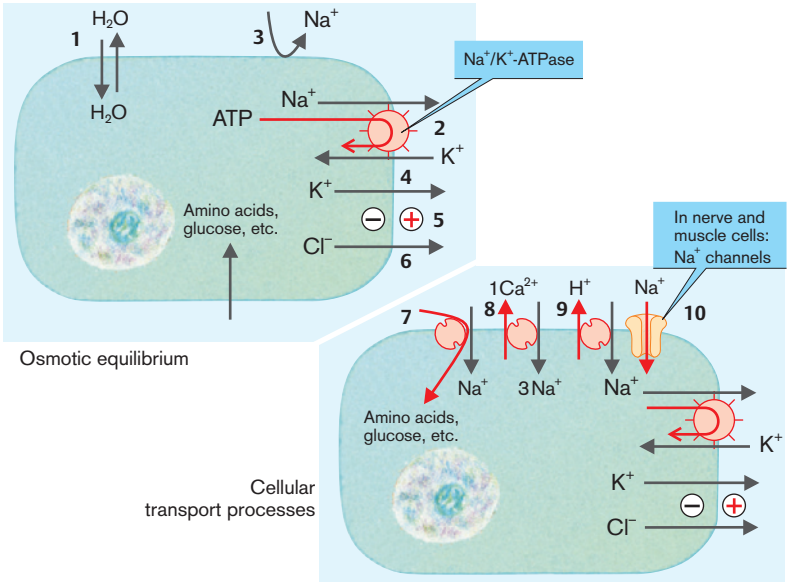
The increase in intracellular Na^+ concentration not only leads to cell swelling, but also, via impairment of the $3Na^+$/Ca^{2+} exchanger, to an increase in cytosolic **Ca^{2+} concentration**. Ca^{2+} produces a series of cellular effects (→ p. 6 ff.); among others it penetrates into the mitochondria and, via inhibition of mitochondrial respiration, leads to ATP deficiency (→ **B**).

If there is a lack of O_2, 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**). The generation of lactate further leads to extracellular acidosis, which influences the cell function through H^+-sensing receptors and channels.

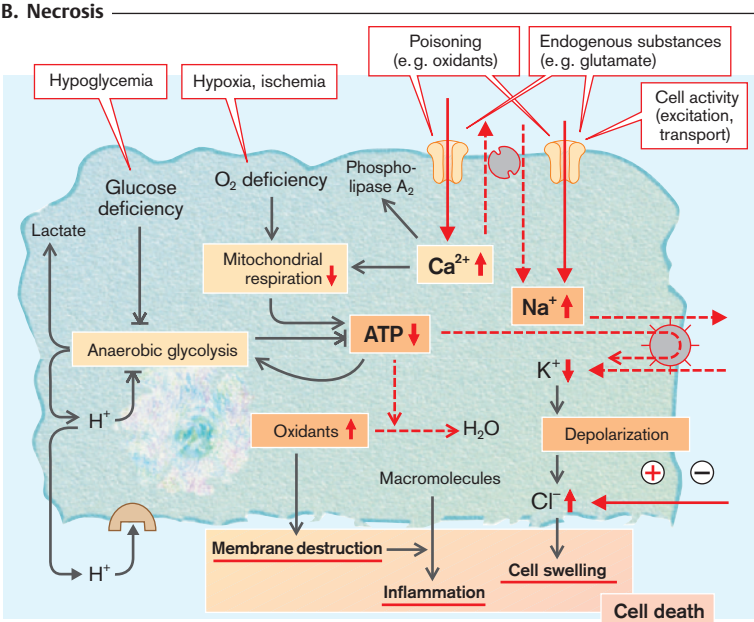
If an energy deficiency arises, the cell is more likely to be exposed to **oxidative damage**, because the cellular protective mechanisms against oxidants (O_2 radicals) are ATP-dependent (→ **B**). There is then a risk of the cell membrane being destroyed (lipid peroxidation) and **intracellular macromolecules** 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^+ and Ca^{2+}-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. Hypothermia decreases the activity of those channels and thus delays the machinery leading to cell death.

A. Homeostasis of Volume and Electrolytes in the Cell



B. Necrosis



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. 12), is a **programmed cell death** and, like cell division (→ p. 2 ff., 16), is a finely regulated physiological mechanism. Apoptosis 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.

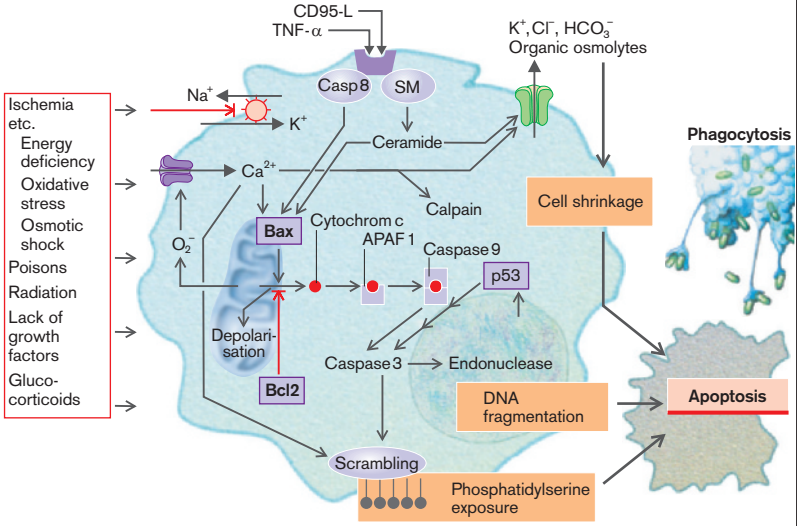
Apoptosis is mediated by a **signaling cascade** (→ **A**): the stimulation of distinct receptors (see below), excessive activation of Ca^{2+} channels, oxidative stress, or cell injury by other mechanisms lead to activation of protein-cleaving caspases and of a sphingomyelinase that releases ceramide from sphingomyelin. Incorporation of the proteins Bak or Bax into the mitochondrial membrane leads to depolarization of the mitochondria and cytochrome *c* release, effects inhibited by the similar proteins Bcl-2 and Bcl-xL. The effect of Bcl-xL is in turn abrogated by the related protein Bad. After binding to the protein APAF-1, the cytochrome *c* released from the mitochondria activates the caspase 9. The cascade eventually results in the activation of caspase 3, which stimulates an *endonuclease* leading to **DNA fragmentation.** The protease calpain is activated, which degrades the cytoskeleton. The cell loses electrolytes and organic osmolytes, proteins are broken down and the cell finally **shrinks** and disintegrates into small particles. Scrambling of the cell membrane leads to phosphatidylserine exposure at the cell surface, which fosters the binding and subsequent engulfment of the cellular particles by macrophages. In this way the cell disappears without intracellular macromolecules being released and, therefore, without causing inflammation. PKB/Akt inhibits apoptosis by phosphorylation and thus inactivation of Bad, caspase 9, and proapoptotic forkhead transcription factors (→ p. 10).

Apoptosis is triggered (→ **A**), for example, by *TNF-α*, *glucocorticoids*, cytotoxic drugs, 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 enter apoptosis. In this way they "anticipate necrotic cell death" and so prevent the release of intracellular macromolecules that would cause inflammation (→ p. 12).

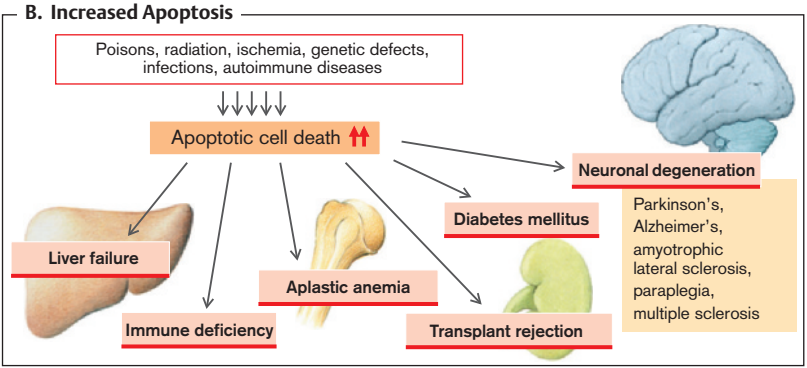
Pathologically increased apoptosis (→ **B**) may be triggered by *ischemia, toxins,* massive osmotic *cell shrinkage, radiation*, or *inflammation* (infections, autoimmune disease). The apoptosis may result in the inadequate death of functionally essential cells, leading to organ insufficiency (→ **B**). 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). 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* (→ p. 60). 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).

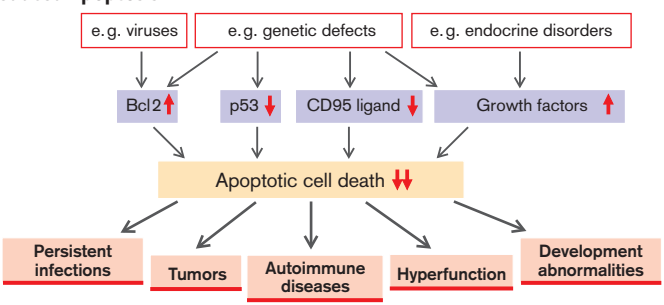
A. Triggering and Development of Apoptosis



B. Increased Apoptosis



C. Reduced Apoptosis



Development of Tumor Cells

Cell division is normally precisely adapted, via growth factors (GFs), to meet the specific requirement of cells (→ p. 4). The **GFs** stimulate tyrosine kinases (→ **A1**). The phosphotyrosine residues bind to adaptor proteins (GRB_2) and the GDP/GTP exchange factor SOS which then activates the small G protein Ras. The latter, via serine/threonine kinase Raf (→ **A2**), stimulates the mitogen-activated protein kinase cascade (MAPK cascade) and thus activates transcription factors which induce the expression of genes essential for cell division, e.g., Fos, Jun, Myc, Myb, Rel, E2F and DP1. The expression of Myc is further stimulated by β-catenin (→ p. 10). Thyroid hormones bind to nuclear receptors (ErbA; → **A3**), the hormone–receptor complex then similarly promotes gene expression and cell division. Substrate uptake and cell proliferation are further stimulated by the kinase mTOR (→ p. 10).

Growth-inhibiting factors 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. The retinoblastoma protein (Rb), e.g., binds to and inactivates the transcription factors E2F and DP1 (→ **A4**). For its part Rb is kept inactivated by the complex consisting of cyclin E and the kinase CDK_2 (= E-CDK_2) as well as the complex of cyclin D and the kinase CDK_4 (= D-CDK_4). In this way E-CDK_2 and D-CDK_4 promote cell division. 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**). The expression of several growth factors is inhibited by the transcription regulator WT1, which is partially effective through p53. Degradation of β-catenin is triggered by binding to the protein complex consisting of von Hippel–Lindau protein (vHL), adenomatous polyposis coli (APC), and glycogen synthase kinase 3β (GSK-3β, → p. 10) and the inactivation of mTOR by a complex consisting of tuberin and hammartin (→ p. 10). The cell proliferation is further inhibited by the Ca^{2+} receptor.

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

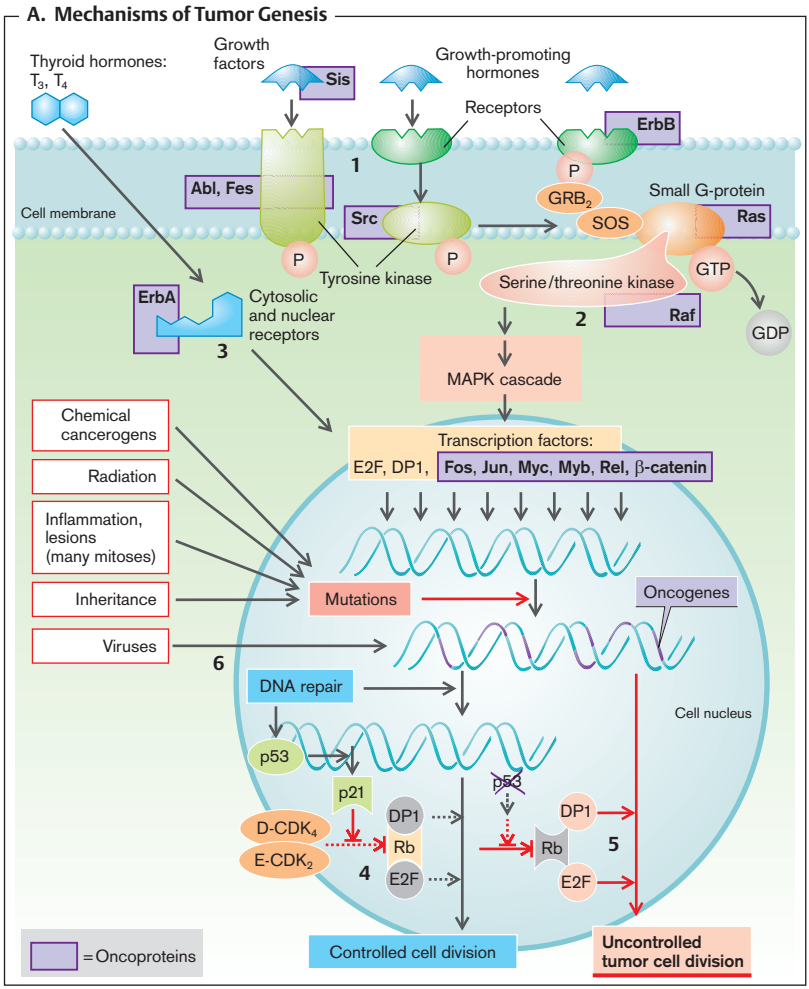
- *growth factors* that are formed by tumor cells and autocrinely stimulate their own cell division (e.g., Sis)
- *receptors* for thyroid hormones (ErbA)
- *receptors for growth factors* (e.g., ErbB, Fms)
- *tyrosine kinases* (e.g., Abl, Src, Fes)
- *small G proteins* (Ras)
- *serine/threonine kinases*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

As an example, inactivation of **Ras** is accelerated by a GTPase-activating protein (GAP) (→ **B**). Mutations of Ras may cancel its sensitivity to GAP, and Ras remains active.

Tumors may result from **defective proliferation-inhibiting proteins**. Thus, a loss of Rb (retinoblastoma) or p53 (LiFraumi syndrome) promotes uncontrolled cell division (→ **A5**). Moreover, genetic defects of WT1 (Wilms' tumor), vHL (von Hippel–Lindau disease), APC (familial adenomatous polyposis coli), tuberin (tuberous sclerosis), and PTEN (→ p. 10, e.g., breast tumors) enhances the tumor incidence.

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 (e.g., *inflammations* and *tissue lesions*) are more frequently subject to mutation than fully differentiated tissue. 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**).



Effects of Tumors

If uncontrolled cell division occurs (→ p. 16), 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 (→ **A 1**) on their surface and thus driving the lymphocytes to apoptosis (→ p. 14). A *compromised immune response* (e.g., HIV infection; → p. 62) 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 (→ **A 2** and p. 360). 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. 380). A bronchial carcinoma can interrupt the supply of air to the related alveoli and thus provoke their collapse (atelectasis; → p. 76).

Markedly dedifferentiated tumors gain the capacity to migrate to other tissues (**metastasis**; → **A 3**). For this to occur, the tumor cell must free itself from the bonds to its neighbor 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 O_2 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**).

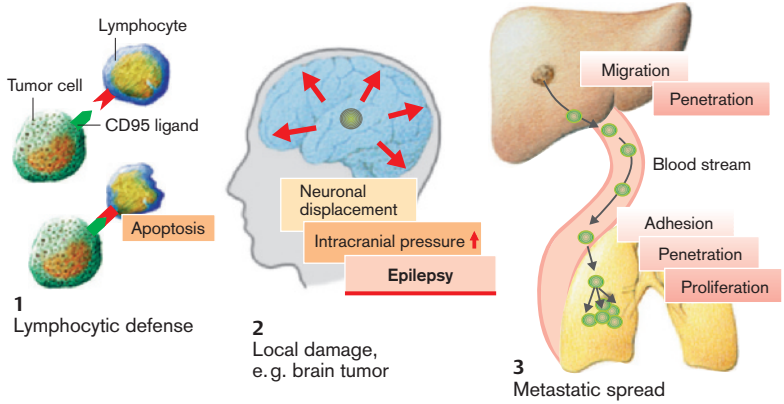
The **energy requirement** of the tumor cells is frequently met by *anaerobic glycolysis,* even if the O_2 supply is adequate, although the energy yield per mol glucose is only 5% of the oxidative glucose breakdown. The result is *hypoglycemia* and *acidosis* (→ **B**). The hypoglycemia stimulates the 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. 42 ff.).

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. 112). 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. 326).

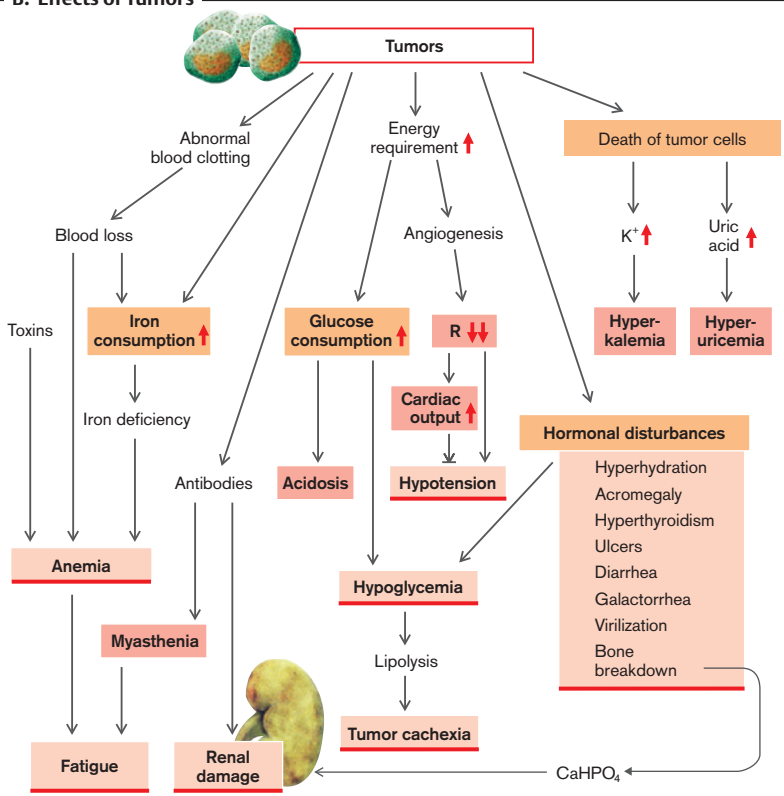
Even small tumors of endocrine tissues and dedifferentiated tumors of non-endocrine tissues (in particular small-cell bronchial carcinoma) frequently cause massive **hormonal abnormalities** (→ **B**). The increased release of hormones can result in numerous abnormalities (→ chap. 9), for example, raised blood pressure, hypotonic hyperhydration, catabolism, acromegaly, hypoglycemia, bone breakdown, hypercalcemia and renal stones, polycythemia, hyperthyroidism, virilization, galactorrhea, diarrhea, and peptic ulcers. On the other hand, hormones are used as diagnostic **tumor markers**, e.g. calcitonin (medullary thyroid carcinoma), choriongonadotropin (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. 268).

A. Tumors: Failure of Lymphocytic Defense, Local Damage, and Metastases



B. Effects of Tumors



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 (→ **A 1**), in 2006 (→ **G**) it was between 34 (Swaziland) and 83 (Andorra) years. Life expectancy is dependent on gender; in Germany it is 76.9 years for males and 82.3 years for females. The mean life expectancy increases with age, as those individuals reaching that age cannot have died earlier. In Germany the mean life expectancy in 2008 for a 70-year-old male was 82 years and for a 70-year-old female 85 years. 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 74 years in men and to 80 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 (→ **A 1**). Thus, of those aged 98 years, only 10% will still be alive three years later and after 10 years only 0.005% (→ **A 2**). The world record set by the French woman Jeanne Calment (122 years) is thus an extremely rare exception.

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** (→ **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* (→ **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 (→ **D**) and wear and tear (e.g., damage to joints), but also by lack of movement, leading to a vicious circle.

Aging of the immune system (**immunosenescence**) contributes to the aging process. Both innate (natural killer cells [NK], neutrophils, monocytes/macrophages, dendritic cells) and acquired immune response (T- and B-lymphocytes) are affected by aging. In the elderly, activation of the immune response is slowed, the protection by vaccination is compromised and the susceptibility to infectious disease, tumor growth, and autoimmune disease is enhanced. Morbidity and mortality increase accordingly.

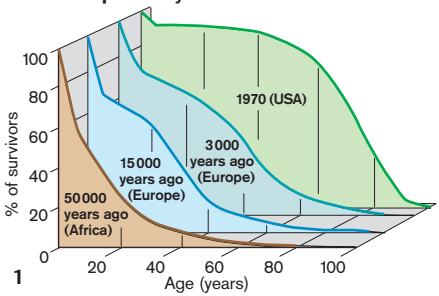
A Swedish study on the **immune-risk profile** (IRP) revealed in 80- and 90-year-old individuals increased numbers of $CD8^+$ T-cells (CMV-specific), decreased numbers of $CD4^+$ T-cells and $CD19^+$ B-cells as well as lack of CD28, the costimulator of T-cell activation. An increased IRP was associated with persistent cytomegalovirus (CMV) infections. It was concluded that immunosenescence results form *chronic antigen exposure* (e.g., CMV).

Age-related *problems with memory* (especially problems of orientation in an unaccustomed 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, as in Alzheimer's disease or atherosclerosis-induced reduction in cerebral blood flow, is part of the normal process of aging.

The **causes** of aging remain ill defined. Cultured cells are "aging," i.e., they stop proliferating after a certain number of replications (e.g., fetal lung fibroblasts after approximately 70 replications, → **B**). Only a few cells are "immortal" (unlimited cell proliferation, e.g., gonadal cells and hemopoietic stem cells, pathologically tumor cells).

Replicative **senescence** (→ **E**) is an age-related disruption of cell division. Similar to apoptosis, replicative senescence prevents *in vivo* tumor growth. Somatic mutations affecting cells in proliferative cell reservoirs may lead to the development of tumors. A barrier against tumors is the *telomere*, a specialized nucleopro-

A. Life Expectancy



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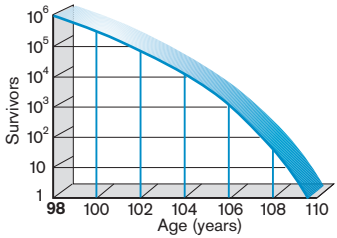
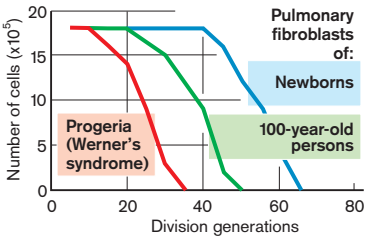
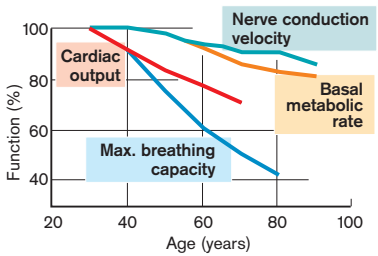


2 Life expectancy of 98-year-old persons

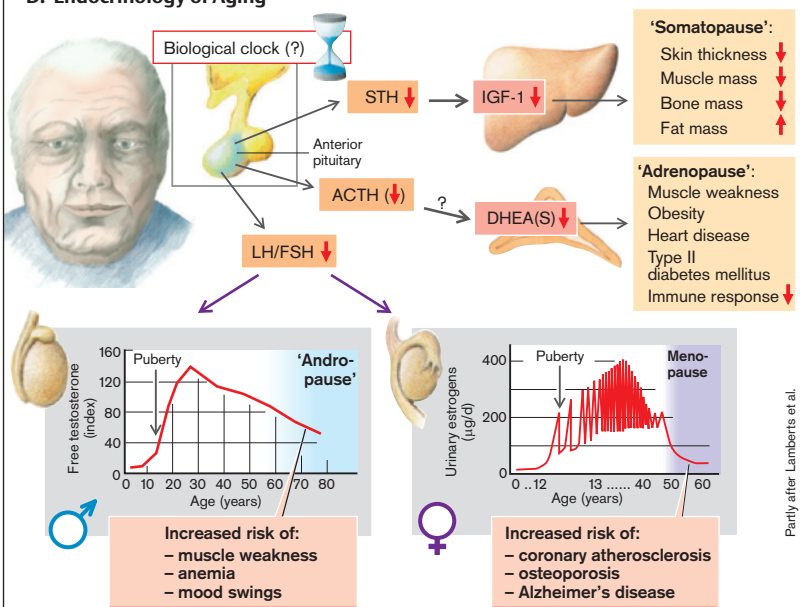
B. Dividing Capacity of Cultured Cells



C. Age-dependent Bodily Functions



D. Endocrinology of Aging



Partly after Lamberts et al.

tein complex capping the chromosomes. In somatic cells the telomere is shortened with each cell division. Replication for several generations (e.g., human fibroblasts ca. 70-fold) leads to gradual shortening of the telomere, eventually resulting in instability of the genome and thus the risk of tumor development. This risk is reduced by "automatic" activation of the *p53 pathway* at deranged telomere function. The p53 pathway prevents further cell replication (replicative senescence) and/or stimulates apoptosis of the affected cells (→ p. 14). *Telomerase,* an enzyme reversing the telomere shortening, counteracts senescence. In humans, telomerase is active in gonadal cells, but is turned off in somatic cells with little proliferative activity. In contrast, telomerase activity renders tumor stem cells immortal, allowing indefinite cell replications. Inhibitors of, or immunization against, *telomerase* are thus novel therapeutic approaches against tumor growth.

Life-span and aging are in part genetically determined. 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*.

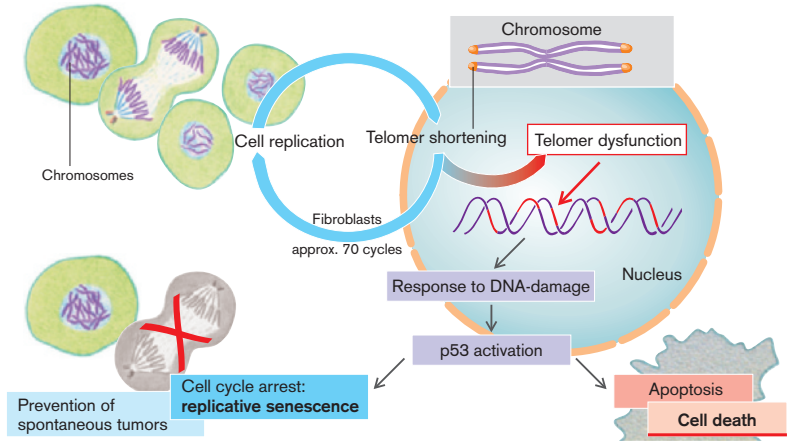
Certain genetic diseases lead to dramatic shortening of the life-span. For instance, the (very rare) mutation of the *LMNA* gene on chromosome 1 leads to defects of the protein laminin A (progerin), which is expressed in the nuclear envelope. The resulting impairment of the cell division leads to *progeria type I* (Hutchinson–Gilford–Progeria syndrome, HGPS), characterized by premature aging of skin, bone, and vascular system from the first year of life. The children hardly reach adult age. Mutations of the *RECQL1* gene on chromosome 8, which encodes a DNA helicase, leads to defective DNA repair. The disease leads to premature aging of adult individuals (*progeria adultorum = Morbus Werner = progeria type II*).

Several mutations or gene deletions are known (e.g., age-1, sgk), which may lead to a several-fold increase of the life-span in the nematode *Caenorhabditis elegans*. The *age-1*-mutation leads to enhanced resistance against oxidative stress. In humans **oxidative damage** similarly contributes to aging, as levels of O_2-radical damaged membrane lipids, DNA, and proteins are enhanced and the activity of enzymes serving antioxidant defense is decreased in the elderly.

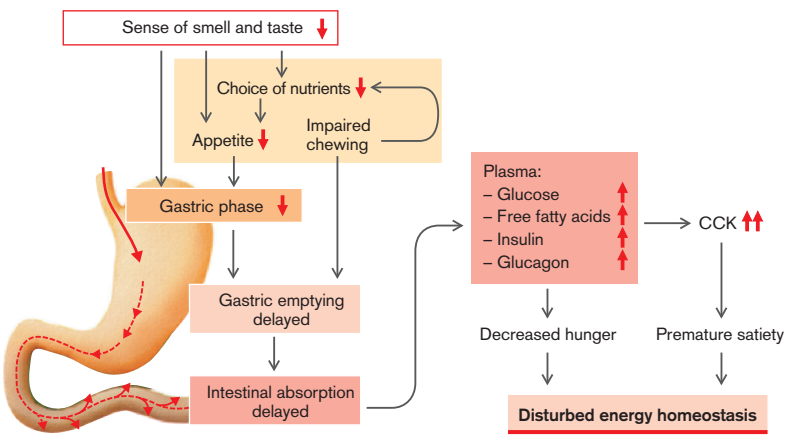
The **regulation of aging at the molecular level** is poorly understood. Aging and life-span is under the profound influence of *KLOTHO*, a single-pass transmembrane spanning protein. Excessive expression of KLOTHO leads to a substantial increase, deletion of KLOTHO to a profound shortening of life-span. KLOTHO binds to the receptor for the fibroblast growth factor (FGF23). KLOTHO/FGF23 suppresses the formation of $1,25(OH)_2\,D_3$ (calcitriol) and participates in the regulation of calcium/phosphate homeostasis. Lack of KLOTHO or of FGF23 results in hyperphosphatemia and hypercalcemia, leading to accelerated aging. Vitamin D deficiency increases the life-span of KLOTHO-deficient mice. Thus, at least part of the accelerated aging of KLOTHO-deficient mice is due to excessive formation of calcitriol. In humans, polymorphisms of the *KLOTHO* gene have been identified, which are associated with longevity. Thus, KLOTHO may be similarly important for aging in humans.

A **low caloric diet** increases the life-span of both humans and animals. The effect may be due to a decrease of fasting plasma glucose concentrations, of plasma-cholesterol levels, of enhanced insulin sensitivity, of decreased visceral fat tissue, and decreased release of adipokins from that tissue (→ p. 256). All those parameters are known as risk factors for coronary heart disease. As a low caloric diet is difficult to maintain, the hormonal and metabolic mechanisms accounting for the influence of such a diet on aging are now being sought, in order to mimic its positive influence on the life-span without individuals having to refrain from their preferred eating habits. The positive effects of a low caloric diet could be elicited by the polyphenol *resveratrol*, which is found in red wine and presumably accounts for the "French paradox," i.e., the positive effect of red wine on life-span. Resveratrol activates the genes encoding the sirtuins (Sirt1-7), NAD-dependent deacetylases. In several species Sirt1 increases resistance against oxidative stress and life-span. The effect on life-span is in part due to a cardioprotective effect of the enzyme. It is presently uncertain, however, whether or not Sirt1 expression influences aging in humans.

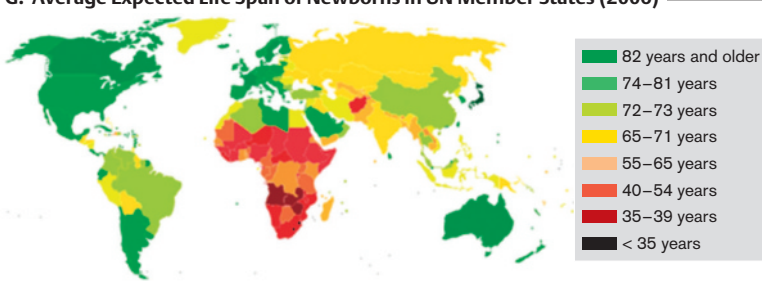
E. Telomer Shortening/Dysfunction and Replicative Senescence



F. Compromised Energy Metabolism in the Elderly



G. Average Expected Life Span of Newborns in UN Member States (2006)



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. 26), the set level is raised in fever, and the thermoregulatory mechanisms are thus responsible for maintaining the raised temperature (→ **A 5**, 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 (→ **A 5**, 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 (→ **A 5**).

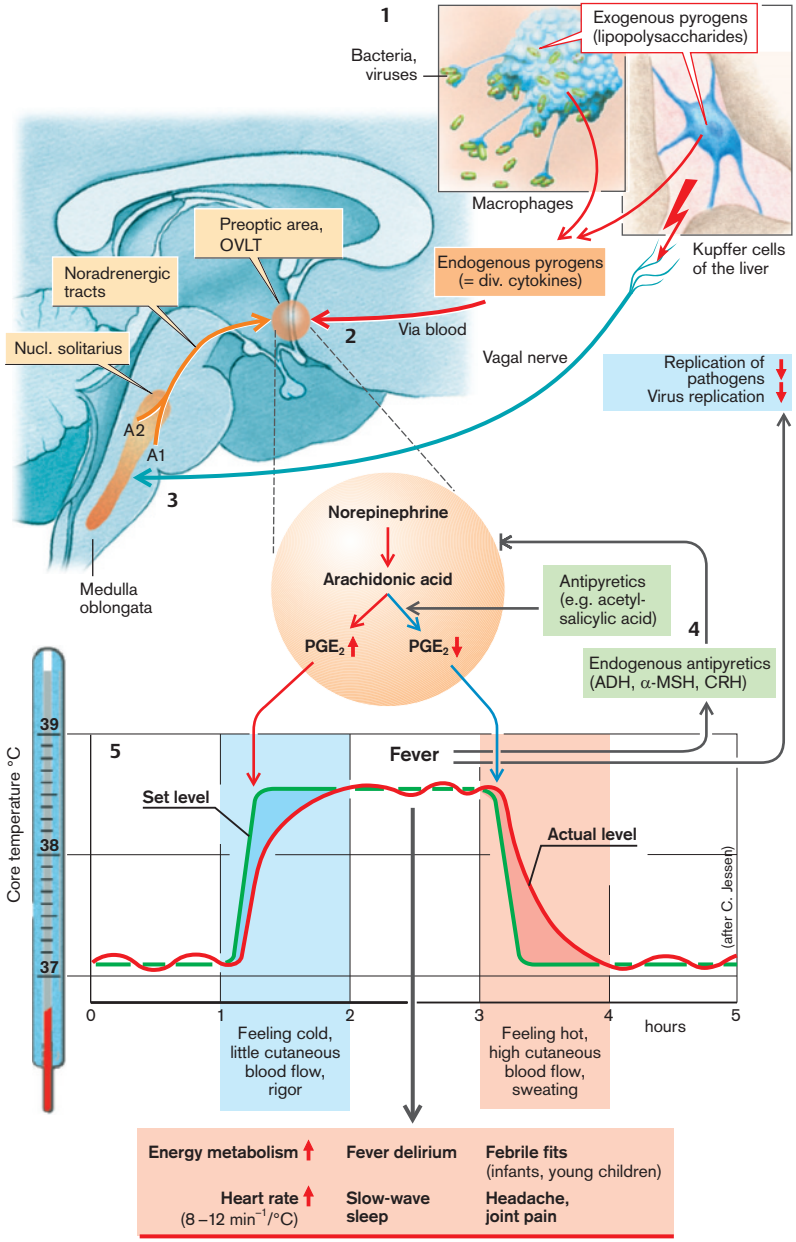
Fever is particularly common with infections in the course of the *acute-phase reaction* (→ p. 54 ff.) in which fever-inducing substances (pyrogens) cause a change in the set point. **Exogenous pyrogens** are constituents of pathogens, among which the lipopolysaccharide complexes (endotoxins) of gram-negative bacteria are particularly effective. Such pathogens, or pyrogens, are opsonized by complement (→ p. 48 ff.) and phagocytosed by macrophages, for example, *Kupffer cells* in the liver (→ **A 1**). These release numerous *cytokines*, among them the **endogenous pyrogens** interleukin 1α, 1β, 6, 8, and 11, interferon α_2 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 (M_r = 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 **PGE_2** (→ **A 2**). Fever-reducing drugs (*antipyretics*) are effective here. Thus, acetylsalicylic acid, e.g., inhibits the enzymes that form PGE_2 from arachidonic acid (cyclo-oxygenases 1 and 2).

As after i.v. injection of lipopolysaccharides the above-mentioned cytokines are released 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 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 (→ **A 3**). Norepinephrine that has been released there causes the formation of PGE_2 and thus fever. This also brings about the release of adiuretin (ADH; V_1 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** (→ **A 4**).

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. 52 ff.), 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 counteracting 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 exogenous 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.

A. Fever



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. 24), 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**; → **A 1**). 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 (→ **A 2**). 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. 24) 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 ratios are larger than adults', and they produce less sweat. *Treatment* of heat stroke consists of bringing the person into a cooler environment and/or submerging them into cool water. However, the body surface must not be allowed to get too cold, because the resulting vasoconstriction 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.

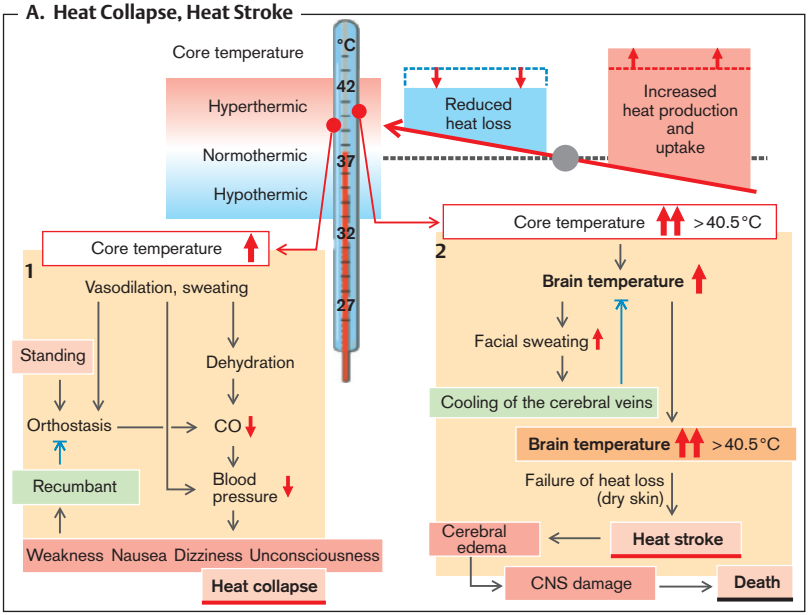
Malignant hyperthermia (→ **B**) is the potentially lethal result of heterogeneous genetic defects of sarcoplasmic Ca^{2+} transport, in which the Ca^{2+}-releasing channel (*ryanodine receptor*) is affected. Some inhalation anesthetics (halothane, enflurane, isoflurane) and depolarizing muscle relaxants (suxamethonium chloride) cause the sudden and excessive *release of* Ca^{2+} 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 Ca^{2+} 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.

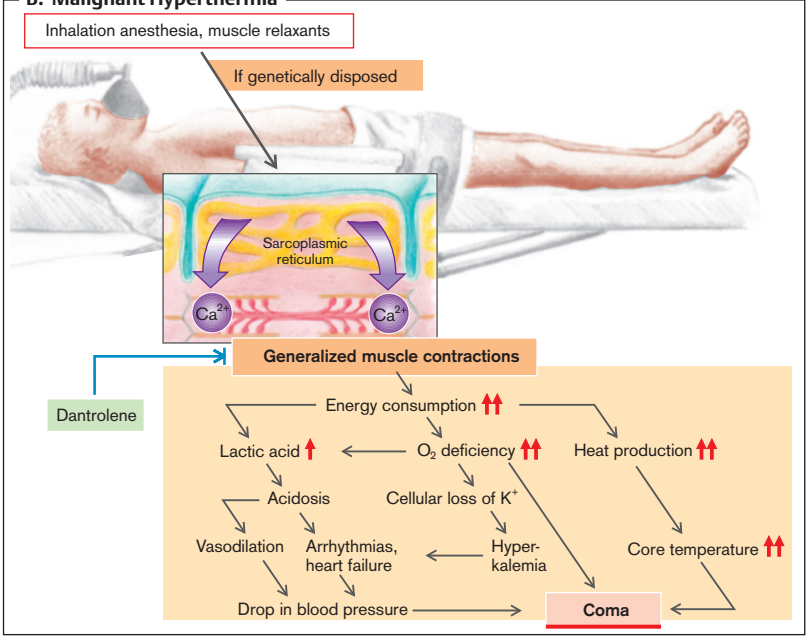
Sun stroke must be distinguished from hyperthermia. It is caused by direct sun radiation on head and neck and causes nausea, dizziness, severe headache, cerebral hyperemia, and serous meningitis and may end fatally.

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



B. Malignant Hyperthermia



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 O_2 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

Core temperature ↓ → Core temperature ↓↓

Core temperature ↓ → Muscle tremors

Core temperature ↓ → Behavioral changes

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

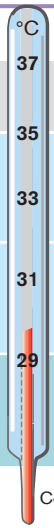
Not possible/insufficient:

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)

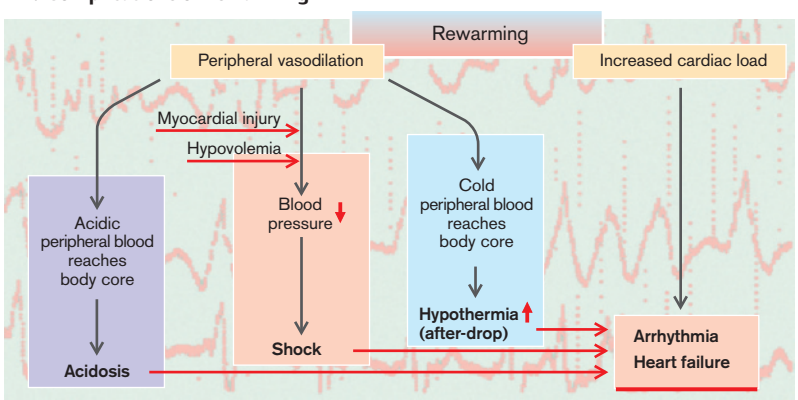
Psychiatric illness, hypothyroidism, Parkinson's disease



Accidental hypothermia

Stage	Symptoms	Metabolism	Level of consciousness	Cardiovascular system, respiration	Rewarming
I Agitation	Cold tremors, pain (distal parts of limbs)	Metabolism ↑↑ Hyperglycemia O_2 consumption ↑	Wide awake and agitated ↓ Confused	Tachycardia, peripheral vasoconstriction Blood pressure ↑	Warm room, blankets
II Exhaustion	Muscle rigidity Pupillary reflex still active	Hypoglycemia Metabolism ↓	Hallucinations, somnolent ↓ Unconscious	Bradycardia Depressed breathing **Arrhythmias** ↓	Electric blanket, warm infusion, hemodialysis
III Paralysis	Wide, light insensitive pupils	Metabolism ↓↓	Coma	**Ventricular fibrillation** **Asystole** **Apnea**	Extracorporeal circulation

B. Complications of Rewarming



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 the basis of a substance that is secreted by the fat cells (*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*) is a *risk factor* for hypertension, type 2 diabetes mellitus, hyperlipidemia, atherosclerosis (→ p. 256) 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 (metabolic susceptibility), partly of environmental origin. 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.

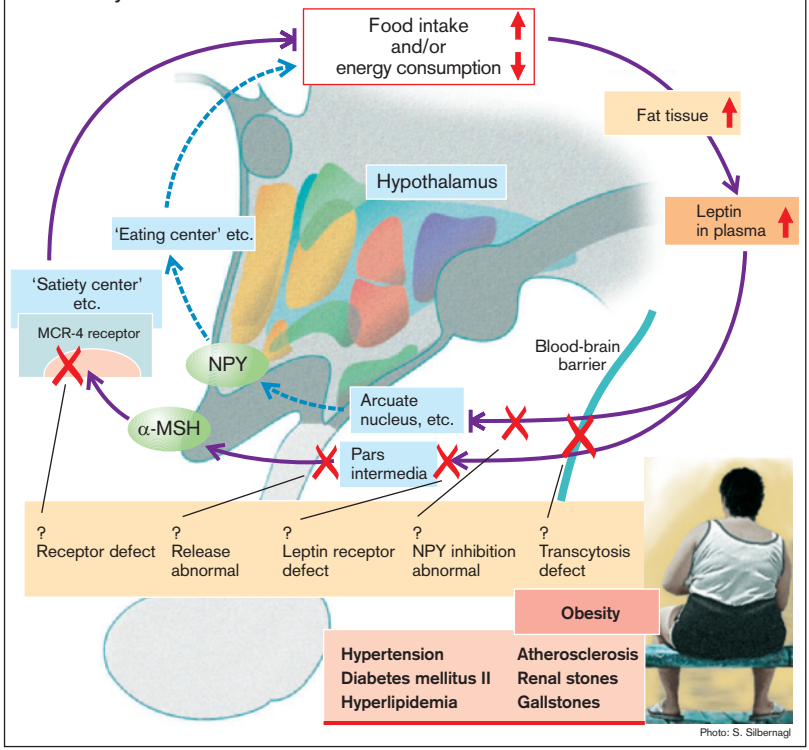
A homozygotic *leptin receptor defect* was found in three very obese sisters. As they had never gone through puberty and the secretion of both somatotropin hormone and thyrotropin-releasing hormone had been reduced, it seems that leptin also plays a part in other endocrine regulatory cycles.

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 *sociocultural influences* (ideals of beauty, social expectations) are probably significant.

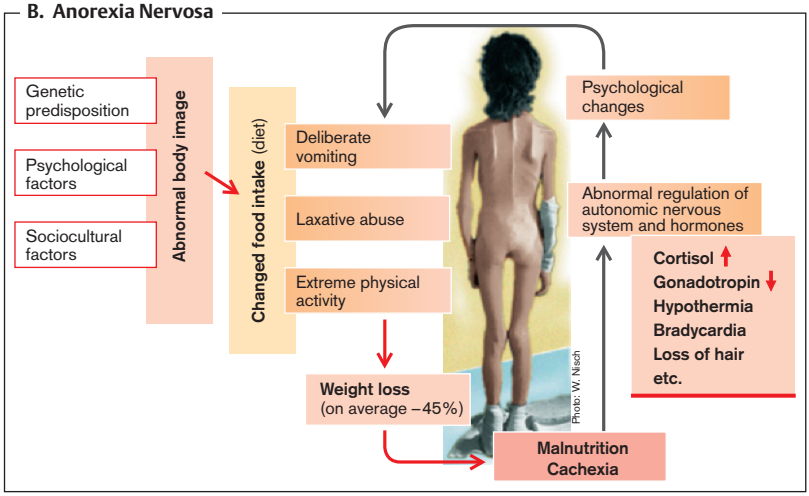
The disorder in *anorexia nervosa* (→ **B**) ranges from eating a very restrictive diet to complete refusal to eat, and often includes purgative abuse. This results in marked weight loss, even cachexia, which may require drip feeding. It leads to severe *autonomic–hormonal disorders*, for example, increased 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



B. Anorexia Nervosa



Overview

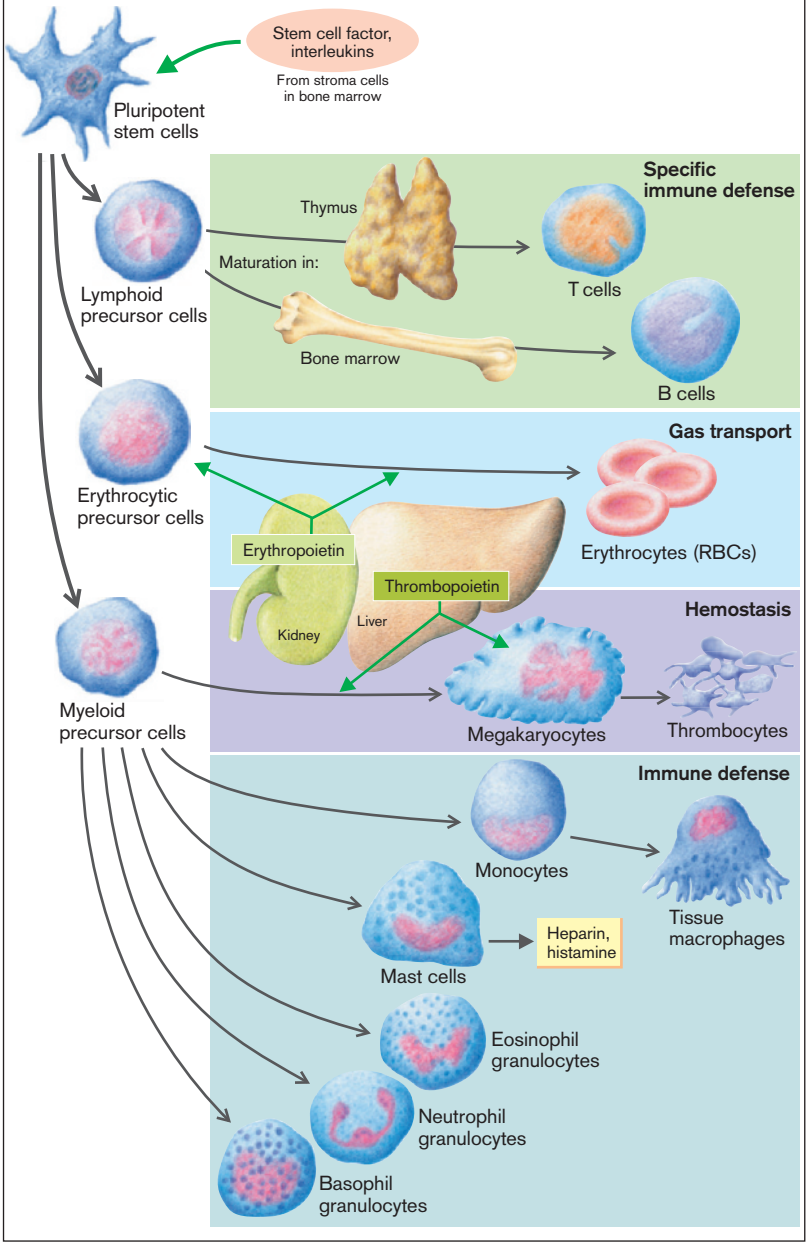
Total blood volume correlates with the (fat-free) body mass (→ Table below) and averages 3.6 L in women and 4.5 L in men. The blood's **tasks** include *transporting* various substances (O_2, CO_2, nutrients, metabolic products, vitamins, electrolytes, etc.), the transport of heat (heating, cooling), *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 O_2 and a part of CO_2 transport and 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. 35 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. 56 f.) as haptens. 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 *hormones* are involved in this, namely *erythropoietin* (secreted by the kidney) for the maturation and proliferation of erythrocytes (→ **A** and p. 36), and *thrombopoietin* (secreted by the liver) 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).

Total Blood	Blood volume (L)	♂ 0.041 · kg KG + 1.53;	♀ 0.047 · kg KG + 0.86
	Hematocrit (L_{cells}/L_{blood})	♂ 0.40 – 0.54;	♀ 0.37 – 0.47
Erythrocytes	Number ($10^{12}/L_{blood} = 10^6/\mu l_{blood}$)	♂ 4.6 – 6.2;	♀ 4.2 – 5.4
	Hemoglobin (g/L_{blood})	♂ 140 – 180;	♀ 120 – 160
Leukocytes	Number ($10^9/L_{blood} = 10^3/\mu L_{blood}$)	3 – 11 (of which 63% granuloc., 31% lymphoc., 6% monoc.)	
Thrombocytes	Number ($10^9/L_{blood} = 10^3/\mu L_{blood}$)	♂ 170 – 360;	♀ 180 – 400
Plasmaproteins	(g/l Serum)	66 – 85 (of which 55 – 64% albumin)	

A. Maturation Sequence and Differentiation of Blood Cells



Erythrocytes

Erythrocytes (red blood cells [RBCs]) are formed in bone marrow from nucleus-containing erythroid precursor cells (→ **B** and p. 33 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 facilitate 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 liter 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^+-ATPase* 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. 12 f.). If ATP production ceases or the membrane is damaged, the RBCs swell and thus have a shorter survival time (premature hemolysis).

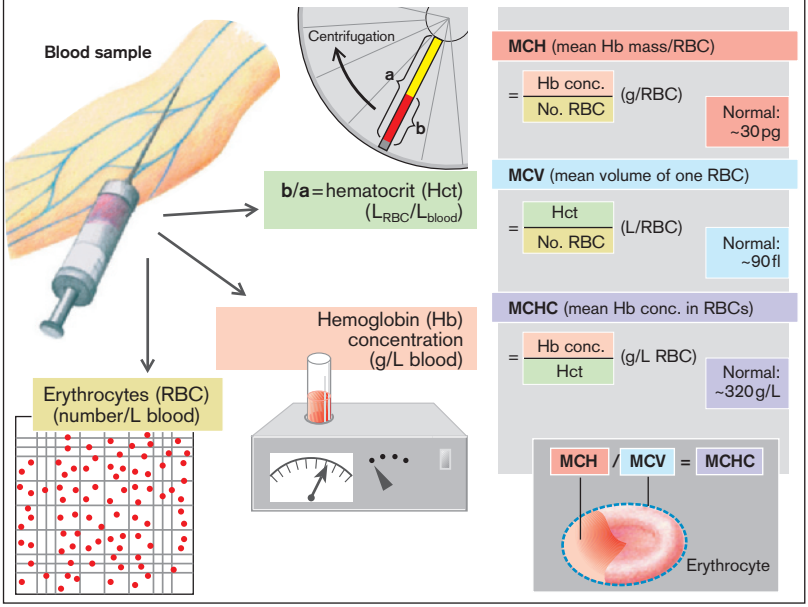
The RBCs regularly leave the arterioles in the pulp of the **spleen** and reach the small pores in the splenic sinuses. Old and abnormally fragile erythrocytes are separated out and destroyed in the region of these pores. The fragments are phagocytized by the macrophages in the spleen, liver, bone marrow, etc. and broken down (**extravascular hemolysis** in the reticuloendothelial system [**RES**], or more precisely, the mononuclear phagocytotic system [**MPS**]; → p. 48). The liberated *heme* is broken down into *bilirubin* (→ p. 182), the liberated iron is reused (→ p. 42). If there is **intravascular hemolysis**, Hb that has been released can to a certain extent be bound to *haptoglobin* (→ p. 42). This reduces the glomerular filtration of Hb and thus its elimination (hemoglobinuria).

Erythropoiesis, Anemia

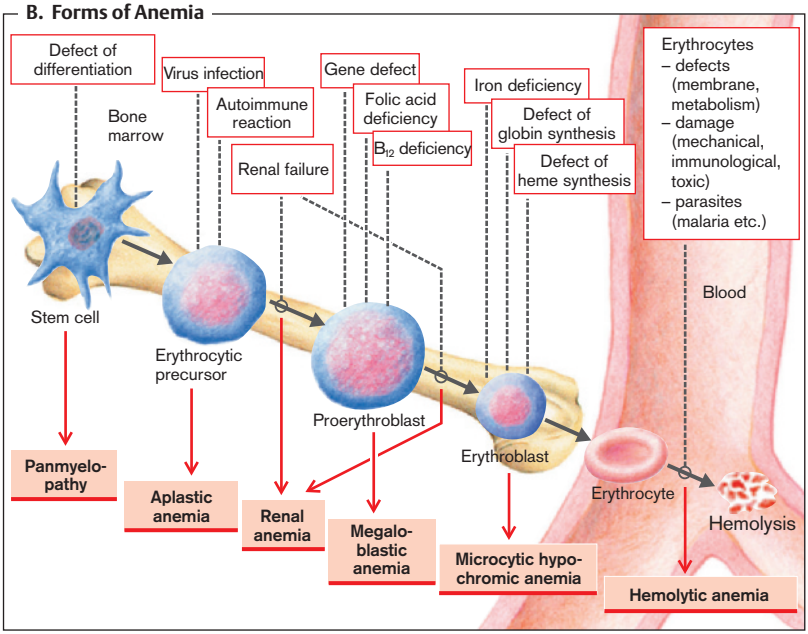
Anemia is the term given to the *reduction in the number of erythrocytes*, in the *concentration of hemoglobin* and/or in the *hematocrit* as long as the total blood volume is normal. Shortly after acute major blood loss, in dehydration, or in hyperhydration the blood volume must first be normalized 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 anemia*; → **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 B_{12} (*megaloblastic anemia;* → p. 38); 6) abnormal Hb synthesis (*microcytic hypochromic anemia*; → p. 40 ff.).

A. The Erythrocyte Parameters MCH, MCV, and MCHC



B. Forms of Anemia



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. 1.6×10^{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) (→ **A 1**).

◆ **Erythroblasts** can be morphologically identified and quantified in a stained bone marrow sample. They decrease in number in aplasia and in defects of stem cell differentiation; they increase if erythropoiesis is stimulated, for example, by increased hemolysis (→ **A 2**).

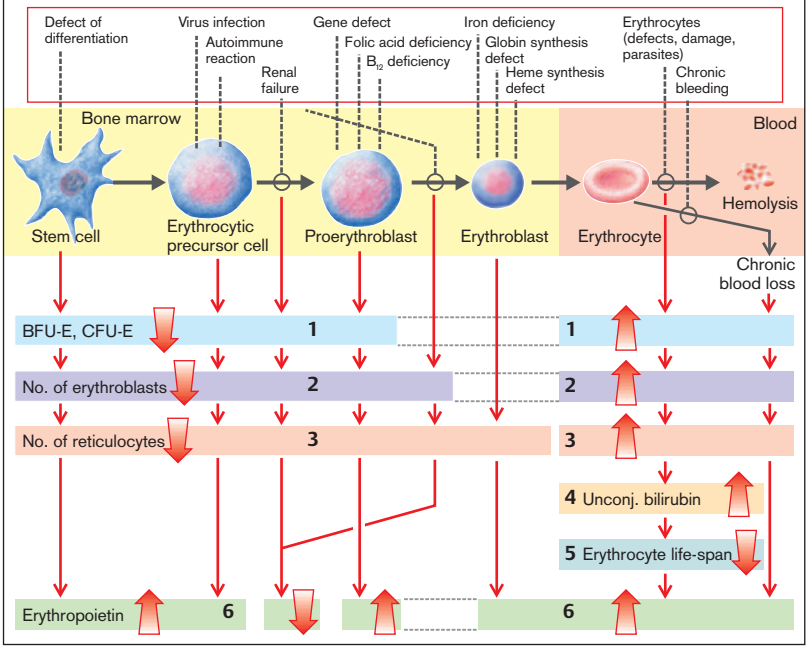
◆ The *efficiency of the entire erythropoiesis* can be measured by determining the **number of reticulocytes** (→ p. 34). If the number of reticulocytes is reduced, one must assume an abnormality of cell formation (→ **A 3**) because the second, theoretically possible cause, a prolongation of RBC life-span, 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; → **B 2, 3**).

◆ When erythrocytes are broken down in macrophages (→ p. 34), **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 (→ **A 4** and p. 178 ff.), but in some circumstances also if hemoglobin turnover is increased as a result of ineffective erythropoiesis.

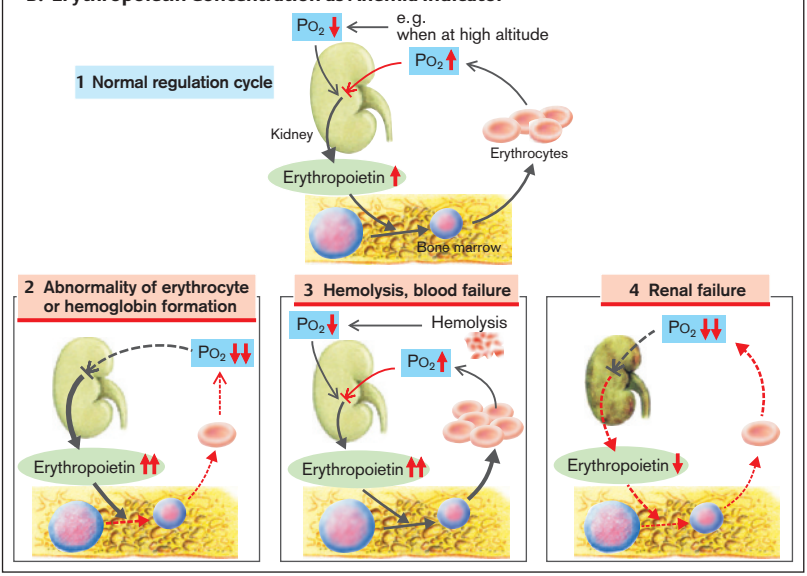
◆ The **life-span of RBCs** (shortened in hemolytic anemia; → **A 5**) as well as their **total volume** can be measured by marking the erythrocytes *in vitro* with radioactive ^{51}Cr (binding Cr to the Hb-β chain) and then re-infusing them. As ^{51}Cr is released in hemolysis and then excreted by the 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** (→ **A 6**). Lowered concentration of plasma erythropoietin suggests the anemia is caused nephrogenically (→ **B 4**). However, most anemias are associated with a (compensatory) increase in erythropoietin concentration (→ **B 2, 3**).

A. Diagnostic Parameters in Anemia



B. Erythropoietin Concentration as Anemia Indicator



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 **cobalamine** (**vit. B_{12}**) (→ **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. 42) as well as by the shortened life-span of the megalocytes that have passed into the blood (*premature hemolysis*).

Folate. The folate metabolite N^5, N^{10}-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**). N^5-methyltetrahydrofolate, the substrate for tetrahydrofolate formation (→ **A2**), is then formed in the intestinal mucosa. Methyl-cobalamine is essential for this step (see below). N^5, N^{10}-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**);
- Cobalamine deficiency (→ **A4**);
- *Inhibition of thymidylate synthase* by the fluorouracil metabolite fluordeoxyuridylate;
- *Inhibition of dihydrofolate reductase* by aminopterin or methotrexate, whose affinity for the enzyme is 100 times that of the natural substrate 7,8-dihydrofolate (→ **A3**).

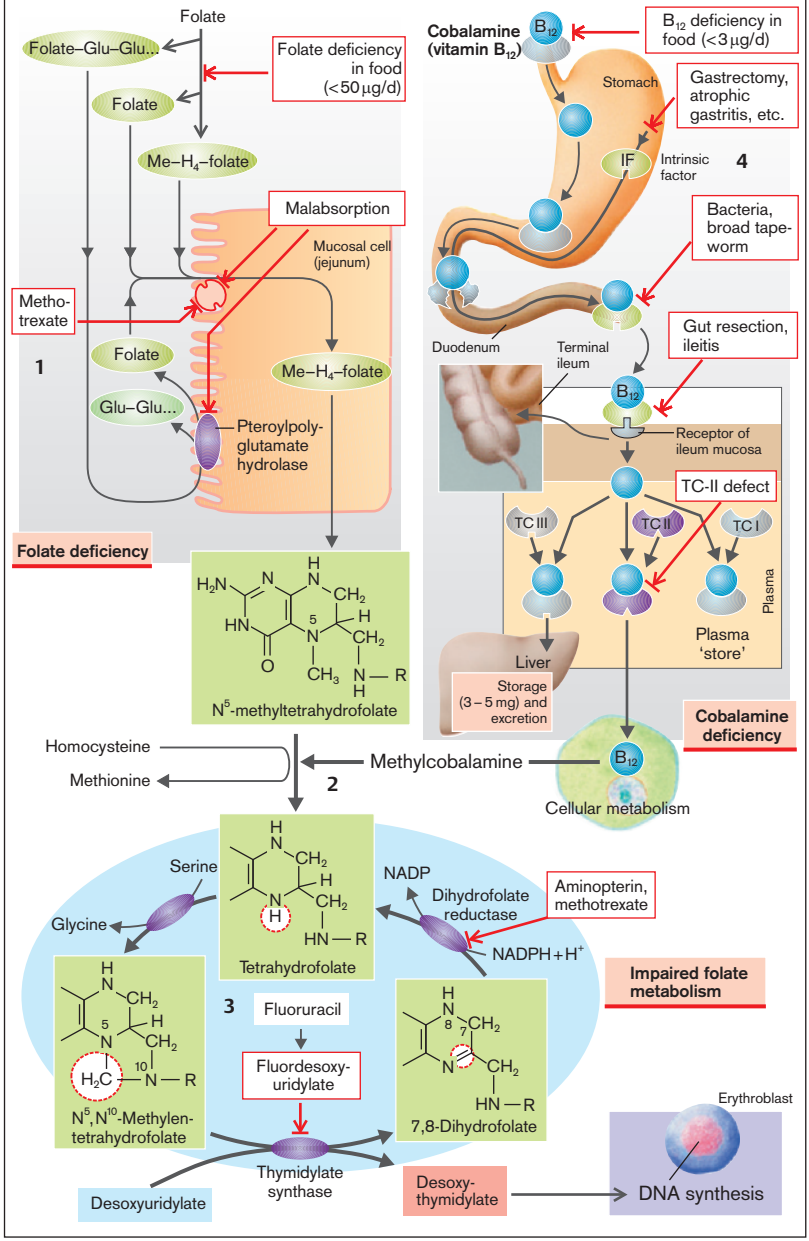
As inhibition of folate metabolism also retards tumor growth, the drugs fluorouracil, methotrexate, and aminopterin are used as *cytostatic chemotherapeutics*. Their side effect on erythropoiesis is usually undesirable and therefore often limits their dosage.

Cobalamine (**vitamin B_{12}**) must be taken up by humans in their food (daily requirement: 3 – 5 µg). About a thousand times this amount is normally 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 *methylcobalamine*, it serves as coenzyme in demethylating N^5-methyltetrahydrofolate (→ **A2**). Among possible **causes of cobalamine deficiency** are (→ **A4**):

- *Too little uptake* with food (e.g., a strict vegetarian diet);
- *Intrinsic factor* (*IF) deficiency* (in atrophic gastritis etc.; see p. 154): IF is essential for the binding and absorption of cobalamine. It is freed from its binding to salivary proteins in the lumen of the small intestine;
- *Competition* for cobalamine and splitting of IF from bacteria (blind-loop syndrome; → p. 160), 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 cobalamine (→ p. 164 f.);
- *Defective transcobalamine II* (TCII), which is responsible for cobalamine transport in plasma and for its uptake into cells.

Because of the great store of cobalamine in the liver, the symptoms of cobalamine deficiency (*pernicious anemia,* neurological abnormalities) occur only after years of blocked supply.

A. Anemias Caused by Disorders of DNA Synthesis



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 (2α, 2β in HbA; see below), each of which is formed from *three components: protoporphyrin, iron* (Fe^{2+}) and *globin* (α or β). 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**).

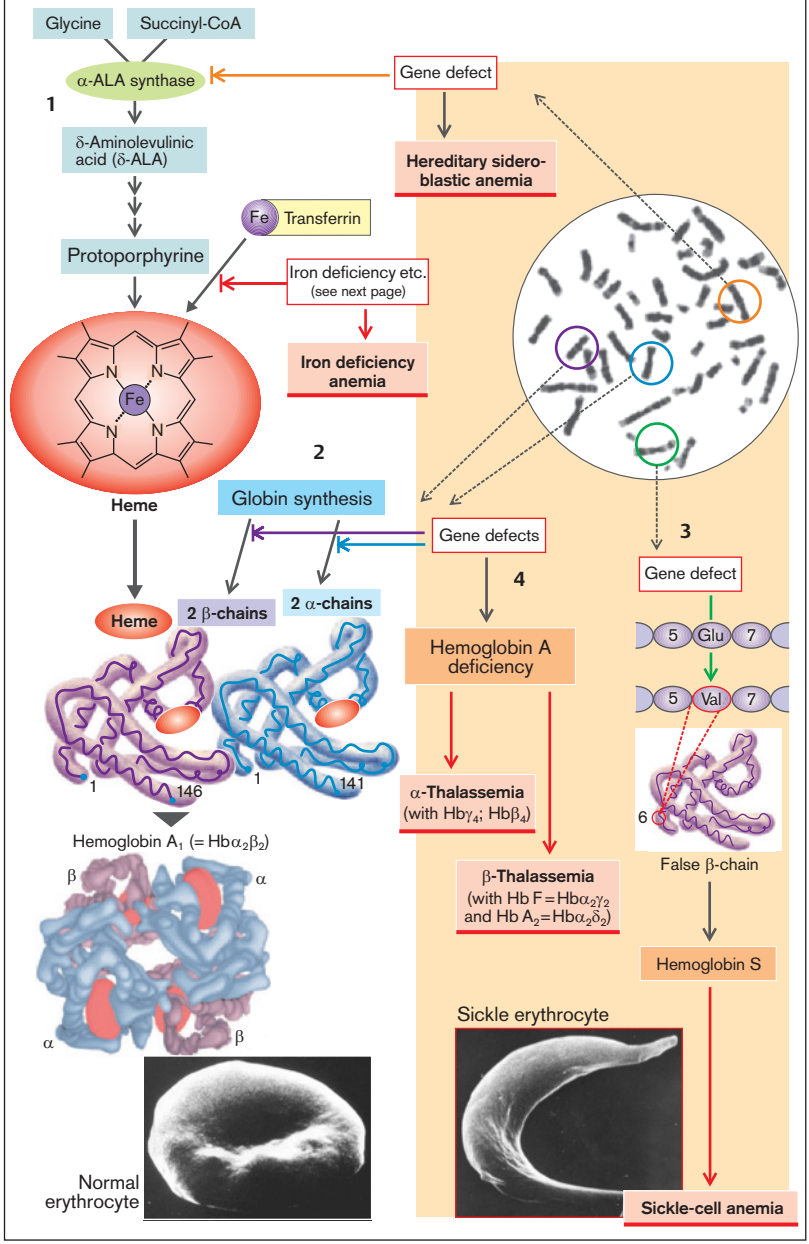
Disorders of protoporphyrin synthesis are due to inherited enzyme defects (→ p. 276), as for example, in *hereditary sideroblastic anemia*, in which the formation of δ-aminolevulinic acid (δ-ALA) from glycine and succinyl-CoA is reduced, and thus also heme synthesis (→ **A 1**). Heme inhibits δ-ALA synthase 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. 276).

Disorders of globin synthesis (→ **A 1**): Normally Hb is made up of 2 α chains of 141 amino acids each and 2 β chains of 146 amino acids (**HbA_1** = $HbA\alpha_2\beta_2$). Only 2–3% of Hb contains so-called δ-chains (**HbA_2** = $Hb\alpha_2\delta_2$) instead of the β-chains. Before birth a form of Hb is formed that has a higher O_2 affinity (adaptation to a lower Po_2 in the placenta). This fetal Hb (**HbF**) contains so-called γ-chains ($Hb\alpha_2\gamma_2$) instead of the β-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 indentified 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 β-chain = **HbS**; → **A 2**) 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. 116). 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 Po_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 (T)** the production of β-chains is restricted, thus leading to a deficiency of HbA. It can be only partly compensated by an increased production of HbA_2 and HbF. The incorporation of Fe^{2+} is diminished so that it remains in the erythrocytes (*sideroachresia*) and may accumulate excessively in the body (secondary hemochromatosis; → p. 270). Although the RBCs' osmotic resistance (→ p. 44) 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



Iron Deficiency Anemia

Of the **iron** (**Fe**) content in the body (2 g in females, 5 g in males) ca. ⅔ is bound to *hemoglobin* (Hb), ¼ 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 by the heme transporter HCP1 as **heme-Fe^{2+}** (found in meat and fish). The Fe (split off from heme) enters the blood or remains in the mucosa as ferritin-Fe^{3+} 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). 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^{3+} in food must be reduced by *ferrireductase* (+ascorbate) to Fe^{2+} on the surface of the luminal mucosa (→ **A 1**, FR). Fe uptake into blood requires the oxidation of Fe^{2+} to Fe^{3+} by the multi-copper ferroxidase *hephaestin* (for uptake from intestinal mucosa) or by ceruloplasmin (for uptake from macrophages). Fe^{2+} exit from the cells is mediated by the Fe-transporter *ferroportin* in the membrane of duodenal epithelial cells, hepatocytes, and macrophages. Ferroportin is internalized and thus downregulated by the hepatic peptide hormone *hepcidin*. In blood, two Fe^{3+} interact with one *apotransferrin* to form *transferrin*, which accomplishes the **Fe transport in plasma** (→ **A**) and delivers Fe^{3+} to *transferrin receptors* in erythroblasts, hepatocytes, and cells of further tissues (e.g., placenta). Following release of Fe^{3+}, apotransferrin is free to take up Fe again from intestinal cells and macrophages (see below).

Iron storage (→ **A 2**, p. 270) is accomplished by *ferritin* (rapidly available Fe) and hemosiderin. For **Fe recycling**, Hb-Fe and heme-Fe, released from malformed erythroblasts (*"inefficient erythropoiesis"*) and hemolyzed 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. Transferrin, which has been filtered in renal glomerula, is retrieved by renal tubular reabsorption involving cubilin.

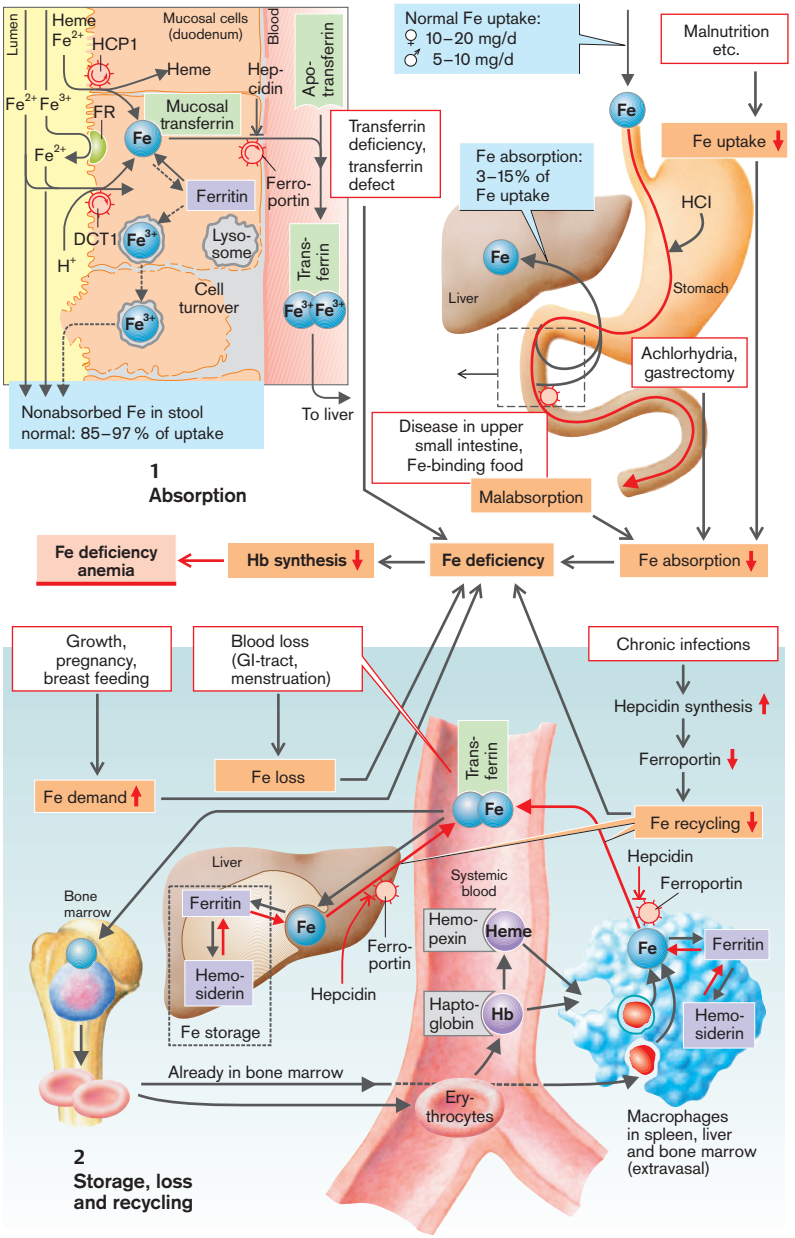
In **iron deficiency** the intestinal Fe-absorption is increased by inhibition of the mucosal ferritin translation (by binding of the Fe-regulating protein IRP1 to ferritin mRNA) and of the hepcidin formation. Clinically overt iron deficiency (serum Fe < 0.4 mg/L; serum ferritin ↓) inhibits Hb synthesis (→ p. 40) 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*, whereby inflammatory cytokines (IL-1 and IL-6, TNF-α etc.) stimulate the hepcidin synthesis leading to decreased formation of ferroportin and thus insufficient reuse of Fe taken up by the macrophages.
- *Fe uptake is too low* (malnutrition, especially in the developing countries).
- *Fe absorption* is reduced due to: a) achlorhydria (atrophic gastritis, after gastrectomy; → p. 154, 160); and b) *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.).
- *Fe requirement* is increased (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. 270).

	Normal	Fe deficiency	Apotransferrin defect	Fe utilization defect	Fe recycling defect
Serum Fe : Fe binding capacity	1 mg/L : 3.3 mg/L	↓:↑	↓:↓	↑: normal	↓:↓
Transferrin saturation	ca. 33%	< 10%	0	> 50%	> 10%

A. Iron (Fe) Deficiency Inhibits Hemoglobin Synthesis



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. 34). 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. 37, 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 (→ **A 1**). 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 hemolyse 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 (→ **A 2**): 1) if *pyruvate kinase* is affected, ATP to Na^+-K^+-ATPase supply is stopped, the cells swell up so that they become vulnerable and hemolyse early; 2) defective *glucose-6-phosphate dehydrogenase* (gluc-6-PDH; → **A 3**) 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 sulfonamides) increase oxidative stress and thus aggravate the situation; 3) a defect of *hexokinase* results in a deficiency of both ATP and GSH (→ **A 2**, **3**).

◆ *Sickle cell anemia* and *thalassemias* (→ p. 40) also have a hemolytic component (→ **A 4**).

◆ 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 the membrane anchor (glycosyl-phosphotidylinositol) of proteins that protect erythrocytes against the complement system (especially the decay accelerating factor [DAF], [CD55] or the membrane inhibitor of reactive lysis [CD59]; → **A 5**). The disorder leads to complement activation with eventual perforation of the erythrocyte membrane.

Examples of the **causes of extracorpuscular hemolytic anemia** are:

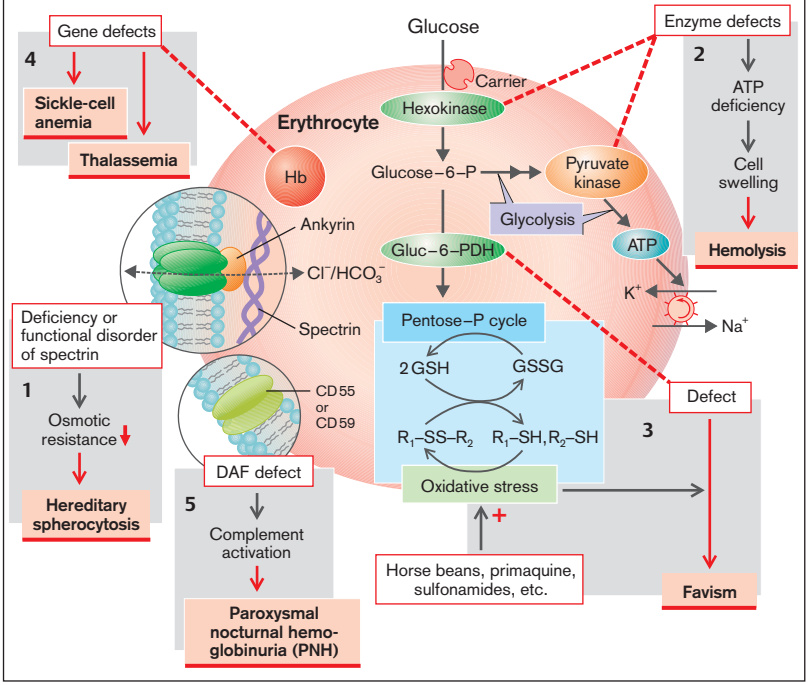
◆ *Mechanical causes*, such as damage to the erythrocytes by collision with artificial heart valves or vascular prostheses, especially if cardiac output (CO) is raised;

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

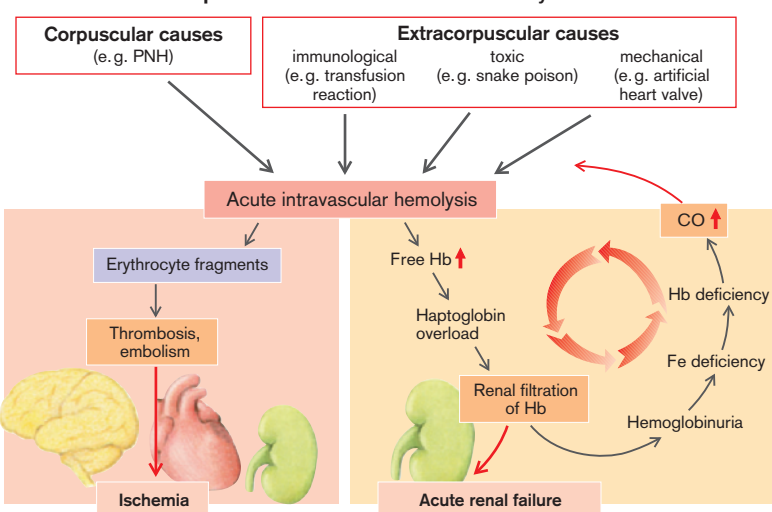
◆ *Toxins*, for example, certain snake poisons.

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. 42). A small amount of Hb released intravascularly is bound to haptoglobin (→ p. 42). In massive **acute intravascular hemolysis** (→ **B**) haptoglobin is, however, overloaded and free Hb is filtered in the kidneys. This results not only in *hemoglobinuria* (dark urine), but can also through tubular occlusion lead to *acute renal failure* (→ p. 118). **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



B. Causes and Consequences of Acute Intravascular Hemolysis



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 > 10^8 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.

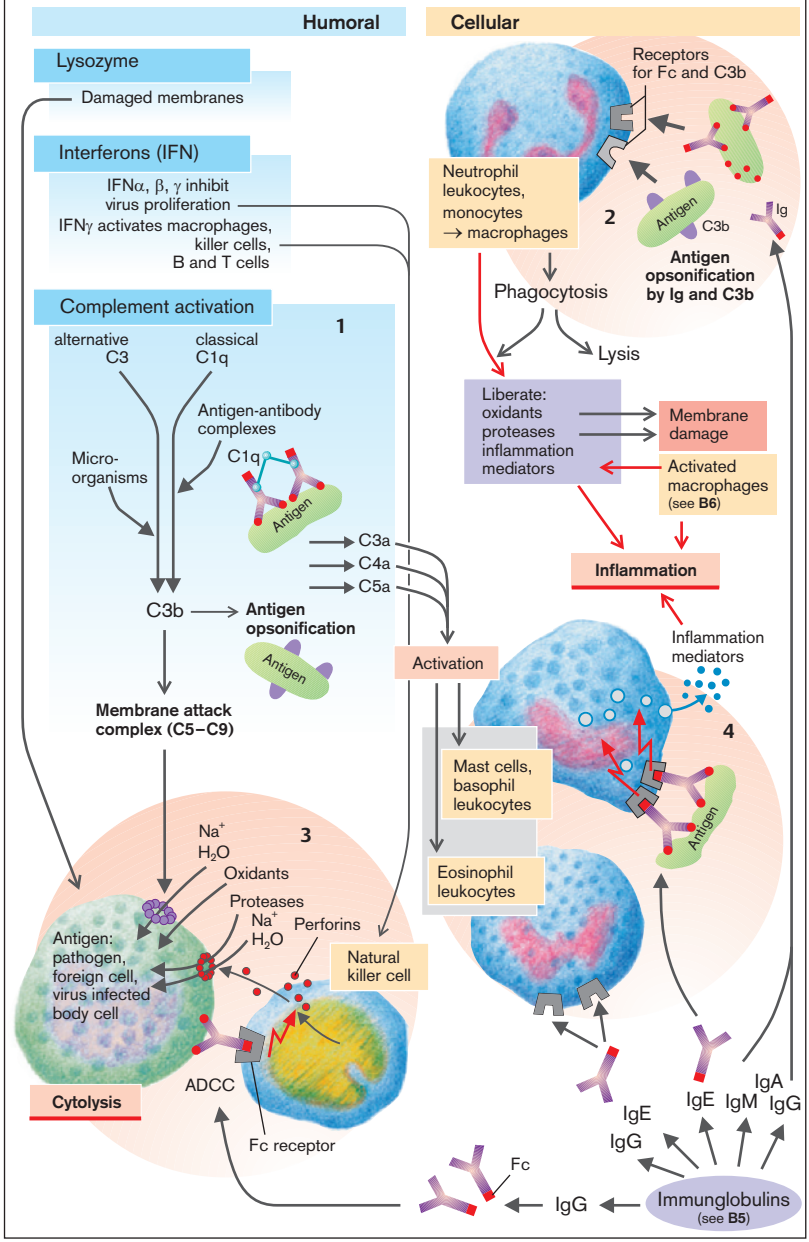
Lymphocytes with receptors against endogenous tissue are prematurely eliminated in the thymus or bone marrow after recognizing their antigen. This **clonal deletion** thus results in (*central*) *immunological tolerance*. The immune system learns around the time of birth to distinguish between foreign 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. 60).

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** at p. 50) and immunoglobulins (at first IgM, then IgG; → **B5** at p. 51) 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 further *mediators* (→ **A2**, **4** and p. 48 ff.).

The phagocytes take up the pathogen (endocytosis), or "catch" it in an extracellular network of pseudopodia, they 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) (→ p. 171, B2). 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 phago- ▶

A. Nonspecific Immune Defense (Enhanced by Specific Antibodies)



cytes themselves and, in 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**; → **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** (→ **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 demise. At the same time, **lysozyme** (also present in plasma, lymph, and secretions) breaks down the wall of bacteria enzymatically (*cytolysis*; → **A3**). Further components of the innate immune system are the **Toll-like receptors (TLR1 to TLR11)**. They are expressed in the membrane of macrophages, dendritic cells, enterocytes (→ p. 171 B1, 2) and renal epithelial cells. They recognize certain components (PAMPS = pathogen-associated molecular patterns) of diverse pathogens and trigger an intracellular signaling cascade leading to host defense (e.g., NFκB-dependent synthesis of defensins, see below). TLR2 recognizes bacterial lipoproteins, TLR7 recognizes single-stranded RNA (ssRNA, → p. 62), TLR9 recognizes bacterial DNA (CpG, → p. 170), and TLR11 uropathogenic *Escherichia coli* bacteria. **Defensins** are peptides (with approx. 30 amino acids) that are released from macrophages and enterocytes (→ p. 171 B1, 2) and act (e.g., by forming ion channels in the target cell membrane) in a nonspecific cytotoxic manner, even affecting pathogens that are resistant to NK cells (see below). 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]; → **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*; → **A3**). This takes away not only the invading virus' 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.

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 phagocytotic system* (**MPS**) or *reticuloendothelial system* (**RES**). Macrophages can recognize relatively nonspecific carbohydrate components on the surface of bacteria and thereupon phagocytoze 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*; → **B1**). As a result the antigen is built into **MHC class I** and **MHC class II proteins**, in humans also called

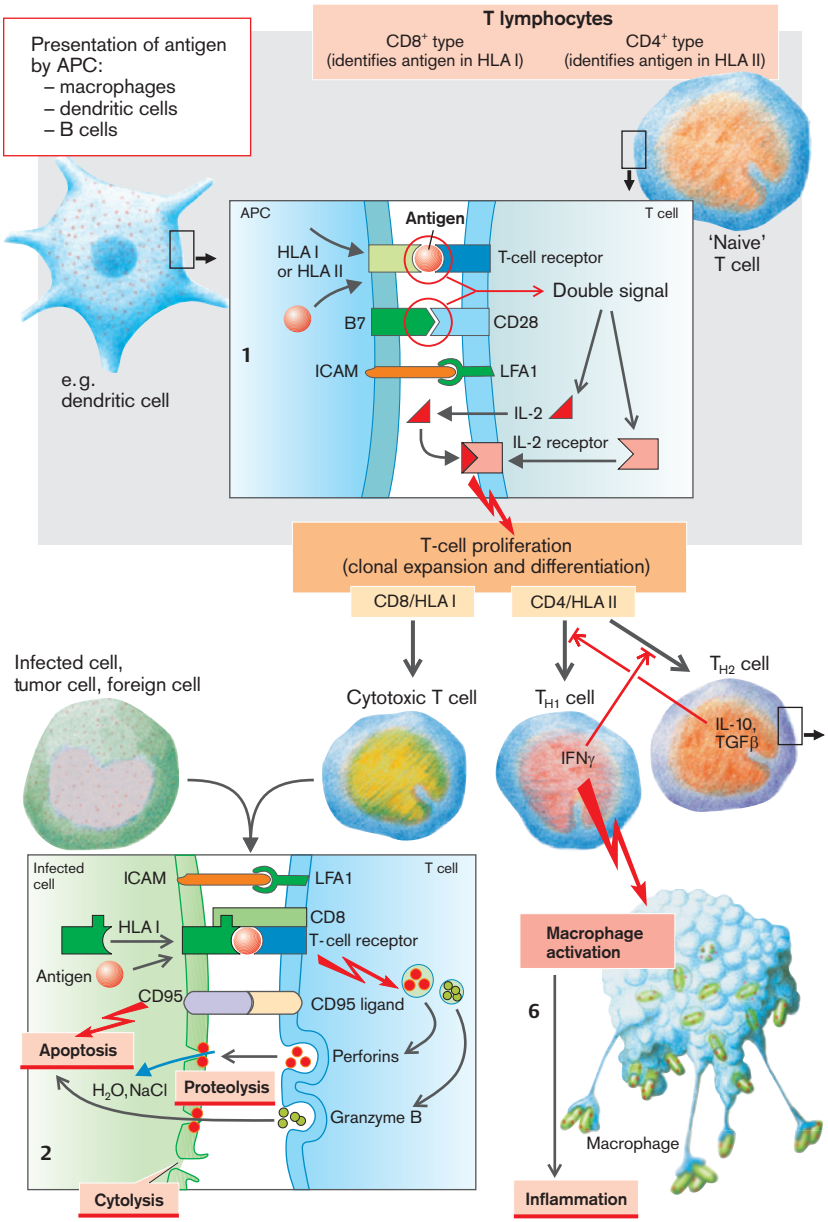
HLA class I or II, respectively (HLA = human leukocyte antigen). (The appropriate gene locus is the major histocompatibility complex [MHC]). Most important APCs are the *dendritic cells*, to be found mainly in lymphatic tissue, but as well in intestinal mucosa (→ p. 171 B). For presentation (→ **B 1**), 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 (→ **B 1**). 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-2 receptor* into the cell membrane. IL-2 (or IL-4, IL-7, IL-15) is the actual (autocrine and paracrine) signal for *clonal expansion* of these monospecific T cells. In this process the T cells differentiate into three armed types (killer T cells, T_{H1}-cells and T_{H2}-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).

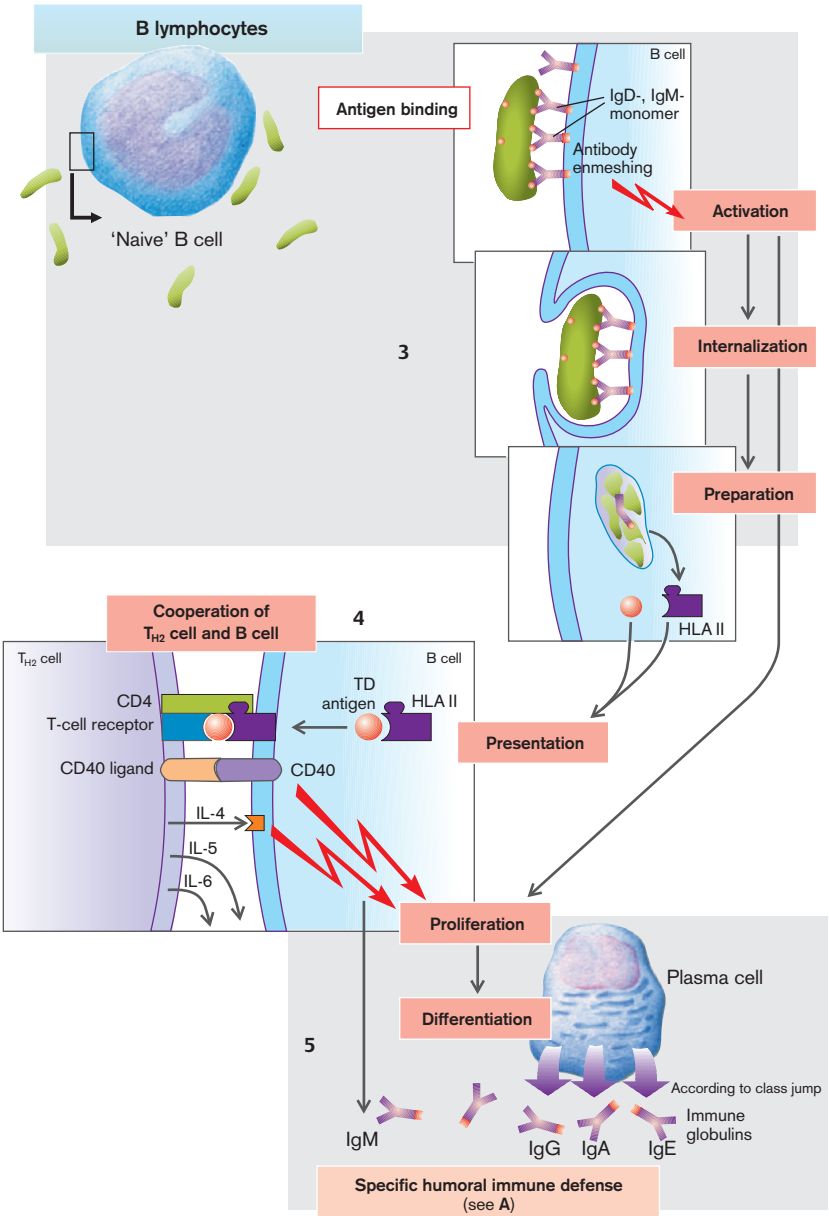
Cytotoxic T cells (**killer T cells**) originate from naive CD8 T cells after HLA I–associated antigen presentation, HLA I having mostly taken its antigen from the *cytosol* (viruses, cytosolic proteins, endogenous antigen presentation). Through their CD8-associated T-cell receptors, the cytotoxic T cells then recognize the corresponding HLA 1–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. 14).

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_{H0}). Through differentiation these turn into helper T cells, either **inflammatory T cells** (T_{H1}), which activate macrophages by means of IFN-γ (→ **B 6**), or **Type 2 helper T cells** (T_{H2}), 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, however, 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 T_{H2} cells to which the B cells present the HLA II–associated TD antigen (→ **B 4**). Should the T-cell receptor of the T_{H2} 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





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. 60), 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. 56). If the body has previously been in contact with an antigen (= allergen in cases of hypersensitivity), for example, with bee-poison protein, B cells will have been sensitized as a reaction to it (cooperation with T_{H2} cells; → p. 51 , B4). The ensuing plasma cells produce IgE that binds to the Fc_ε 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 haptens).

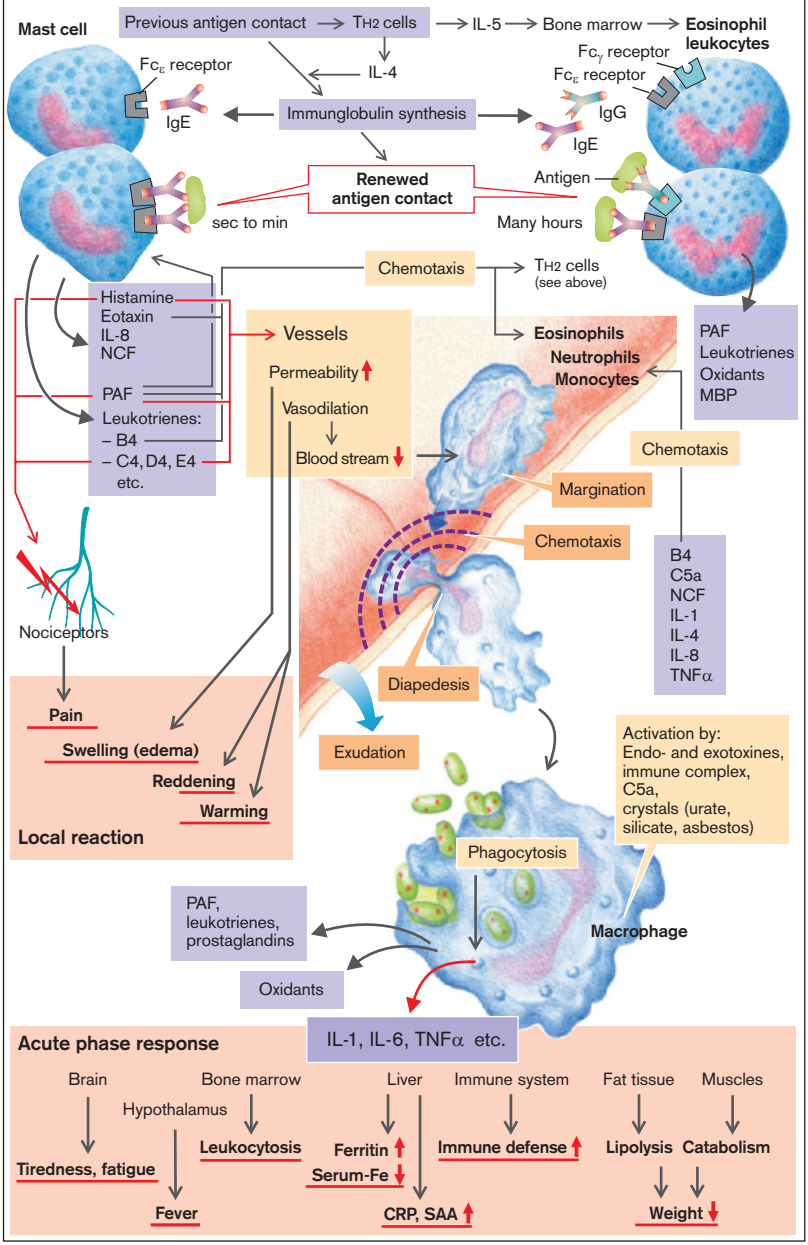
Cross-linking of the antibodies by the antigen sets free second messengers in the mast cell (cGMP, inositol phosphate, Ca^{2+}) that trigger a rapid *degranulation* of the mast cells, i.e., exocytosis of the **inflammation mediators** and **chemokines** stored within the granules (*histamine, interleukin 8 [IL-8], eotaxin, neutrophilic chemotactic factor [NCF], etc.*). Ca^{2+} also activates phospholipase A_2 that splits off arachidonic acid from the phospholipids in the cell membrane. This is the starting substance for other important inflammation mediators, namely *prostaglandins* (E_2 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 **chemokines** (**chemotaxis**). Eotaxin, PAF, and leukotriene B4 act chemotactically on eosinophils (and T_{H2} 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 E_2, 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 T_{H2}-lymphocytes) pushes *selectins* out into the lumen. These selectins, in the guise of adhesion molecules, cause the leukocytes to roll along the endothelium and thus

A. Acute Inflammation



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*; → **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 **phagocytoze** the pathogens causing the inflammation and to digest them by means of their lysosomes. Their "appetite" is increased by *opsonification* of the pathogens with IgG or C3 b (→ p. 48).

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 **C3 b** 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 (→ p. 48). The complement system can, in addition, break up virus particles and antigen–antibody complexes. Side products of the complement system (C3 a, C4 a and C5 a, so-called *anaphylaxins*) act chemotactically and activate macrophages.

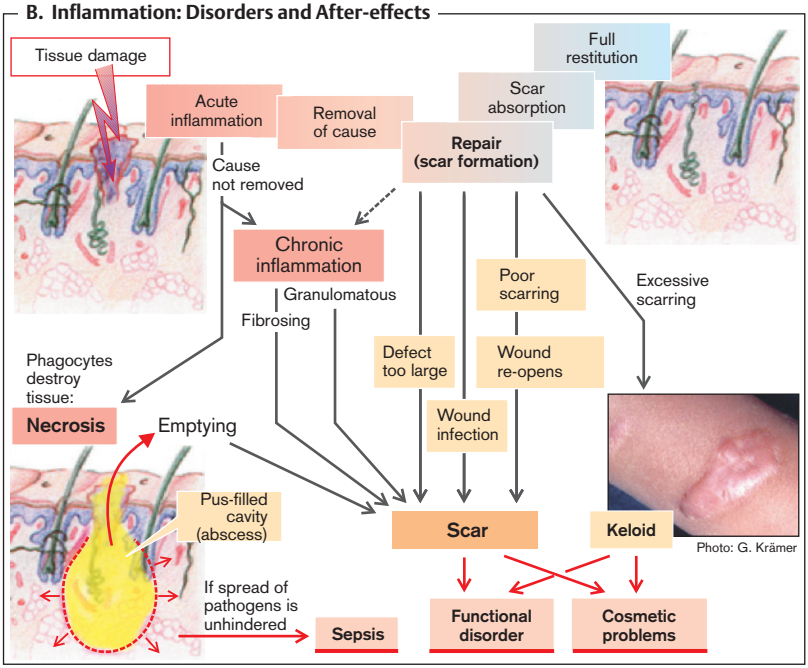
Macrophages are activated mainly by pathogen exotoxins and endotoxins, by antigen–antibody complexes, C5 a, crystals (see above), and by phagocytosis, whereupon oxidants like O_2^-, OH·, $^1O_2$, and H_2O_2 are liberated and damage the pathogens (→ **A**). The macrophages also release inflammation mediators, for example, PAF, leukotrienes, prostaglandins, IL-1, IL-6, and TNF-α. The latter do not only act locally and chemotactically, but also include the entire organism in the inflammation reaction (**acute-phase response**; → **A**). Mediated by IL-1, IL-6, and TNF-α, 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*; → p. 24);
- 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 cell-rich *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*; → **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 (anerobic 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*; → p. 12), which can progress to *abscess* formation (→ **B**), is the price paid for preventing the spread of inflammation and usually results in a permanent **scar**. This also occurs when the defect is too large (e.g., a gaping wound).

B. Inflammation: Disorders and After-effects



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. 186 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. 208 ff.), or in the abdomen (adhesions or strictures of the gut; → p. 168).

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)

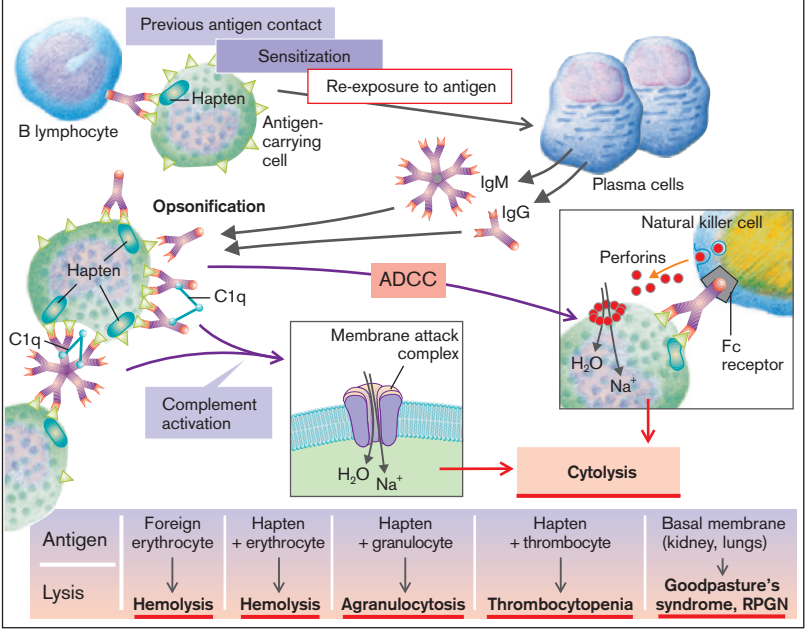
An allergy is a specific overreaction of the immune system to a substance that is foreign to the body but otherwise harmless, i.e., an antigen (→ p. 46), which now becomes an *allergen*. By binding to small-molecule foreign substances (so-called *haptens*), endogenous proteins can have the same effect as an allergen. While normally the increased immune (secondary) reaction can act protectively on repeated antigen contact (*immunization*; → p. 46 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. 58). In each case it is *inflammatory reactions* (→ p. 52 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_{H2} 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. 51 B4), and eosinophils in bone marrow are stimulated by IL-5 to differentiate and then enter the bloodstream (→ p. 53, 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, neutrophils and *IgG* (→ p. 53, 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 (wheals), and atopic dermatitis. If the allergen gains direct access into blood through injection (e.g., serum or haptens such as penicillin), an immediate systemic reaction occurs and the resulting liberation of vasoactive mediators can lead to a life-threatening drop in blood pressure (*anaphylactic shock*; → p. 246 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.

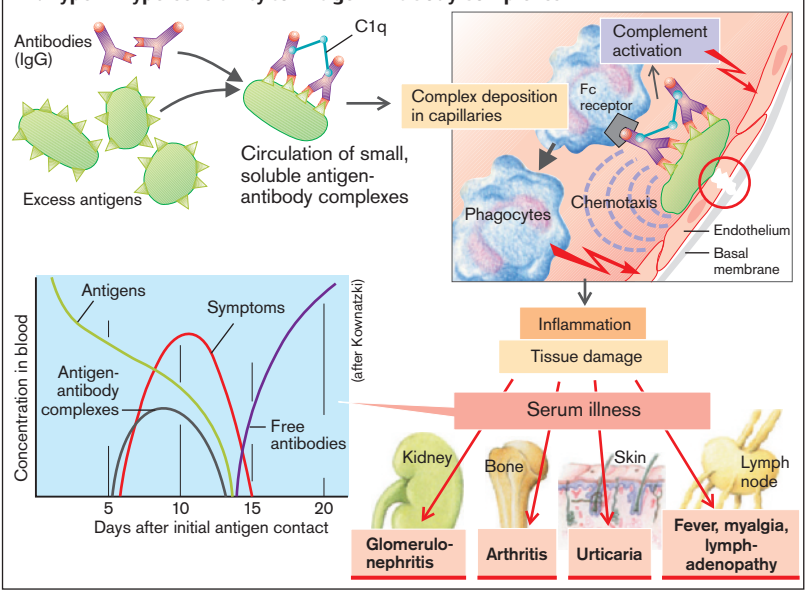
In **type II**, or **cytotoxic hypersensitivity** (→ **A**), the focus is usually on antigen-effective *cells* or extracellular matrix proteins, in that either *haptens* (e.g., drugs) bind to endogenous (blood) cells, or foreign blood cells enter the organism. After allergization on first contact with 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 (*opsonification*; → **A**). In this way the *complement system* is activated (→ p. 47, A1), and natural killer cells unfold their cytotoxic action (antibody-dependent cell-mediated cytotoxicity [ADDC]; → p. 47, 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. 44), and hapten binding to thrombocytes results in thrombocytopenia. The two cell types are especially exposed to complement attack, because they possess only a few membrane proteins protecting against complement attacks (see also p. 44). 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. 45, B). In a basically similar (but not as yet fully clarified) way, autoantibodies against α3(IV)-collagen of the basement membrane (→ p. 114) 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 glomerulo-

A. Cytotoxic (Type II) Hypersensitivity to Cellular Antigens



Antigen	Foreign erythrocyte	Hapten + erythrocyte	Hapten + granulocyte	Hapten + thrombocyte	Basal membrane (kidney, lungs)
Lysis	**Hemolysis**	**Hemolysis**	**Agranulocytosis**	**Thrombocytopenia**	**Goodpasture's syndrome, RPGN**

B. Type III Hypersensitivity to Antigen-Antibody Complexes



nephritis with impending renal failure [RPGN]; → p. 112 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. 47, 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**.

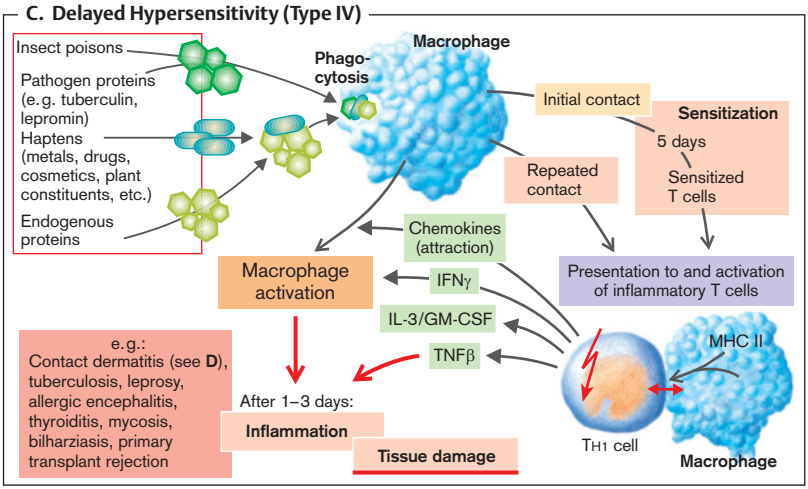
A type III reaction can also be caused by infections, if the immune system is unable to eliminate the pathogens completely (e.g., streptococci or certain malaria protozoa), but enough antibodies are formed to maintain a high concentration of immune complexes in the blood. Systemic lupus erythematodes is a type III reaction resulting from activation of the Toll-like receptors TLR7 and TLR9 (→ p. 48). Those receptors may mistakenly consider their own nucleic acids as viral, thus triggering an autoimmune response with the respective tissue damage. 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).

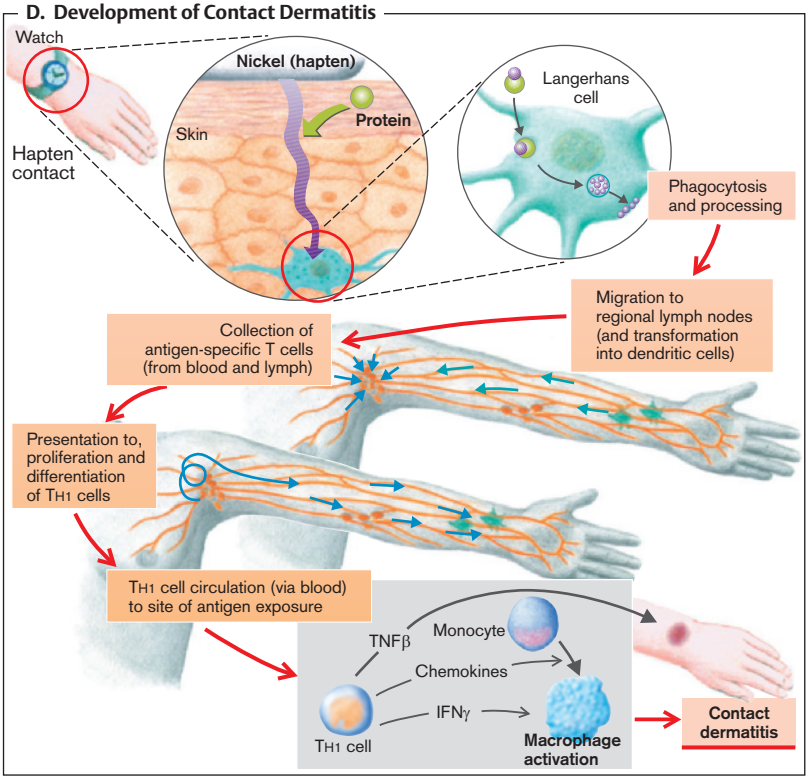
A **type IV reaction** (→ **C**, **D**) is borne mainly by T_{H1} cells, killer T cells and macrophages, reaching its maximum effect in two to four days (delayed reaction type or **delayed hypersensitivity type** [**DHT**]). It is triggered mainly by *proteins from pathogens* (viruses, tuberculosis, 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., pentadecacatechol in *poison ivy [Rhus radicans]*, or *poison oak* [*Rhus toxicodendron*]). *Primary rejection of transplanted organs* is also a type IV reaction.

The antigen is phagocytozed by *macrophages*, processed and presented to the (DHT-) T_H cells (→ **C**). Sensitization takes more than five days. On renewed contact, numerous T cells are activated into T_{H1} cells (→ p. 49 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_{H1} 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. 60).





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. 46);
- mature T cells are **clonally inactivated** (*anergy*; → p. 49). The reason for this is that cells in tissue do *not* give off any *costimulation signals* (e.g., B7-protein; → p. 50, 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. 308).

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

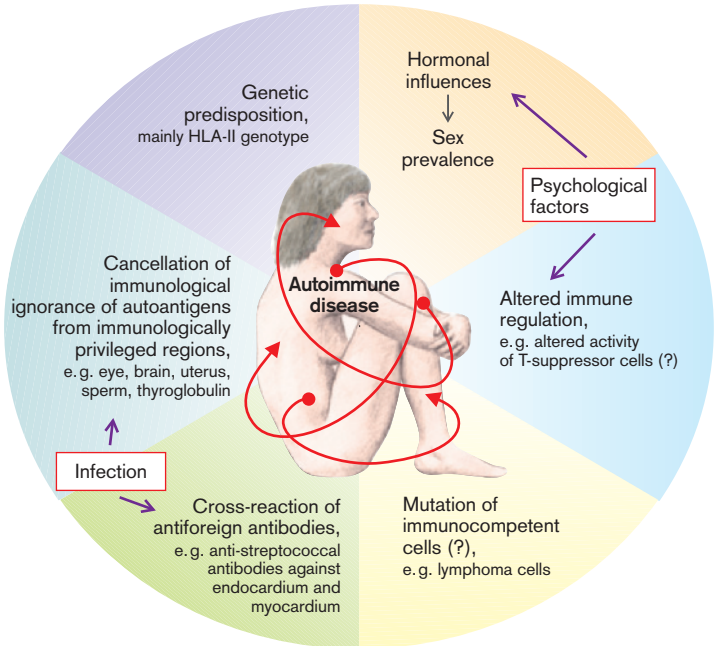
3. AAG from **immunologically privileged regions** (brain, eye, testis, uterus) may leave these (via blood vessels, but not via lymphatics) and interact with T cells, but this does usually not trigger AID, because AAGs are accompanied by TGFβ. This is probably responsible for T_{H2} cells being activated (instead of the destructive T_{H1} 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 tolerance or anergy of the T cells, but rather an *immunological ignorance*; this is transformed into destruction of myelin when (e.g., with an infection) MBP-specific, inflammatory T_{H1} cells are activated elsewhere and then penetrate into the brain. In a similar fashion proteins may be released in an injury to the eye and the immune response to it can endanger the other, intact, eye (sympathetic ophthalmia). Infertility due to sperm-AABs is another example. Normally the embryo or fetus with its numerous foreign antigens (inherited from the father) is immunologically tolerated, since the placenta induces anergy (→ p. 49) of maternal lymphocytes. Inability of the placenta to do so leads to abortion.

4. **Infections** may be involved in the development of AID. For example, MBP-specific T cells (see above) are activated when certain bacteria are present (experimentally, for example, by mycobacteria in *Freund's adjuvant*). These pathogens may elicit the missing costimulation signal (see above). In addition, antibodies against certain pathogen antigens or T cells may *cross-react* with AAG (*molecular mimicry*), such as antibodies against A streptococci with AAG in the heart (endocarditis), joints (rheumatoid arthritis), and kidney (glomerulonephritis).

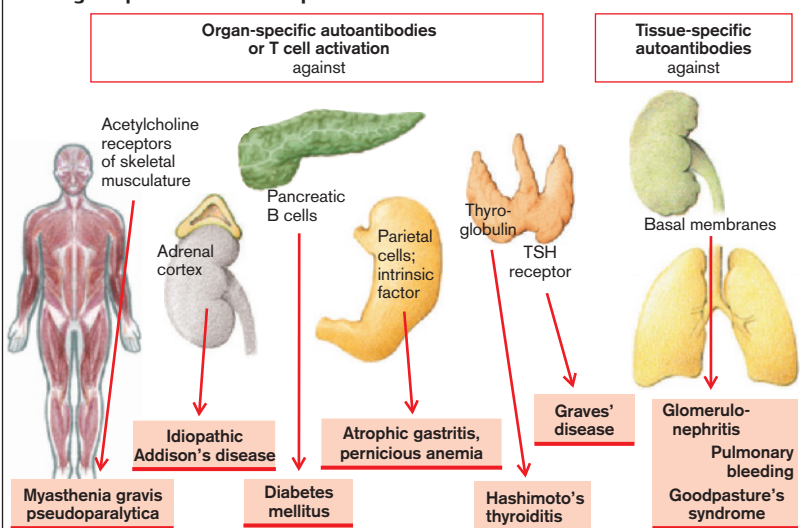
5. **Faulty regulation of the immune system** of an unknown kind (absence of suppressive CD8 cells that kill antigen-presenting CD4 cells?) may also be involved.

The immune mechanisms of AID correspond to type II–V hypersensitivity reactions (→ p. 56 ff.). One also distinguishes *systemic AID* (e.g., systemic lupus erythematodes [type III reaction]) from *organ-specific* and *tissue-specific AID* (→ **B**). Examples of type II reactions are autoimmune hemolytic anemia and Goodpasture's syndrome; rheumatoid arthritis, multiple sclerosis (?) and type I diabetes mellitus (in which CD8-T cells destroy the own pancreatic B cells; → p. 308) are examples of type IV reactions. Examples of type V reactions are hormone receptor–activating (Graves' disease) or hormone receptor–blocking (myasthenia gravis) AAD.

A. Causes of Autoimmune Disease



B. Organ-Specific and Tissue-Specific Autoimmune Diseases



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. 48). 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 gastrointestinal 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. 51, 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-cell 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-stranded 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_H cells* that are affected. In the latter, ssRNA is transcribed to cDNA by a virion-endogenous *reverse transcriptase*, finally being incorporated as a double-stranded 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 *NF*κb from the host cell, take part in the formation of new virions that are exocytozed (*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). Non-infected 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 T_{H1} 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 (10^6), inactive CD4 cells (mostly in lymph nodes).

A. AIDS

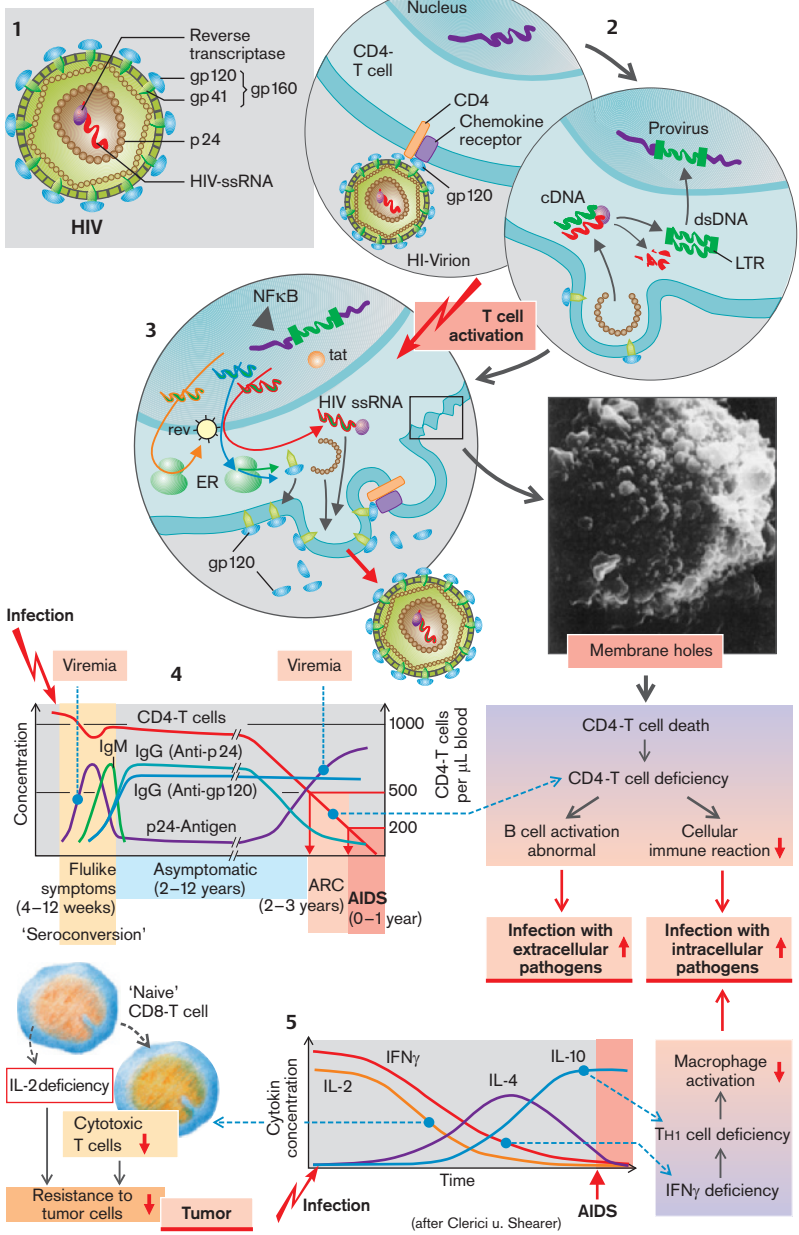


Photo from: Gallo RC. J. Acquired Immune Deficiency Syndromes. 1988; 521-535. ©1988 Raven Press.
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Hemostasis and Its Disorders

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. 258) 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 (→ **E**).

Thrombocytes (TCs or platelets; 170 – 400 × 10^3/µL blood) are nucleus-free cytoplastic bud-like particles split off from the megakaryocytes in bone marrow (→ p. 32). 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 (→ **G 1**). 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. 52) 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 (→ **G**). Activated TC release stores PAI-1 (plasminogen-activator inhibitor). PAI-1 is produced in the endothelium. It inhibits the plasminogen activators tPA and urokinin and thus counteracts fibrinolysis (→ **E**).

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)

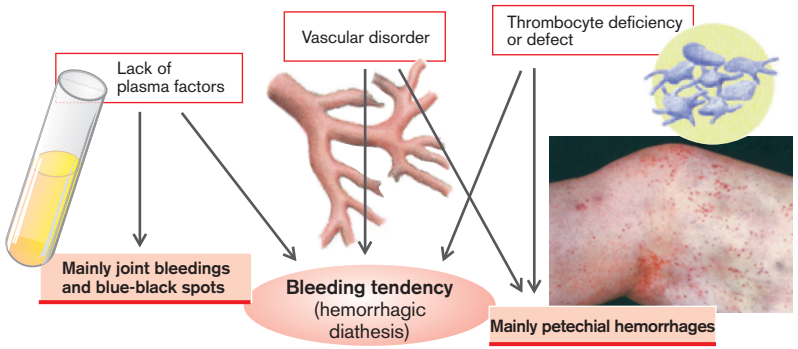
and the *inhibitory factors* (→ **F**):

- antithrombin III
- α_2-macroglobulin
- α_1-antitrypsin
- protein C^K, and
- protein S^K

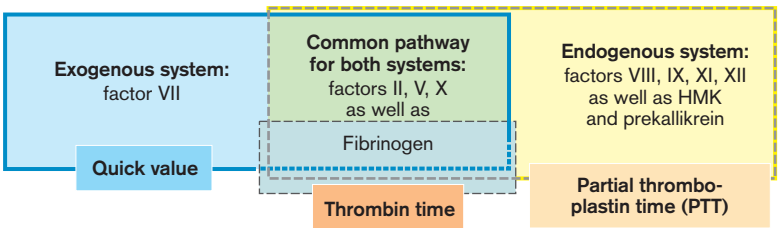
With the exception of Ca^{2+}, they are all globular proteins with a molecular mass between 54 kDa (α_1-antitrypsin) and 2 000 kDa (factor VIII), most of which are synthesized in the liver (I, II^K, V, VII^K, IX^K, X^K, XIII, kininogen). *Vitamin K* is essential for the formation of those factors and 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**, above). Most coagulation factors are normally not active (= zymogen). They are activated (Index a) by an amplifying cascade. The coagulation can be triggered exogenously or endogenously. The **exogenous** (extravascular) activation after vascular injury (→ **D**, above left) is triggered by forming a complex of tissue factor (TF = tissue thrombokinase, an integral membrane protein), bloodborne coagulation factor VII a and Ca^{2+} at phospholipid surfaces (PL). The complex activates the factors VII, IX, and X, leading to the formation of small quantities of thrombin starting a reaction, (→ **D**, thin arrows). The thrombin activates the factors V, VIII, XI, IX, and X (→ **D**, bold arrows) and initiates a positive feedback loop resulting in the release of large quantities of thrombin, sufficient for the formation of a **thrombus** (see below). The effects of the TF-PL-Ca^{2+}-VII a complex are now inhibited by TFPI (tissue factor ▶

A. Causes and After-effects of Bleeding Tendency



B. Clotting Tests for Diagnosing Plasmatic Hemorrhagic Diatheses



C. Interpretation of Clotting Test Results

Quick value	PTT	Thrombo-cyte count	Bleeding time	Probable causes of hemorrhagic diathesis (applied to moderate to severe disorders)
normal	normal	normal	normal	Vascular cause, factor XIII deficiency
↓	normal	normal	normal	Factor VII deficiency
normal	↑	normal	normal	Heparin administration, deficiency of factor VIII, IX, XI, XII, HMK or prekallikrein
normal	normal	↓	↑	Thrombocytopenia
↓	↑	normal	normal	Administration of coumarin derivatives, vitamin K deficiency, factors I, II, V, X deficiency
normal	↑	normal	↑	v. Willebrand's disease
↓	↑	↓	↑	Liver damage, consumption coagulopathy, sepsis

(after E. Lechler)

↓ reduced ↑ prolonged

Photo: Siegenthaler W. Differentialdiagnose innerer Krankheiten. 17th ed. Stuttgart: Thieme; 1993.

pathway inhibitor, → **D**, left). The **endogenous** activation (→ D, above right) is triggered by contact activation of factor XII. As patients with genetically defective XII do not suffer from a bleeding disorder, it is now assumed that this type of activation is only relevant for the stimulation of coagulation at exogenous (test tubes) or endogenous (vascular stents) surfaces of foreign materials.

The coagulation is followed by **fibrinolysis** (→ **E**).

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 (bruises) 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 severe HD can be elucidated with a few simple **clotting tests** (Quick test, partial thromboplastin time [PTT], [plasma] thrombin time, platelet count and bleeding time) (→ **B**).

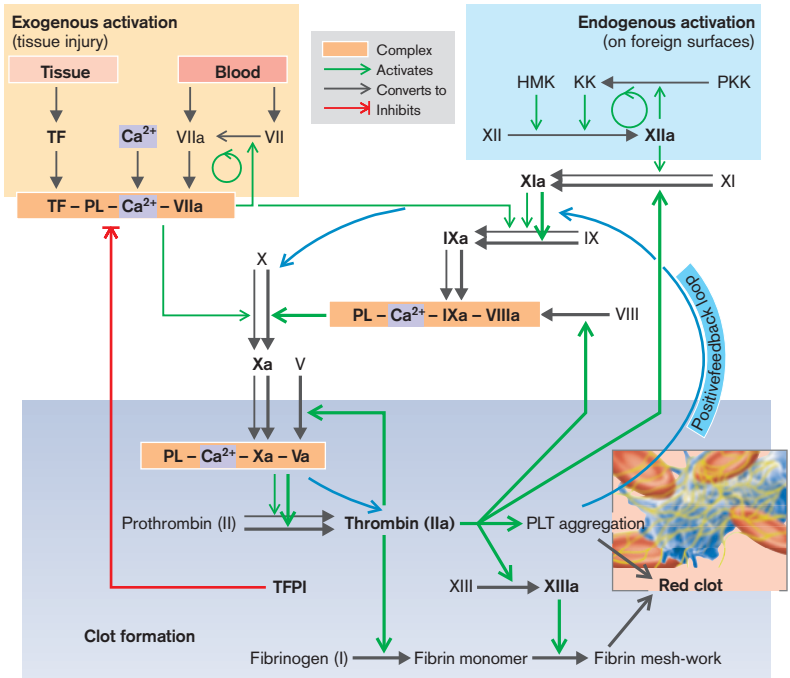
Plasma hemorrhagic diathesis (coagulopathies) are caused by congenital or acquired clotting factor deficiency. The **hereditary coagulopathies** can affect practically each of the plasma factors, but deficiency of some of the factors may produce relatively few symptoms (e.g., factors of the contact phase, factor XI). The most common (one of 10 000 newborn boys) of the 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 α_2-antiplasmin, an important inhibitor of fibrinolysis (→ **E**) 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 (→ **D 2**) occur when formation of the various factors is reduced, when they are inhibited (e.g., by administration of heparin [→ **F**] 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. 186 ff.) results in clotting disorders. Simultaneously occurring portal hypertension further increases the risk of hemorrhages (mainly from esophageal varices; → p. 184 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*. Causes of vitamin K deficiency are:

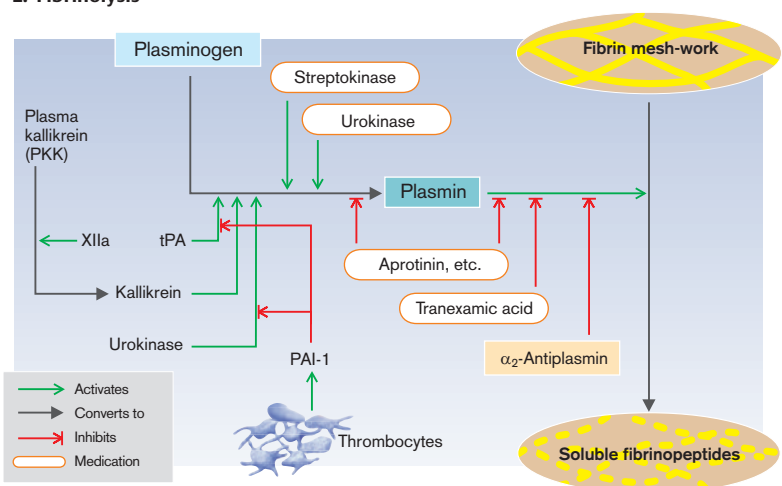
- obstructive jaundice, in which fat-soluble vitamins (e.g., vitamin K_1 from green plants or synthetic vitamin K_3) fail to be absorbed due to the lack of bile salts (→ p. 182);
- generalized malabsorption (→ p. 164 ff.);
- destruction by antibiotics of the intestinal flora, which through its synthesizing vitamin K_2 contributes significantly to supplying the body with this substance.

Disseminated intravascular coagulation (*consumption coagulopathy*; → **D 2**) 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. 252 ff.), or in vascular malformations as well as in ABO blood group mismatches, and due to enzyme action with certain snake poisons.

D. Blood clotting



E. Fibrinolysis



Causes of **thromboses** include obesity (→ p. 256), postoperative state, immobilization (e.g., air travel, bed rest), estrogen treatment, pregnancy (especially postpartum), and APC resistance (see below). The most important plasma factor providing protection against thrombosis is **antithrombin III**. It complexes with, and thus inhibits, thrombin and the factors IXa, Xa, XIa, and XIIa. The action of antithrombin III is amplified by endogenous (from mast cells and granulocytes) or injected **heparin** as well as by endothelial heparin-like glycosaminoglycans. Protection against thrombosis is further provided by the binding of thrombin to endothelial *thrombomodulin* with subsequent activation of protein C (to Ca), which, coupled to protein S, inhibits the factors Va and VIIIa (→ **F**). Thrombin thus triggers an anticoagulatory negative feedback. A genetic defect of factor V (factor-V Leiden mutation) prevents the binding of protein Ca to the factor Va (APC resistance), thus abrogating this anticoagulatory mechanism.

Conditions with enhanced thrombosis may warrant the prophylactic decrease of coagulatibility (**anticoagulant therapy**), which may be accomplished by immediately effective *heparin* or by oral treatment with cumarins. The cumarins inhibit the vitamin K dependent γ-carboxylation of coagulation factors in the liver (*vitamin K antagonists*). Cyclo-oxygenase inhibitors such as *acetylsalicylic acid* (aspirin®) inhibit the aggregation of thrombocytes by blocking the synthesis of thromboxan TXA_2.

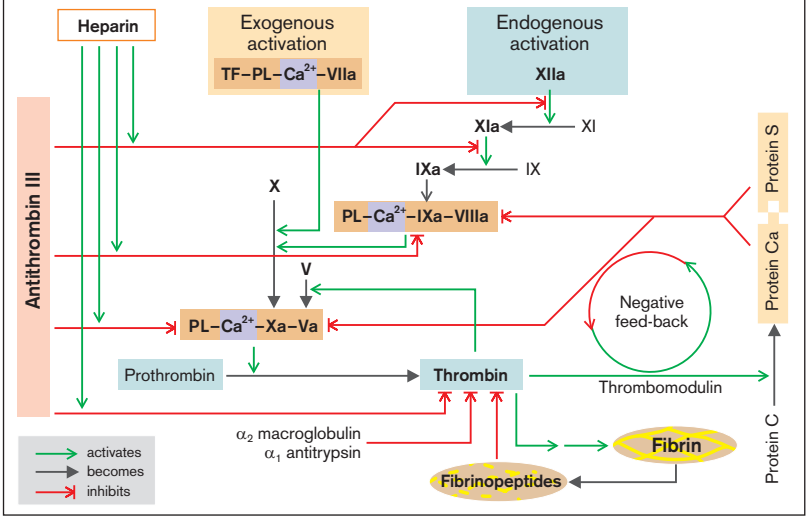
The two groups of **hemorrhagic diathesis caused by platelet abnormalities** are thrombocytopenias and thrombocytopathies. **Acquired thrombocytopenias** (**TCPs**) are the most common HD. TCP is due to *diminished platelet formation* (aplastic TCP, e.g., in bone marrow tumors, radiation damage, or cobalamine 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 20×10^3/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 haptens (→ p. 56). **Acquired thrombocytopathies** 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 thrombocytic HDs are the autosomal-dominant and autosomal-recessive hereditary thrombocytopenias (abnormal platelet production) with the following functional disorders:

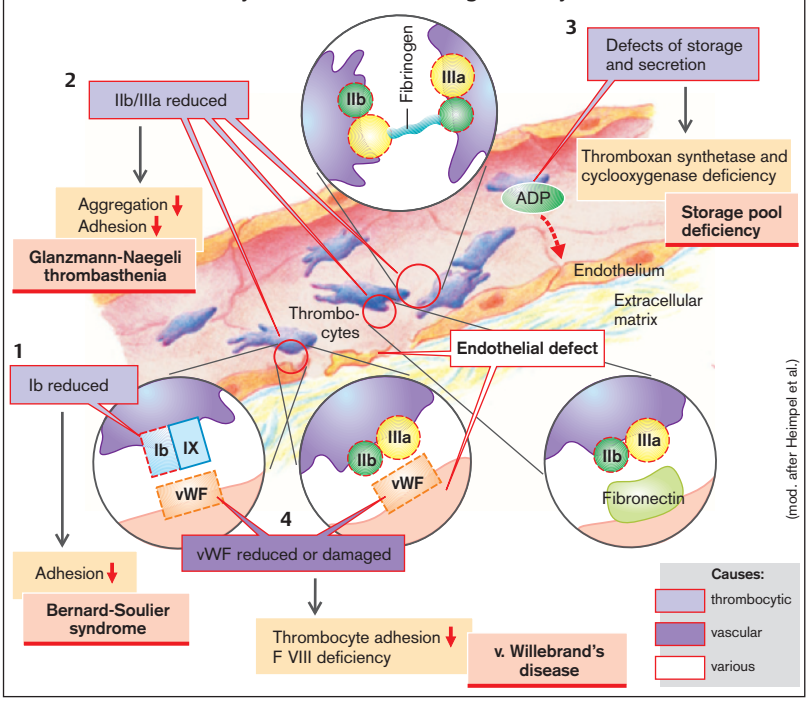
- *Membrane defects* such as 1) deficiency of platelet glycoprotein Ib (→ **G1**) that disturb adhesion (Bernard–Soulier syndrome); 2) deficiency of glycoprotein complex IIa/IIIb (→ **G2**), which inhibits aggregation and adhesion (Glanzmann–Naegeli thrombasthenia);
- Diverse *defects of storage* or *secretion,* for example, deficiency of cyclo-oxygenase and thromboxane synthetase, in which ADP release is reduced (storage pool deficiency); (→ **G3**).

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 (→ **G4**). 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 tisue that are either congenital (purpura simplex; Osler–Weber–Rendu disease; Schönlein–Henoch disease), or acquired (scurvy in vitamin C deficiency; drug-mediated immune reactions).

F. Inhibition of Blood Clotting System



G. Causes of Thrombocytic and Vascular Bleeding Tendency



Overview

Breathing through the lungs has two functions: firstly, to supply O_2 to the blood and, secondly, to regulate the acid–base balance via the CO_2 concentration in the blood. The mechanics of breathing serve to ventilate the alveoli, through whose walls O_2 can diffuse into the blood and CO_2 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 O_2 uptake and CO_2 release can no longer be guaranteed.

In **obstructive lung disease** (→ p. 80) flow resistance in the respiratory tract is raised and ventilation of the alveoli is thus impaired (→ **A 1**). The primary consequence is hypoventilation in some alveoli (abnormal distribution; → p. 76) 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. 78) the distensibility of the lung (compliance) is decreased. The disorder may result from impairment of respiratory movements or from a loss of functioning lung tissue. The latter reduces the area of diffusion and in this way impairs gaseous exchange. The diffusion area is similarly decreased in lung emphysema (→ p. 82), which is characterized by a decreased number of enlarged alveoli ("bullae"). Disorders of diffusion can also be caused by an increased distance between alveoli and blood capillaries (→ **A 2**; → p. 74, 84). If alveoli and capillaries are completely separated from one another, this results in both a functional dead space (nonperfused alveoli) and an arteriovenous shunt.

Lung and cardiovascular disease may affect **lung perfusion** (→ **A 3**; → p. 72). Decreased perfusion results in a reduced amount of gases being transported in blood, despite adequate O_2 saturation and CO_2 removal in the alveoli. Increased pulmonary vascular resistance enhances the workload for the right ventricle of the heart, as it requires an increased pressure to force the total cardiac output (CO) through the pulmonary circulation (→ p. 80 and 228).

Breathing is also impaired in **dysfunction of the respiratory neurons** (→ p. 86) as well as of the motorneurons, nerves, and muscles that are controlled by them (→ p. 72). 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** (→ **A 5**; → p. 90), **hypercapnia** or **hypocapnia** (increased or decreased CO_2 content, respectively; → **A 4**; → p. 94 ff.) in arterialized blood. The supply of O_2 to the cells as well as the removal of CO_2 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).

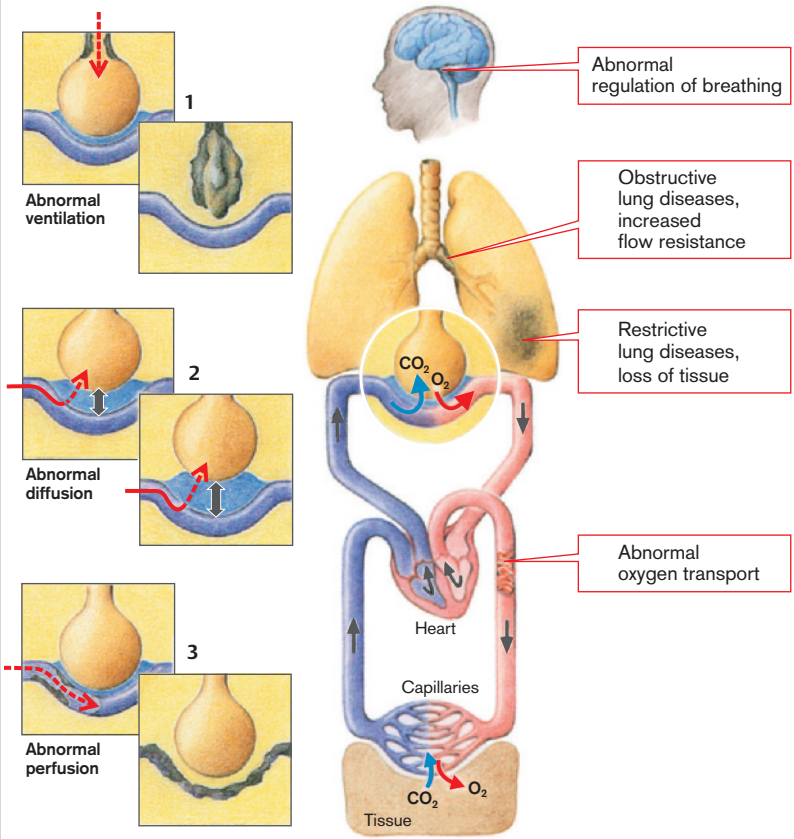
Table 1 Terms for Various Breathing Activities

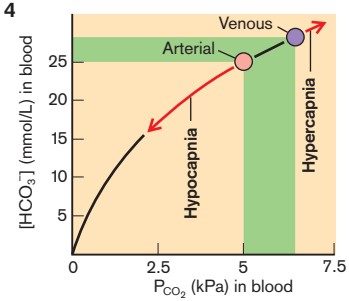
Hyperpnea	increased breathing movement
Eupnea	normal breathing movements
Hypopnea	decreased breathing movements
Apnea	arrested breathing
Bradypnea	decreased rate of breathing
Tachypnea	increased rate of breathing
Dyspnea	labored breathing (subjective feeling)
Asphyxia	inability to breathe
Orthopnea	labored breathing, except in the sitting or upright position

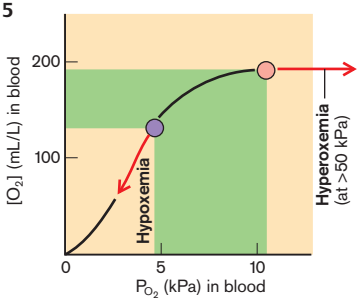
Table 2 Definition of Some Parameters of Ventilation

Tidal volume (V_T)	volume of normal inspiration and expiration
Vital capacity (VC)	volume of maximal expiration after maximal inspiration
Maximal breathing capacity ($\dot{V}_{max}$)	maximal ventilation (L/min) achieved in a short period of time (usually 10 s)
Compliance (C)	lung distensibility
Forced expiration volume (FEV_1)	maximal volume expired in 1 second
Functional residual capacity (FRC)	total residual volume after normal expiration

A. Pathophysiology of Respiration (Overview)







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

Increased ventilation can occur as a result of either physiologically (e.g., during work) or pathophysiologically (e.g., in metabolic acidosis; → p. 96) increased demand, or due to an inappropriate hyperactivity of the respiratory neurons (→ p. 86).

Decreased ventilation can occur not only when the demand is reduced, but also when the respiratory neurons 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, obesity), enlargement of the pleural space by pleural effusion or pneumothorax (→ p. 78) as well as restrictive or obstructive lung disease (→ p. 78 ff.). Particularly in obese individuals, the respiratory drive decreases during sleep (→ p. 86) resulting in sleep apnea.

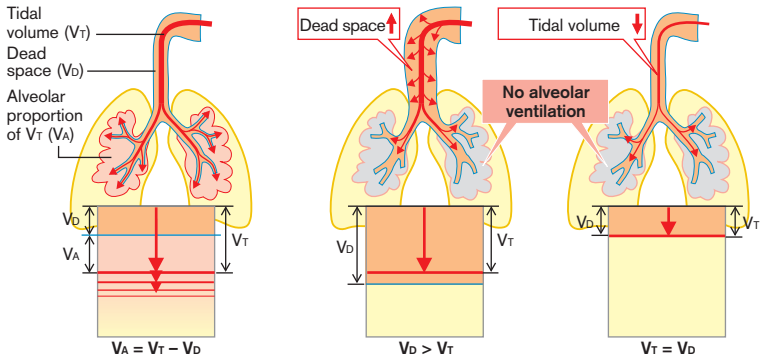
Changes in alveolar ventilation do not have the same effect on **O_2 uptake** into the blood and **CO_2 release** into the alveoli. Because of the sigmoid shape of the O_2 dissociation curve, O_2 uptake in the lungs is largely independent of alveolar partial pressure ($P_{A_{O_2}}$). If there is only *minor hypoventilation*, the partial pressure of O_2 in the alveoli and thus in blood is reduced, but the O_2 dissociation is at the flat part of the curve, so that the degree of hemoglobin saturation and thus O_2 uptake in blood is practically unchanged (→ **B**, right). On the other hand, the simultaneous increase in CO_2 partial pressure in the alveoli and blood leads to a noticeable impairment of CO_2 release (→ **B**, left). *Massive hypoventilation* lowers the O_2 partial pressure in the alveoli and blood, so that oxygen is at the steep part of the O_2 binding curve of hemoglobin and O_2 uptake is therefore impaired much more than CO_2 release is. *Hyperventilation* increases the O_2 partial pressure in the alveoli and blood, but cannot significantly raise the level of O_2 uptake into the blood because the hemoglobin is already saturated. However, hyperventilation boosts CO_2 release.

Lung perfusion is increased, for example, during physical work. It can be reduced by heart or circulatory failure (→ p. 238), or by constriction or occlusion of pulmonary vessels (→ p. 228).

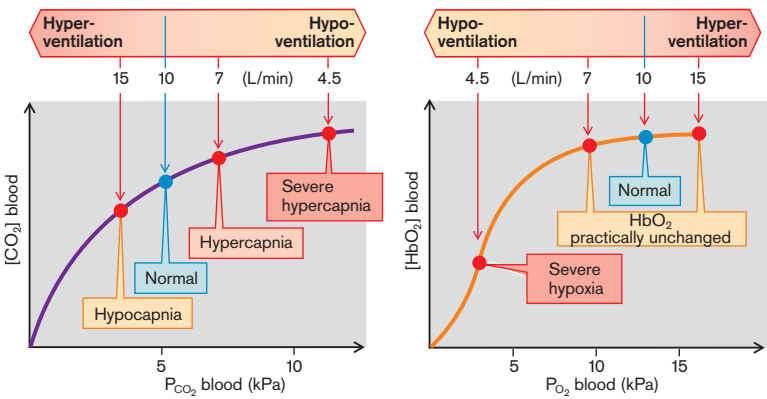
A moderate increase in lung perfusion while ventilation remains unchanged increases **O_2 uptake** virtually in proportion to the amount of blood flow (→ **C**, right). Even though the alveolar O_2 partial pressure falls slightly because of the increased O_2 uptake from the alveoli into the blood, this has little influence on O_2 saturation in the blood (see above). It is only when the alveolar partial pressure of O_2 falls into the steep part of the O_2 dissociation curve that a decrease of alveolar O_2 partial pressure significantly affects O_2 uptake into blood. At those O_2 partial pressures a further increase in lung perfusion only slightly increases O_2 uptake. Furthermore, at very high lung perfusion flow, the contact time in the alveoli is not sufficient to guarantee that partial O_2 pressure in blood approaches that in the alveoli (→ p. 74). If lung perfusion is reduced, O_2 uptake is proportionally decreased.

CO_2 removal from blood is dependent on lung perfusion (→ **C**, left) to a lesser extent than O_2 uptake. In case of reduced lung perfusion (but constant ventilation and venous CO_2 concentration) the CO_2 partial pressure in the alveoli falls and thus favors the removal of CO_2 from the blood. This, in turn, attenuates the effect of the reduction in perfusion. At raised lung perfusion an increase of alveolar CO_2 concentration prevents a proportional rise in CO_2 release.

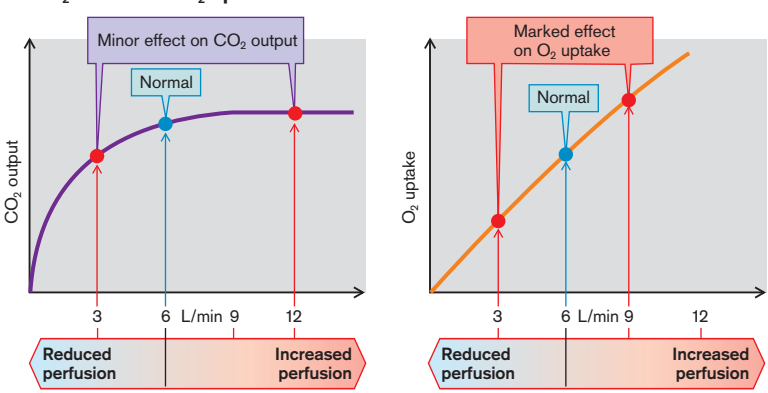
A. Dead Space (V_D), Alveolar Volume (V_A) and Tidal Volume (V_T)



B. O_2 and CO_2 of Arterial Blood in Abnormal Ventilation



C. CO_2 Release and O_2 Uptake at Different Perfusion Levels



Diffusion Abnormalities

O_2 has to diffuse from the alveoli to hemoglobin in the erythrocytes, and CO_2 from the erythrocytes into the alveoli. The *amount of gas* ($\dot{M}$) that diffuses across the diffusion barrier between alveoli and blood per unit time is proportional to the diffusion area (F) and the difference in partial pressure between alveolar gas (P_A) and blood (P_{blood}), and inversely proportional to the length of the diffusion pathway (d):

$$\dot{M} = K \times F\,(P_A - P_{blood})/d.$$

Krogh's diffusion coefficient K is about 20 times greater for CO_2 than for O_2. 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. 84), 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. 78), 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.

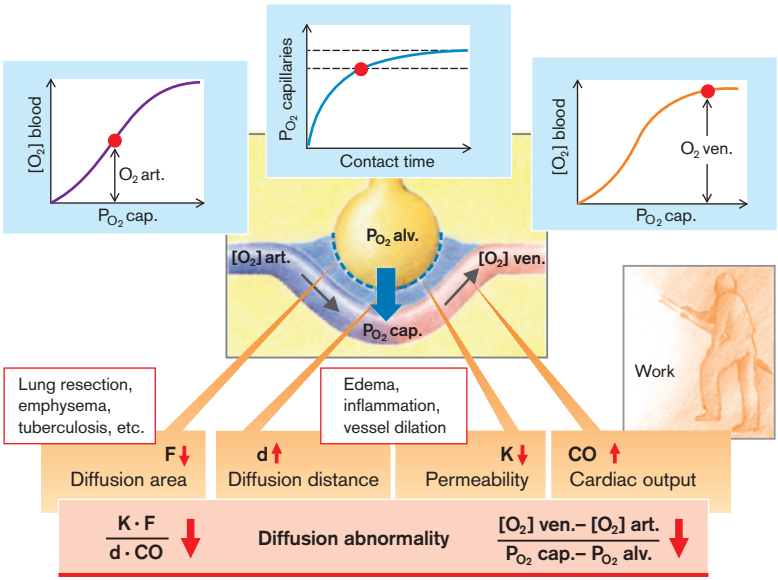
A diminished diffusion capacity may also be caused by a **reduction of the diffusion area** (→ **A**), as after unilateral lung resection, loss of alveolar septa (pulmonary emphysema; → p. 82), or in loss of alveoli in pneumonia, pulmonary tuberculosis, or pulmonary fibrosis (see above). The diffusion area can also be reduced by alveolar collapse (atelectasis; → p. 76), pulmonary edema, or pulmonary infarction (→ p. 84).

Usually gas exchange is virtually complete within one-third of the contact time between the capillary blood and the alveoli.

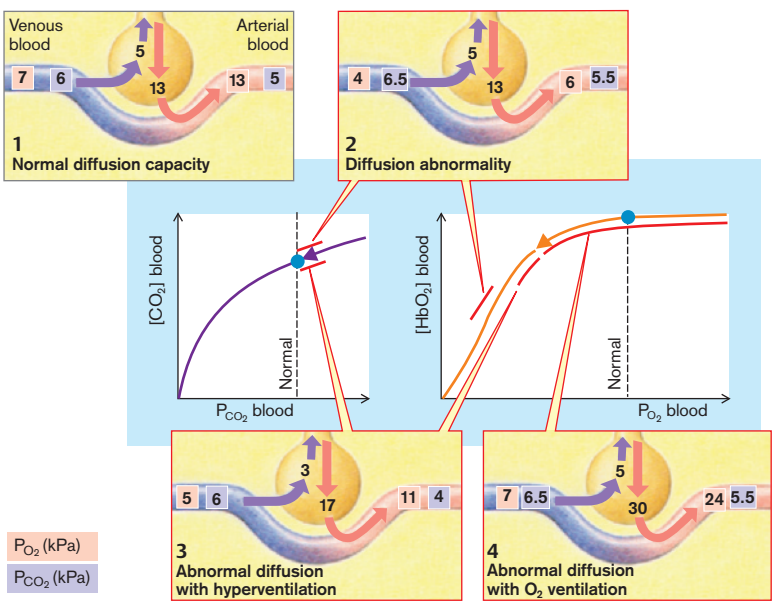
Diffusion abnormalities become obvious when cardiac output is large (→ **A**), blood flows rapidly through the lungs, and the contact time of blood in the alveoli is thus brief. The increased O_2 demand during physical exercise requires an increase of cardiac output and may thus unmask a diffusion abnormality. 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.

Abnormal diffusion primarily **affects** O_2 transport. In order for the same amount of gas to diffuse per time, the O_2 gradient must be twenty times greater than the CO_2 gradient. Should the diffusion capacity in an alveolus be diminished while ventilation remains constant, O_2 partial pressure will fall in the blood leaving the alveolus. If all alveoli are similarly affected, O_2 partial pressure will fall in the pulmonary venous (and thus systemic arterial) blood. If O_2 consumption remains constant, O_2 partial pressure will necessarily be lower also in systemic venous blood (→ **B2**). Due to incomplete oxygenation of hemoglobin patients with a diffusion abnormality get blue lips on physical exertion (*central cyanosis*; → p. 90). The primary effects of abnormal diffusion on CO_2 transport and acid–base metabolism are much less marked. Hypoxia stimulates the respiratory neurons, and the resulting increase in ventilation can even 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 O_2 consumption increases alveolar O_2 partial pressure by only 4 kPa to 17 kPa (30 mmHg to 129 mmHg), but the increased O_2 gradient does not normalize the O_2 saturation of the blood. At the same time, *respiratory alkalosis* develops, despite the abnormal diffusion, because of the increased CO_2 removal (→ p. 94). Hypoxemia due to abnormal diffusion can be neutralized with O_2-enriched inspiratory air (→ **B4**). The degree of hypoxemia can be lessened by decreasing O_2 consumption.

A. Development of Diffusion Abnormalities



B. Abnormal Diffusion: Concentrations of CO_2 and HbO_2 in Blood



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 ($\dot{V}A$) to perfusion ($\dot{Q}$). In the ideal case this relationship ($\dot{V}A/\dot{Q}$) 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 $\dot{V}A/\dot{Q}$ 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 (→ p. 228). In addition, capillaries can be separated from their related alveoli by proliferating connective tissue, as is the case in pulmonary fibrosis (→ p. 74, 78). Lastly, capillary supply to the alveoli may also fade away if the alveolar septa are destroyed, as is the case in pulmonary emphysema (→ p. 82).

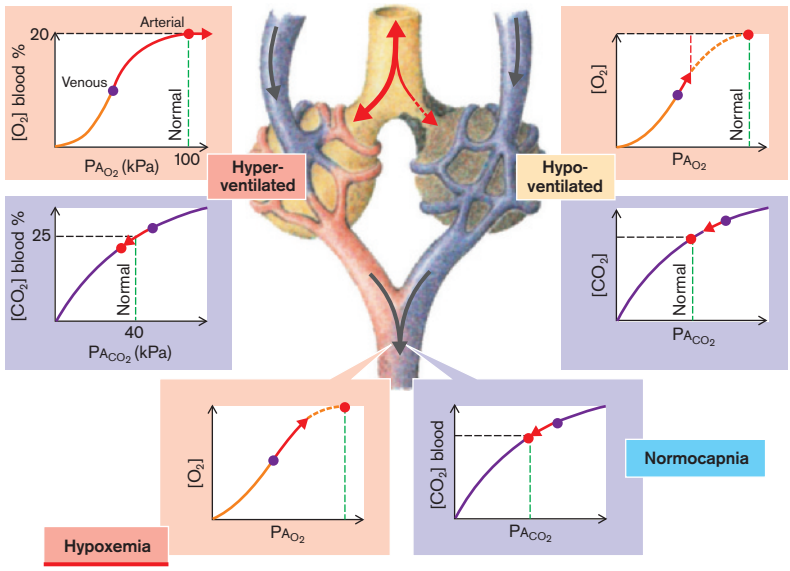
The impaired perfusion of ventilated alveoli *increases the functional dead space*, because the air in these alveoli no longer takes part in the gaseous exchange. This condition can be compensated by deeper breathing (increased V_T). If a large proportion of alveoli are not perfused, the *diffusion area* also *decreases* (→ p. 74), and this can no longer be compensated by deeper breathing.

◆ In **impaired ventilation** of perfused alveoli (→ **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 (→ p. 80), 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 or by diaphragmatic paralysis. Oxygenation of blood is further compromised by (functional) arteriovenous shunts, e.g., as a result of lung fibrosis or of pathological vessel formation (e.g., at liver insufficiency or hereditary hemorrhagic teleangiectasy Osler–Rendu–Weber).

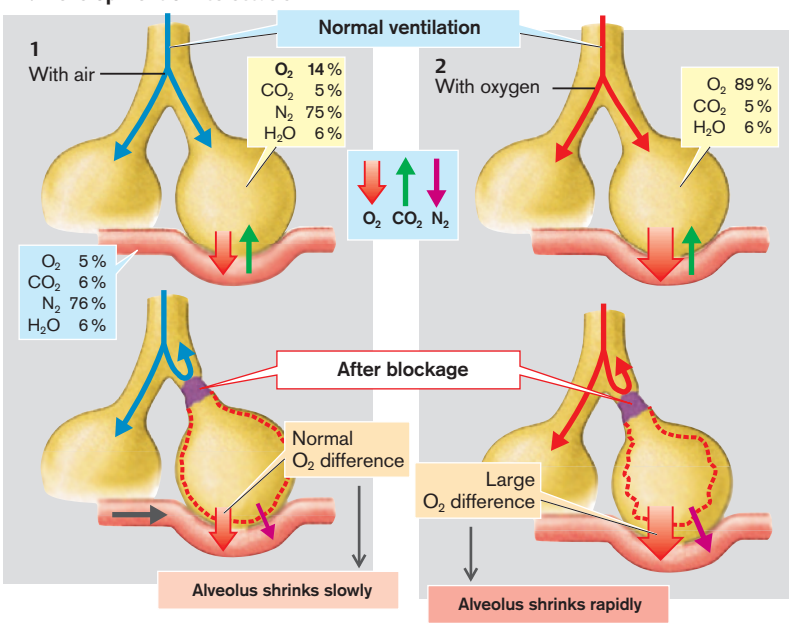
Perfusion of inadequately ventilated alveoli leads to an *admixture of nonarterialized blood* with pulmonary venous blood. This results in *hypoxemia* (→ **A**; P_A = partial pressure in alveolar gas mixture), which cannot be compensated by hyperventilation of "intact" alveoli (this is because O_2 uptake by the blood that passes along ventilated alveoli can be increased only minimally by hyperventilation; → p. 72). On the other hand, hypercapnia hardly ever occurs because the reduced CO_2 release from underventilated alveoli (→ **A**, right) can be well compensated by increased release into hyperventilated alveoli (→ **A**, left). On the contrary, the hypoxemia frequently leads to *excess hyperventilation*, and the development of *hypocapnia*. 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 (→ **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 (→ **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 O_2 Uptake and CO_2 Release



B. Development of Atelectasis



Restrictive Lung Disease

Restrictive lung disease denotes an anatomical or functional loss of gaseous exchange area (parenchymal) or a restriction of respiratory movements (extraparenchymal).

Extraparenchymal causes include neuromuscular disease (e.g., myasthenia gravis), obesity, malformations of the thorax (kyphoskoliosis), joint stiffening, and pleural scarring.

An **anatomical loss** of lung tissue occurs after removal (resection) or displacement (e.g., by a tumor) of lung tissue as well as following atelectasis (→ p. 76).

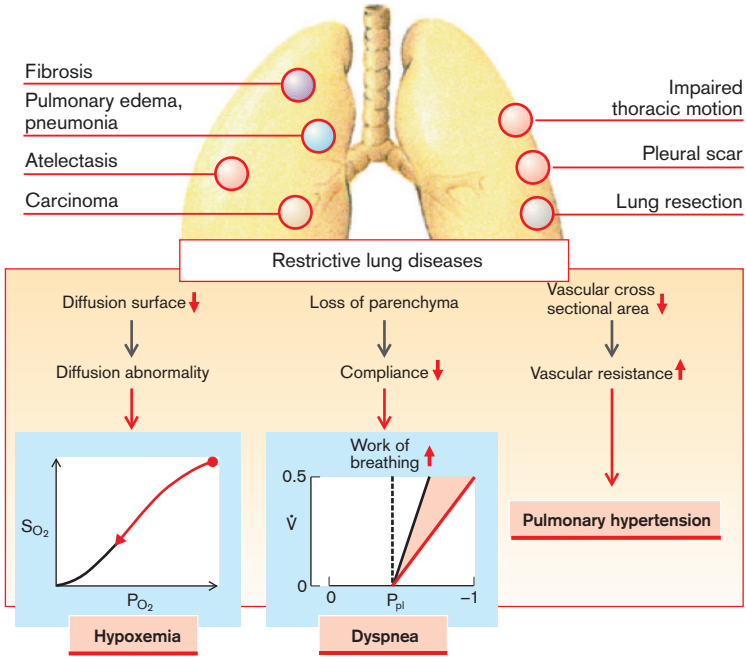
A **functional decrease** in exchange area occurs if *plasma water* is *exuded* into alveoli, for example, in pulmonary edema (→ p. 84) or in inflammation (increased vascular permeability, e.g., in pneumonia). In *pulmonary fibrosis* proliferating connective tissue displaces intact pulmonary parenchyma (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 ("collagen disease") or by inhalation of dust which contains silicate or asbestos. Sometimes no cause is found (idiopathic pulmonary fibrosis [Hamman–Rich syndrome]). Stimulators of fibrosis include TGF-β and IGF (transforming and insulin-like growth factor).

The consequences of restrictive pulmonary disease include a decrease in compliance (C), vital capacity (VC), functional residual capacity (FRC), and diffusion capacity (→ p. 70). The latter leads to *diffusion abnormality* (→ p. 74) and thus to *hypoxemia* (→ **A**; SO_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_{PGL}), thus more energy 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, which must be generated by the right heart, is required to pump the blood through the pulmonary vascular bed. The consequence is an increased *load on the right ventricle* (cor pulmonale; → p. 228).

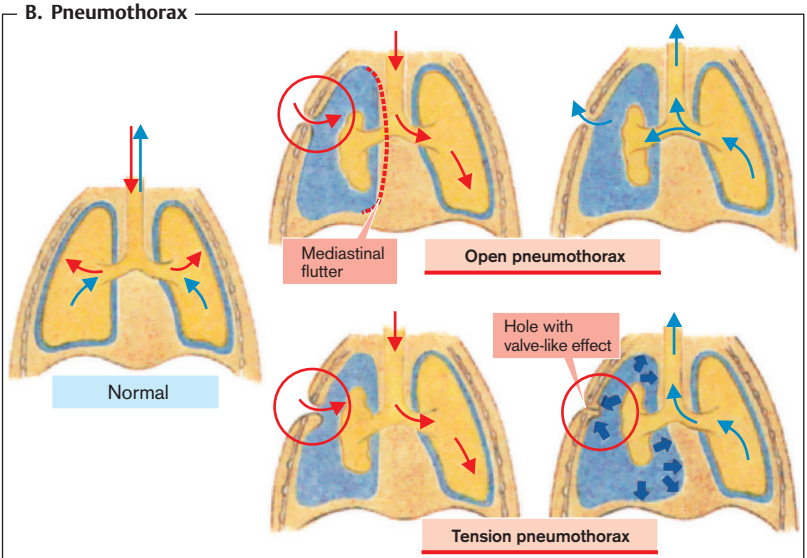
Pneumothorax is also a restrictive lung disease (→ **B**). If there is an *open connection* between the pleural space and outside air (thoracic injury; → **B**, top) or the alveoli (torn alveolar wall due to overdistension), air enters and the ipsilateral lung collapses. Breathing is also impaired in 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.

A. Causes and Effects of Restrictive Lung Diseases



B. Pneumothorax



Obstructive Lung Disease

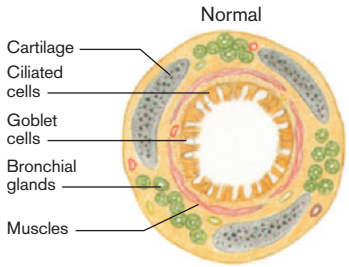
In order to reach the alveoli air must pass through the respiratory tract or airways (→ p. 72), which present a resistance to the flow. This resistance is determined by the lumen in the tract. In particular the narrow lumen of the bronchioles can be further narrowed by mucus and the contraction of the 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.

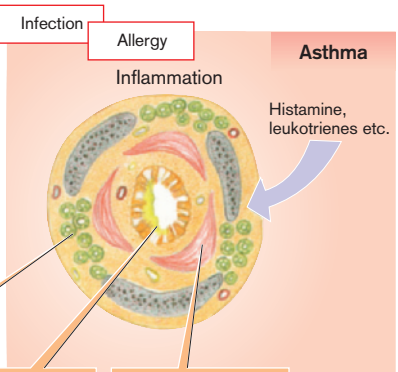
Intrathoracic increase in resistance is usually due to a narrowing or obstruction of the bronchi, by either external compression, contraction of bronchial muscles, thickening of the lining mucus layer, or obstruction of the lumen by mucus. Most of these changes are the result of *asthma* or *chronic 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 (e.g., LTD_4), prostaglandins, thromboxan, platelet activating factor (PAF), cytokines, bradykinin, tachykinins, adenosine, anaphylatoxins, growth hormones, endothelin, NO, and reactive oxygen species. In the following, 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. 176) 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. 82) 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. 302 ff.). In tracheomalacia the tracheal wall is softened and collapses on inspiration.

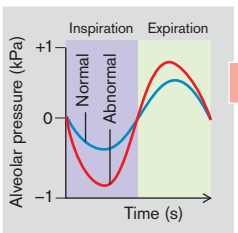
The **effect** of obstructive lung disease is reduced ventilation. If *extrathoracic obstruction* occurs, it is mainly inspiration that is affected (inspiratory stridor), because during expiration the pressure rise in the prestenotic lumen widens the narrowed portion. *Intrathoracic obstruction* mainly 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. 82), lung recoil decreases (compliance increases), and the midposition of breathing is shifted toward inspiration (*barrel chest*; → p. 82). 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 ($\dot{V}_{max}$) and FEV_1 (→ Table 2 on p. 70), and the differing ventilation of various alveoli results in *abnormal distribution* (→ p. 76). The hypoxia of underventilated alveoli leads to vasoconstriction, increased pulmonary vascular resistance, pulmonary hypertension, and an increased right ventricular load (cor pulmonale; → p. 228).

A. Obstructive Lung Diseases

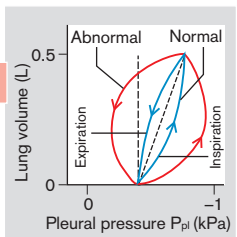




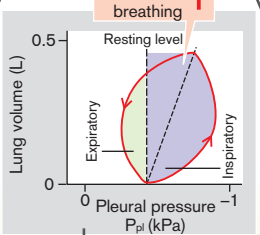
Mucus secretion ↑ | Mucosal edema | Muscle contraction



Increased resistance to breathing



Work of breathing ↑



Abnormal ventilation

Expiration requires increased pressure

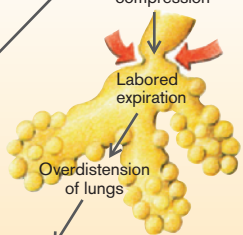
Bronchial compression

Hypoxia

Dyspnea

Constriction of pulmonary vessels

Compression of blood vessels



Pulmonary hypertension

Emphysema

Right heart failure

Pulmonary Emphysema

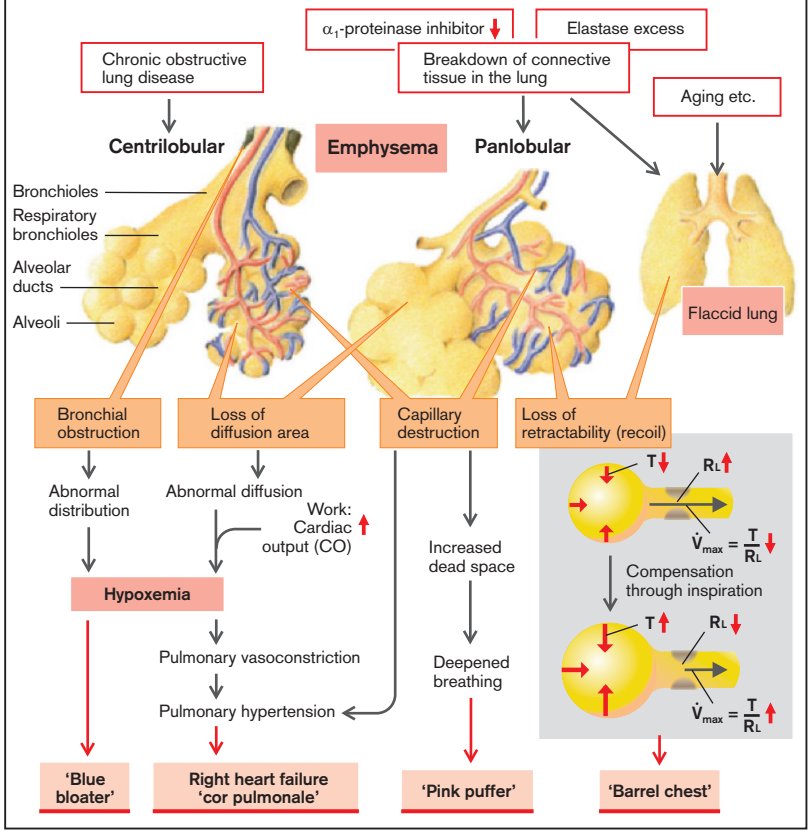
Emphysema is characterized by an increase in the volume of the airways distal to the bronchioles. **Centrilobular emphysema**, with predominant distension of the alveolar ducts and respiratory bronchioles, is distinguished from **panlobular emphysema**, in which the terminal alveoli in particular are 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; 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 α_1-proteinase inhibitor** (α_1-antitrypsin), which normally inhibits the action of proteinases (e.g., leukocyte elastase), serine protease 3, cathepsin, and matrix metalloproteinases). Decreased inhibition of the proteinases leads to enhanced protein breakdown and thus to 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. α_1-Antitrypsin is oxidized and thus inhibited by *smoking,* which thus promotes the development of emphysema even in someone without a genetic predisposition.

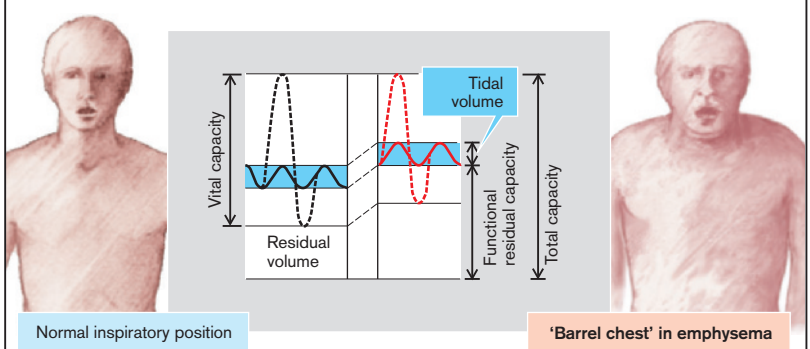
In addition to a lack of inhibitors, **increased elastase production** may be a cause of emphysema (e.g., of a serine elastase from granulocytes, a metalloelastase from alveolar macrophages, and various proteinases from pathogens). The excess of elastases in chronic inflammatory disease leads, for example,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

When considering the **effects** of pulmonary emphysema, the consequences of *reduced elastic recoil* are important. 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 an increase in flow resistance. Maximal expiratory flow rate ($\dot{V}_{max}$) is thus a function of the ratio between elastic recoil (T) and resistance (R_L) (→ **A**, right). Reduced elastic recoil can thus have the same effect as obstructive lung disease (→ p. 80). 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 shift of the resting position leads to flattening of the diaphragm, which requires (according to the LaPlace law) enhanced tension of the muscle. The loss of alveolar walls leads to a *diminished diffusion area* (→ p. 74); 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. 228). In centrilobular, but not panlobular, emphysema a *distribution abnormality* develops, too (→ p. 76), 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. 74).

A. Emphysema



B. Development of Barrel Chest in Emphysema



Pulmonary Edema

In pulmonary capillaries, as in systemic capillaries (→ p. 250), 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** (→ **A1**), and the passage of plasma water into alveoli causes **alveolar pulmonary edema** (→ **A2**).

A **rise in hydrostatic pressure** in the pulmonary capillaries occurs when the left ventricle's forward pumping action is inadequate (→ **A3**, right). Causes are reduced myocardial power or excess demand on it (heart failure; → p. 238), mitral valve stenosis or regurgitation (→ p. 208 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** (→ **A4**, 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* (→ **A5**, 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. 120 ff.). A reduction in plasma protein formation in the liver (liver failure; → p. 188) or loss of plasma proteins, for example, via the kidneys (nephrotic syndrome; → p. 114), also decreases plasma protein concentration.

Finally, **increased capillary permeability** can result in pulmonary edema (→ **A6**, 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 O_2 (→ p. 92).

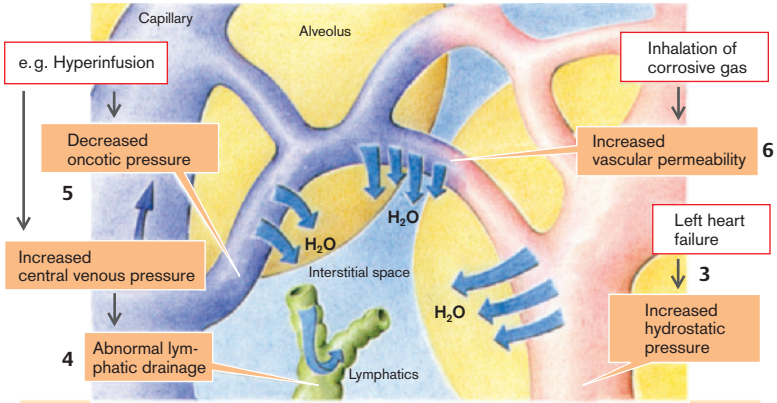
Effects of pulmonary congestion are reduced pulmonary perfusion, and thus impaired maximal O_2 uptake. The distension of the congested vessels prevents enlargement of the alveoli and decreases lung compliance. In addition, the bronchi are narrowed by the distended vessels (→ **A7**) and resistance to breathing increases (→ p. 80), discernable through diminution of the maximal breathing capacity and of FEV_1 (→ Table 2 on p. 70).

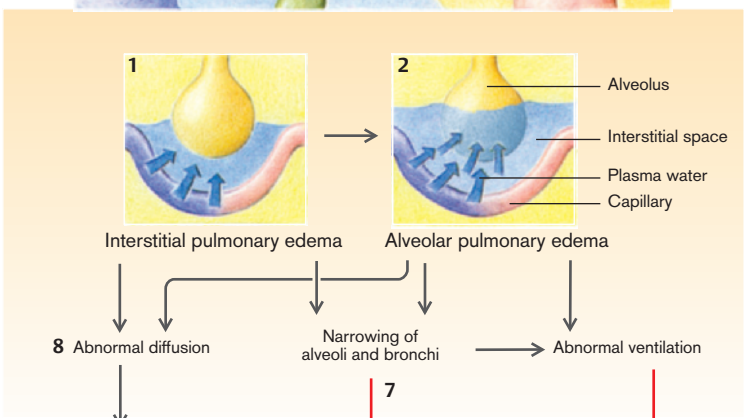
In **interstitial pulmonary edema** the interstitial space between capillary and alveolus is increased. As a result, diffusion is disturbed (→ **A8**) with impairment mainly of O_2 uptake (→ p. 74). If, due to physical activity, O_2 consumption rises, O_2 concentration in blood falls (hypoxemia, cyanosis).

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 O_2 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**; → **A9**). 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





Pathophysiology of Breathing Regulation

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

Ventilation is increased by acidosis, hypercapnia, hypoxia, hormones (progesterone, testosterone, ACTH), transmitters (blood [nor]epinephrine; cerebral histamine, acetylcholine, prostaglandins), and a decrease of Ca^{2+} and Mg^{2+} in cerebrospinal fluid (CSF). Pain, fear, an increase or moderate fall in body temperature, intense cold or heat stimuli to the skin, a drop in blood pressure, and muscular activity all increase ventilation.

Conversely, **ventilation is reduced** by alkalosis, hypocapnia, cerebral hypoxia, peripheral hyperoxia, ganglion blockers, high concentrations of atropine, catecholamines, endorphins, and glycin, increase of CSF, Ca^{2+} and Mg^{2+}. Deep hypothermia, rise in blood pressure, and sleep also diminish ventilation.

Sleep apnea, an arrest of breathing lasting several seconds to minutes, results from reduced sensitivity of the respiratory neurons to CO_2 (central apnea) or from a collapse of the airways due to relaxation of muscles during sleep (obstructive apnea). Sleep apnea is favored by nonrespiratory alkalosis and obesity. The apnea may stimulate the sympathic nerve tone with resulting tachycardia, arterial hypertension, and myocardial ischemia. The hypokapnia resulting from reduced respiratory drive during sleep may lead to cerebral vasodilatation resulting in morning headaches.

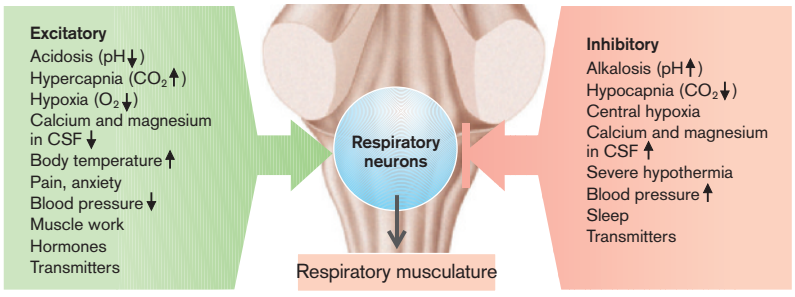
Barbiturates (soporific drugs) and **chronic respiratory failure** decrease the sensitivity of the respiratory neurons to pH or CO_2 in CSF. *Lack of O_2* thus becomes the *most important stimulus to breathing*. In both cases the supply of O_2-enriched air leads to hypoventilation and respiratory acidosis (→ p. 96 ff.). This response is increased by, for example, uremia (→ p. 120 ff.) or sleep. Because O_2 uptake varies within a wide range independently of alveolar ventilation (→ p. 72), 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.

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. 96 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.

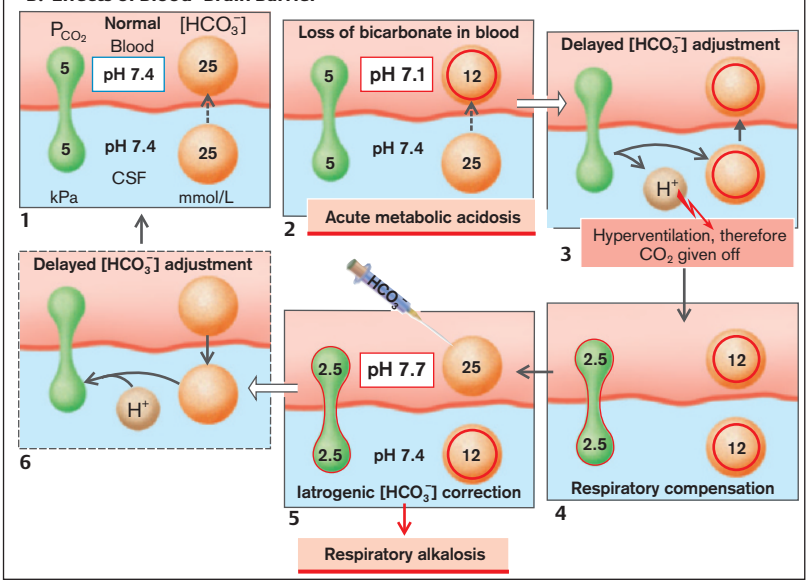
Damage or massive stimulation of the respiratory neurons can cause **pathological breathing** (→ **C**):

- **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 hypoperfusion of the brain, or when breathing is regulated by a lack of oxygen. The delayed response of respiratory neurons to changes in blood gases results in an overshooting reaction.
- **Biot 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.

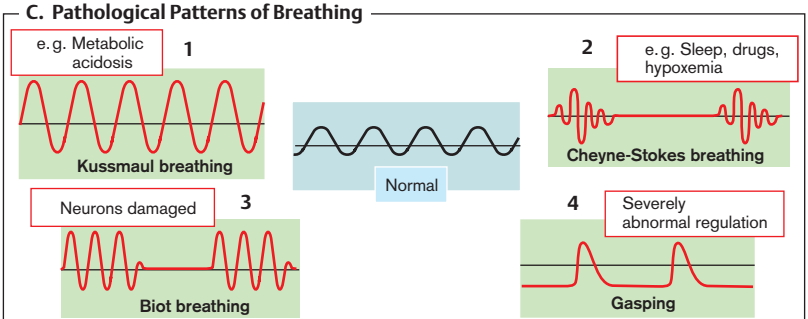
A. Modulators of Respiratory Neurons



B. Effects of Blood–Brain Barrier



C. Pathological Patterns of Breathing



Acute Respiratory Distress Syndrome

The acute respiratory distress syndrome (ARDS) is a life threatening impairment of pulmonary function.

Causes of ARDS include among others severe sepsis, bacterial pneumonia, near-drowning, inhalation of toxic vapors, intoxications, pulmonary contusion, severe trauma (particularly thorax, head trauma, multiple bone fractures), burns, multiple transfusions, aspiration of gastric content, and pancreatitis. ARDS may further develop after surgery with cardiopulmonary bypass. The risk to develop ARDS is increased by the coincidence of more than one of the causes. For instance, the incidence of ARDS increases from 25% in patients with severe trauma to 56% in patients with severe trauma and sepsis.

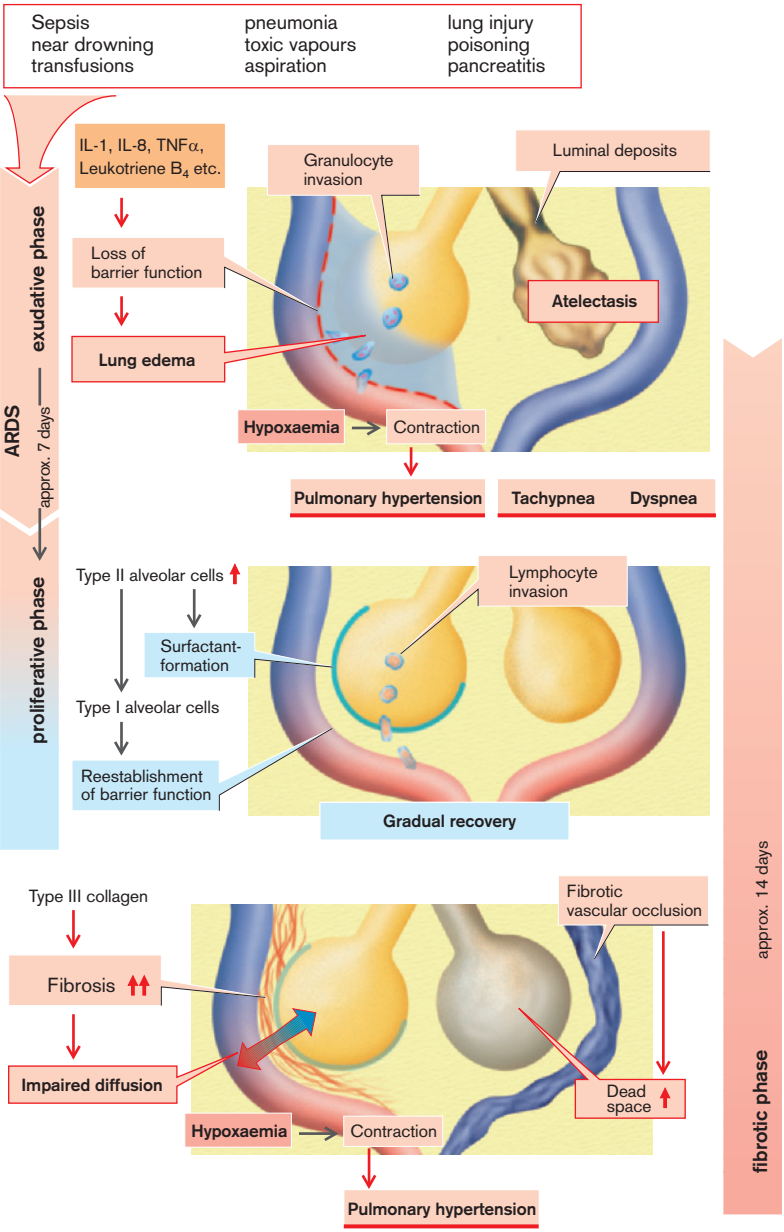
The clinical course of ARDS is characterized by three phases:

In the initial **exudative phase** of ARDS, injury of the pneumocytes and pulmonary endothelial cells is paralleled by the release of several inflammatory mediators including interleukin 1 (IL-1), interleukin 8 (IL-8), tumor necrosis factor (TNF-α), and leukotriene B4 (LTB4). Leukocytes (especially neutrophils) invade the pulmonary tissue. The injury of the pneumocytes and endothelial cells as well as the influence of the inflammatory mediators lead to loss of the barrier function between capillaries and alveoli with entry of plasma proteins and fluid into the alveolar space. Cellular debris, plasma proteins, and defective surfactant aggregate in the alveolar lumen to hyaline membranes, thus impairing the ventilation of the affected alveoli. The occlusion of airways may lead to the development of atelectases. The lung compliance is decreased, and the work of breathing increased accordingly. The loss of contact between capillaries and ventilated aveoles leads to vascular shunting with decreased oxygenation of blood and thus to hypoxemia. The decrease of the alveolar O_2 concentration leads to pulmonary vasoconstriction, which increases pulmonary vascular resistance and thus results in the development of pulmonary hypertension. The pulmonary vascular resistance is further increased by microvascular occlusions. The disruption of contact between alveoli and pulmonary capillaries leads to an increase of the dead space. Despite the increased dead space, breathing is typically shallow and frequent and the patient feels unable to inhale sufficient air. The impairment of gas exchange results in hypoxemia, hyperkapnia, and dyspnea.

Typically, after some 7 days, the **proliferative phase** develops. During this phase, the neutrophil leukocytes in lung tissue are largely replaced by lymphocytes. The type II alveolar epithelial cells may proliferate, produce surfactant, and differentiate into type I alveolar epithelial cells. In this phase the patient may gradually recover. However, the hypoxemia, tachypnea, and dyspnea frequently disappear only slowly. In many patients recovery is observed within 3–4 weeks from the initial injury.

In a subset of patients, signs of fibrosis develop during the proliferative phase, which may be followed by a **fibrotic phase**. In those patients, alveolar edema and exudate are followed by massive formation and deposition of matrix proteins in the interstitial space and the airways. Fibrotic lung tissue typically produces type III procollagen peptide, which is thus a diagnostic indicator for the development of pulmonary fibrosis. The presence of this peptide points to a protracted clinical course of ARDS and is associated with enhanced mortality of the affected patients. Due to the fibrosis, the delicate lung architecture is disrupted with the appearance of widened alveoli ("bullae") similar to emphysema. The compliance is decreased and the dead space increased. The patient is at an increased risk of developing pneumothorax. The lumen of pulmonary microvessels is decreased by intimal fibroproliferation and by compression due to perivascular fibrosis. The occlusion of the vessels increases the pulmonary vascular resistance with development of pulmonary hypertension. The patients suffering from this course of ARDS are left with substantial loss of pulmonary function.

A. Acute Respiratory Distress Syndrome (ARDS)



Hypoxia

Hypoxia occurs when O_2 transport from ambient air to the cell is impaired. There may be several causes: (→ **A**):

◆ **Hypoventilation** reduces alveolar O_2 and thus impairs O_2 uptake. However, ventilation has to be markedly reduced before O_2 uptake is noticeably decreased (→ p. 72).

◆ **Reduced diffusing capacity** (→ p. 74) prevents equilibration of gas concentrations in alveoli and capillary blood.

◆ **Reduced O_2 uptake capacity of the blood** occurs in anemia (→ p. 34 ff.) or can be caused by the inability of hemoglobin to bind or release O_2. Carbon monoxide (CO), for example, binds to hemoglobin with an affinity that exceeds that of O_2 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 O_2 but is also less ready to release the oxygen bound to it. Increased O_2 affinity with reduced peripheral O_2 release also occurs in a deficiency of 2,3-bisphosphoglycerate (2,3-BPG) or alkalosis.

◆ **Circulatory failure** (→ p. 238) or local ischemia impairs vascular O_2 transport.

◆ **Tissue diffusion** is impaired if the distance between a cell and its nearest capillary is increased, as in tissue hypertrophy without accompanying increased capillary formation, or in edema. The diffusion distance is also increased when the precapillary sphincter of the nearest capillary contracts, because the O_2 supply must then come from the second nearest capillary.

◆ Several **poisons of the respiratory chain** can inhibit O_2 utilization.

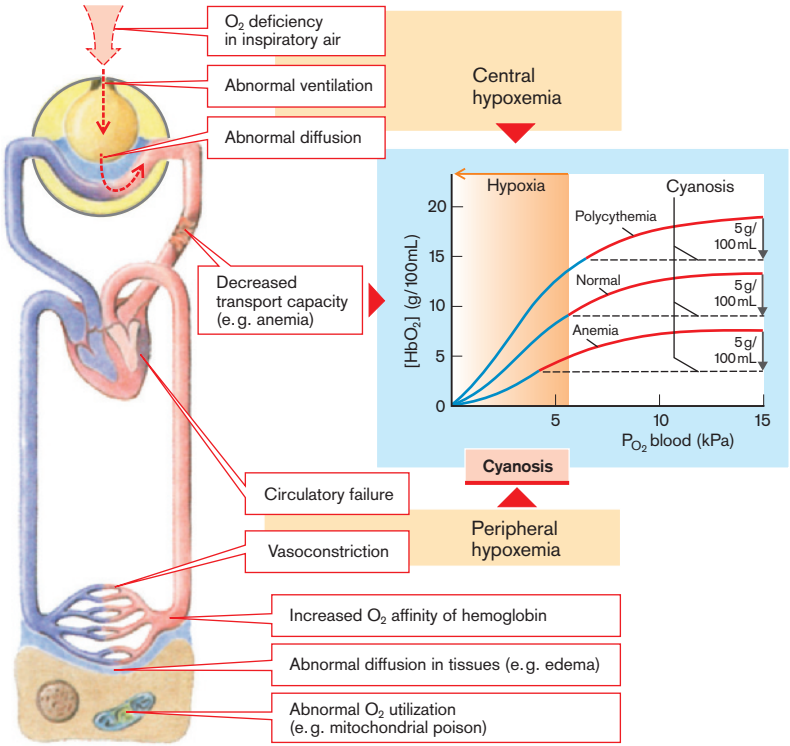
The most important **effect** of all the abovementioned causes is the impairment of the cells' aerobic energy supplies.

At hypoxia, cells may 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 about 32 ATPs in oxidative metabolism), and the dissociation of lactic acid results in metabolic (nonrespiratory) **acidosis** (→ p. 96). The lack of energy at first causes a reversible impairment of function, but ultimately leads to irreversible cell damage (e.g., p. 12 and 232). The maximal anoxic period until irreversible damage depends on the cell type. Neurons survive some 10 minutes, renal and liver cells survive several hours. The total organism usually survives, however, only 4 minutes. Irreversible damage can be significantly delayed by decrease of energy consumption (e.g., by hypothermia).

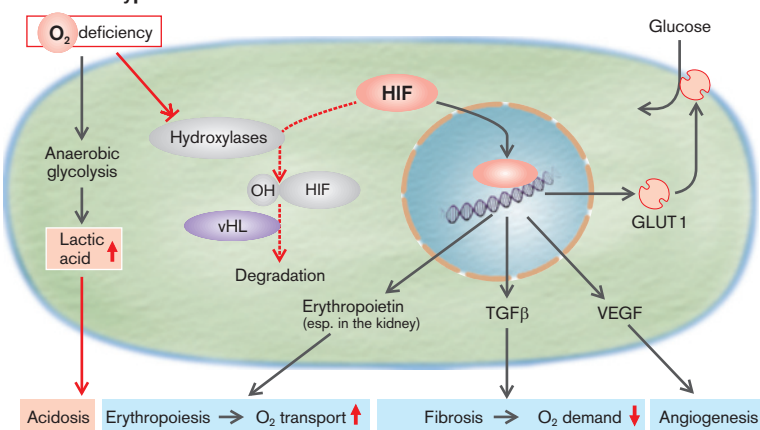
Hypoventilation, abnormal pulmonary diffusion, and circulatory failure cause **cyanosis** (blue discoloration of the skin and mucous membranes) if the average concentration of deoxygenated hemoglobin in the capillaries is lower than ca. 0.7 mmol/L (5 g/100 mL) (→ **A**). In hypoventilation and disorders of pulmonary diffusion the arterialized blood is hypoxic (*central cyanosis*). It must be stressed that cyanosis does not always reflect O_2 deficiency. If the hemoglobin concentration in blood is increased, cyanosis may occur even without lack of O_2 (**pseudocyanosis**). Conversely, an O_2 deficiency may occur in hemoglobin deficiency (anemia), without the concentration of deoxygenated hemoglobin reaching the level required for cyanosis.

O_2 depletion upregulates the hypoxia inducible factor **HIF** (→ **B**). With a sufficient O_2 supply, the transcription factor is hydroxylated by HIF-prolyl-4-hydroxylases with following ubiquitination, a reaction mediated by the von Hippel–Lindau protein (vHL). The ubiquitination prepares HIF for proteasomal degradation. The hydroxylases are activated by O_2 and are inactivated by hypoxia. Thus, at hypoxia HIF escapes degradation, travels into the nucleus, binds to hypoxia-responsive elements of the DNA, and stimulates the expression of several genes important for survival under hypoxic conditions. HIF-sensitive genes include *VEGF* (vascular endothelial growth factor), which stimulates the formation of new capillaries (angiogenesis), and TGF-β (transforming growth factor β), which stimulates the formation of matrix proteins (fibrosis). The replacement of cells with matrix proteins decreases the local O_2 demand. By the same token, however, the loss of cells compromises the organ function (e.g., the contractility of cardiac muscle). The change of cellular expression pattern at repeated short or extended transient periods of hypoxia increase the resistance of the tissue to hypoxia or ischemia (preconditioning and hibernation). In the kidney, HIF stimulates the formation of erythropoietin (→ p. 36), which enhances the formation of new erythrocytes and thus the O_2-transport capacity of blood.

A. Causes of Oxygen Deficiency



B. Effects of Hypoxia



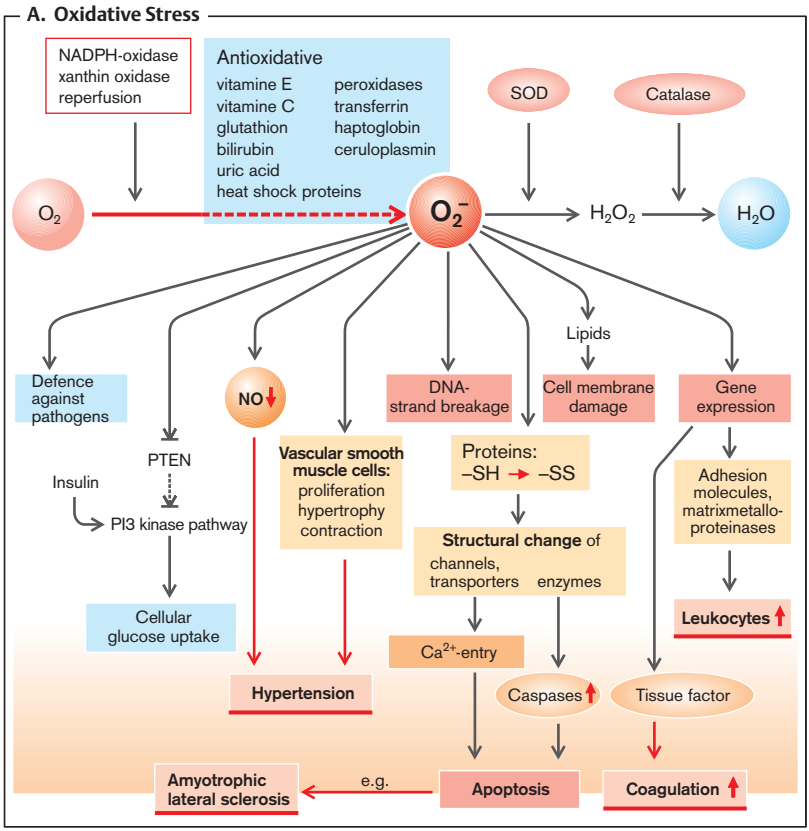
Hyperoxia, Oxidative Stress

O_2 is reactive and generates a number of highly **reactive oxygen species** (ROS), including superoxide anion O_2^-, hydrogen peroxide H_2O_2, and the hydroxyl radical $OH^•$. O_2^- may be generated during oxidative phosphorylation or by *NADPH oxidase* and *xanthinoxidase* (→ **A**). O_2^- is converted by the *superoxide dismutase* (SOD) to H_2O_2, which is subsequently degraded by *catalase*. A genetic defect resulting in loss of SOD function leads to amyotrophic lateral sclerosis, a neurodegenerative disorder with neuronal cell death in the spinal cord (→ p. 328). ROS are further degraded by peroxidases. Proteins with antioxidative activity further include metal-binding proteins, such as transferrin, haptoglobin, and ceruloplasmin. Moreover, the effects of ROS are blunted by heat shock proteins. ROS scavenging small molecules include α-tocopherol (vitamin E), vitamin C, glutathione, bilirubin, and uric acid.

ROS are formed by leukocytes to damage membranes of pathogens. Accordingly, ROS formation plays an important role in the defense against pathogens. Moderate, physiological concentrations of O_2^- participate in the regulation of diverse cellular functions. O_2^- may inhibit the phosphatase PTEN and may thus stimulate the phosphatidylinositol-3 (PI3) kinase pathway (→ p. 10) and enhance insulin- and growth factor-dependent cell signaling. At high concentrations, ROS exert **toxic effects** on cells. O_2 and ROS oxidize lipids and thereby interfere with the structure and function of cell and mitochondrial membranes. Oxidation damages DNA and may cause DNA strand damage. ROS oxidize free –SH– groups at proteins to –S–S– groups and thus modify the structure and activity of enzymes, ion channels, and further proteins. The modification of the membrane proteins may enhance the Ca^{2+} permeability of the cell membrane. In addition, ROS may activate caspases (→ p. 14). The stimulation of Ca^{2+} entry and the activation of caspases may trigger suicidal cell death (apoptosis) (→ p. 14). O_2^- inactivates NO, fosters the proliferation, hypertrophy, and contraction of vascular smooth muscle cells (→ p. 252) and thus favors the development of vascular hypertension. ROS stimulate the expression of tissue factor (→ p. 64) and may thus trigger coagulation. ROS stimulate the expression of adhesion molecules and the expression of matrix metalloproteinases. By these effects they foster the invasion of leukocytes in the affected tissue. As a result of those and further effects, enhanced formation of ROS accelerates aging.

ROS are particularly important for the tissue injury following transient ischemia (**reperfusion injury**). Re-entry of O_2 after a period of O_2 depletion is followed by enhanced formation of O_2^- and H_2O_2. The stimulation of adhesion molecule expression leads to invasion of leukocytes, which generate additional ROS eliciting additional tissue injury.

Hyperoxia (→ **B**) of the organism may result from ventilation with breathing apparatus during diving or by inhalation of pure O_2 over many days, and can inhibit the cellular *oxidation of glucose*. High O_2 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. 84). Oxidation can inactivate surfactant, which normally reduces surface tension in the alveoli and ensures that they unfold evenly. The lack of surfactant may lead to different sizes of alveoli with subsequent abnormal distribution of ventilation (→ p. 76). Artificial ventilation with O_2 also facilitates the collapse of alveoli (*atelectasis*; → p. 76). In neonates, mixtures containing over 40% O_2 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*).



Development of Alkalosis

The pH of blood depends on the ratio of HCO_3^- to CO_2 concentration:

$$pH = pK + \lg [HCO_3^-]/[CO_2]$$

pK contains the dissociation constant of H_2CO_3 and the reaction constant of CO_2 to H_2CO_3. Alkalosis (pH > 7.44) 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. 86). Causes include emotional excitement (fear, pain), pregnancy (progesterone), fever, heat, salicylate poisoning, or damage to the respiratory neurons (e.g., by inflammation, injury, or liver failure). Occasionally hypoxia (ventilation to perfusion distribution abnormality, severe anemia, low O_2 pressure 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** (causes → p. 134) 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, increases 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 (alkali tide).

◆ 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. 132). 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 its proximal renal tubular HCO_3^- absorption (→ **A4**). **Hypoparathyroidism** can thus lead to alkalosis.

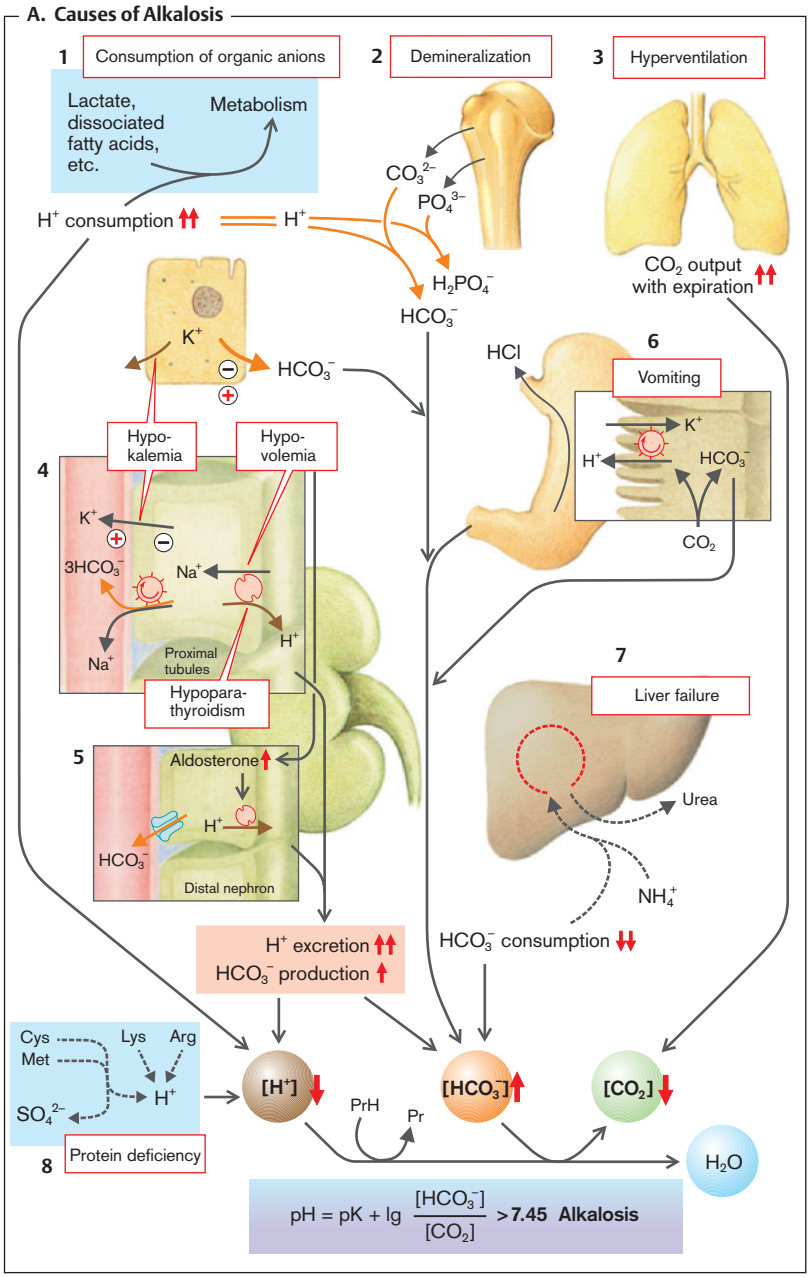
◆ The liver forms either glutamine or urea from the NH_4^+ generated by amino acid catabolism. The formation of urea requires, in addition to two NH_4^+, the input of two HCO_3^- that are lost when urea is excreted. (However, NH_4^+ is split off from glutamine in the kidney and then excreted as such). 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 inadequate stimulation of 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 (e.g., release of H^+ from plasma proteins), which is reduced when the plasma protein concentration is lowered.



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. 70 – 84) as well as abnormal regulation of breathing (→ p. 86) can lead to **respiratory acidosis** (→ **A 3**). 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** (→ **A 4**, causes p. 134) the chemical gradient across the cell membrane is reduced. The resulting depolarization diminishes the electrical driving force for the electrogenic HCO_3^- transport out of the cell. It slows down the efflux of HCO_3^- in the proximal tubules via $Na^+(HCO_3^-)_3$ 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. 120 ff.), **transport defects** in the renal tubules (→ p. 104 ff.), and **hypoaldosteronism** (→ **A 5**). (Normally aldosterone stimulates H^+ secretion in the distal tubules; → p. 292).

◆ 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. 142), an acidosis only rarely results. Massive renal loss of HCO_3^- occurs if **carbonic anhydrase is inhibited** (→ p. 104 ff.), because its activity is required for HCO_3^- absorption in the proximal tubules.

◆ Loss of bicarbonate from the gut (→ **A 6**) 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. 94), increased urea production can lead to acidosis. In this way the **supply of NH_4Cl** can cause acidosis (→ **A 7**).

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 (→ **A 2**) in the form of alkaline salts (calcium phosphate, calcium carbonate). H^+ ions, formed when bicarbonate and phosphate dissociate, can cause acidosis.

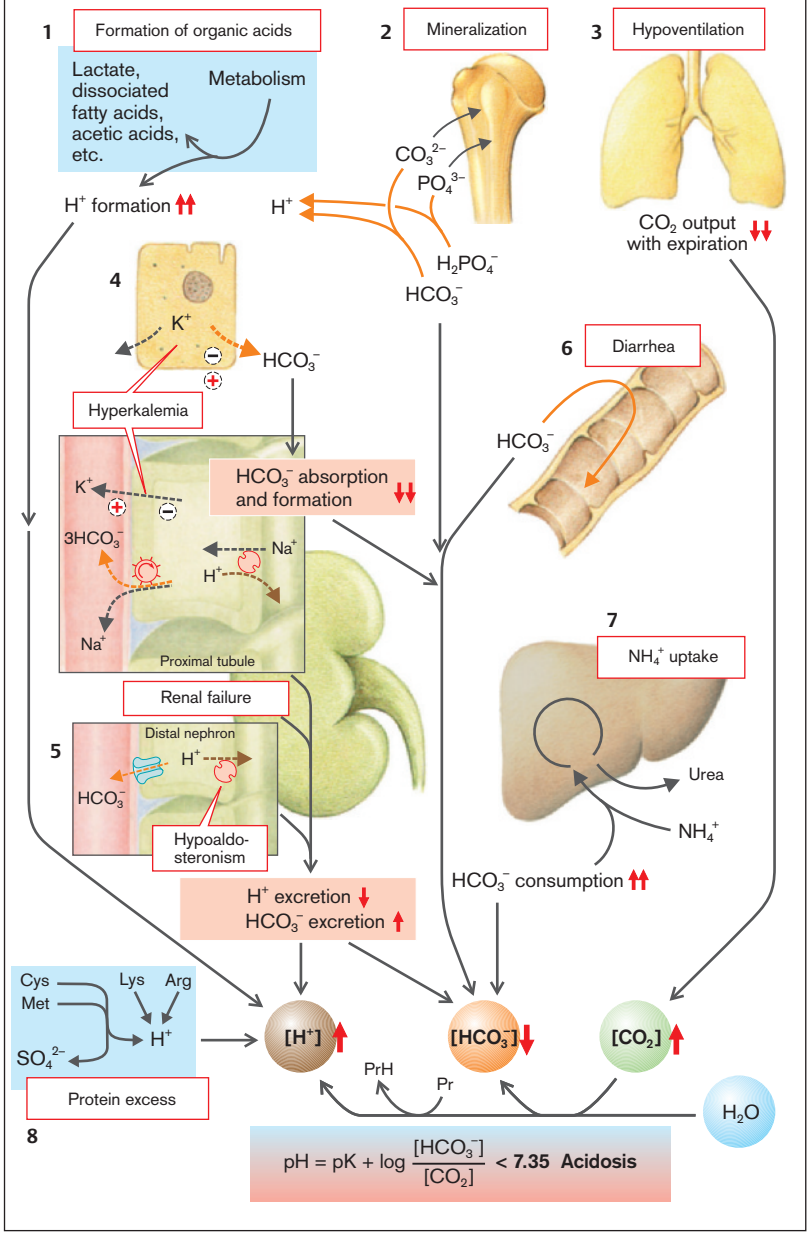
◆ **Mineralization of bone**, even without $CaCl_2$, favors the development of acidosis (→ **A 2**).

◆ Acidosis can also develop when there is increased formation or decreased breakdown of **organic acids** (→ **A 1**). 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. 90), circulatory failure (→ p. 248), severe physical exercise, fever (→ p. 26 ff.), or tumors (→ p. 18 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 acetoacetic acid accumulate in certain enzyme defects but especially in increased fat mobilization, for example, in starvation, diabetes mellitus (→ p. 310 ff), alcohol withdrawal, 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 (→ **A 8**).

The extent of acidosis depends, among other factors, on the blood's **buffering capacity** (e.g., binding of H^+ to plasma proteins).

A. Causes of 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 HCO_3^- and CO_2 concentrations in blood, when acid–base balance is abnormal, and how they are compensated can be demonstrated in graphs (e.g., $[HCO_3^-]$ may be plotted as a function of P_{CO_2} [→ **A**, left] or the logarithm of P_{CO_2}, plotted as a function of pH [→ **A**, right]; Siggaard-Andersen nomogram: gray lines = CO_2 equilibration lines).

◆ **Respiratory alkalosis** (→ **A 1**) is compensated by decreased reabsorption of HCO_3^- in the kidneys.

◆ **Metabolic alkalosis** (→ **A 2**) can theoretically be compensated by hypoventilation. But the need to take up sufficient O_2 sets narrow limits to this form of compensation.

◆ **Respiratory acidosis** (→ **A 4**) is compensated by increased renal excretion of acids (or through forming HCO_3^-). The increased plasma HCO_3^- results in more HCO_3^- being filtered at the glomeruli. The kidney must therefore continually reabsorb an increased amount of filtered HCO_3^- if renal loss of HCO_3^- is to be avoided.

◆ **Metabolic acidosis** (→ **A 3**) can be compensated by respiratory reduction in plasma CO_2 concentration. However, the lower the plasma CO_2 concentration the less CO_2 is given off with each breath. Thus, in order to exhale the particular amount of CO_2, hyperventilation must be maintained until the plasma HCO_3^- concentration is again normal, either through raised renal excretion of acid or through the breakdown of organic anions (→ p. 94).

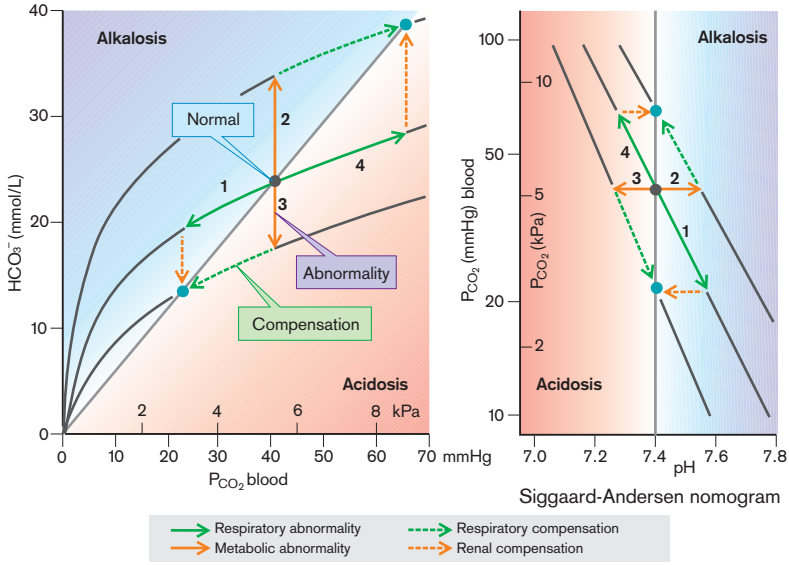
Effects of alkalosis include *hypokalemia*, because the cells release less HCO_3^-, depolarize less, and thus lose less K^+. If H^+ is removed from the cell by Na^+/H^+ exchange, Na^+ gains access to the cell, but is again pumped out of the cell in exchange for K^+ (→ **B**). Partially through the hypokalemia alkalosis may trigger cardiac arrhythmia.

In addition, more Ca^{2+} is bound to plasma proteins in alkalosis (→ **B**, right). As a result, *there is a fall in the concentration of ionized* Ca^{2+} in plasma. As part of Ca^{2+} in plasma is also bound to HCO_3^-, the concentration of free Ca^{2+} falls more in metabolic than in respiratory alkalosis. Effects, especially of respiratory alkalosis (hypocapnia), include among others *raised neuromuscular excitability* with cramps, in large part 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 lactacidemia* may occur. Intracellular alkalosis further favors *cell division*. Inhibition of the respiratory drive in alkalosis could result in hypoxemia.

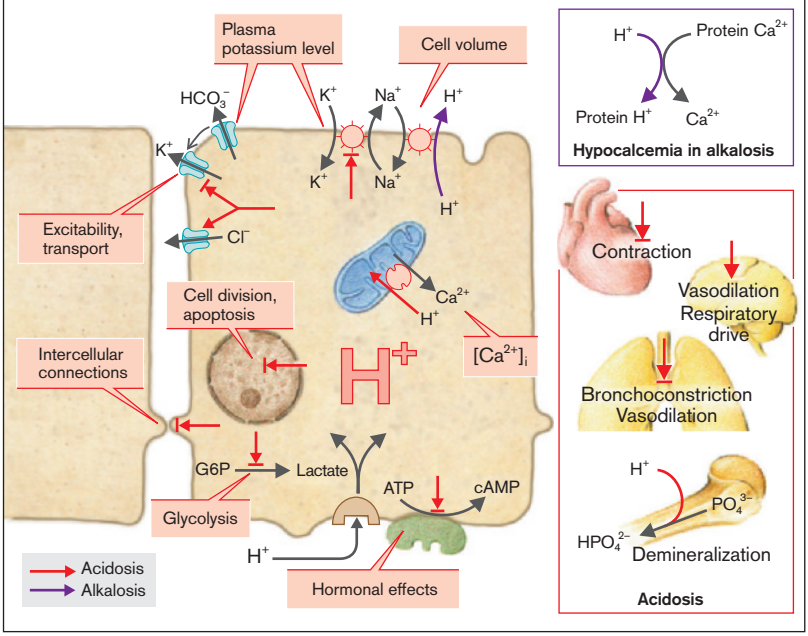
The **effects of respiratory and metabolic acidosis** (→ **B**, red arrows) are largely similar. They are in part due to activation of H^+ sensing receptors. In extracellular acidosis the cells lose HCO_3^-; through depolarization they also lose K^+. In addition, acidosis inhibits the Na^+/K^+-ATPase. *Hyperkalemia* develops (→ p. 134). 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). Acidosis and hypercapnia may induce relaxation of the bronchial muscles and constriction of the pulmonary arterioles. The latter may increase pulmonary vascular pressure and predispose to the development of pulmonary edema. Hyperkapnia may further lead to peripheral *vasodilation* (fall in blood pressure, rise in intracerebral pressure, headache, lethargy, and coma). Intracellular acidosis inhibits the pacemaker enzymes of glycolysis and *hyperglycemia* occurs. Prolonged acidosis promotes *demineralization of bone* (→ **B**, right), because of dissolution of alkaline bone salts as well as inhibition of osteoclast apoptosis, of renal Ca^{2+} reabsorption, and of calcitriol formation (→ p. 142). In intracellular acidosis H^+ is taken up by the mitochondria in exchange for Ca^+. H^+ also inhibits adenylylcyclase and thus impairs hormonal effects. Finally, cellular acidosis inhibits cell division and favors apoptotic cell death. Stimulation of respiration during acidosis may result in Kussmaul breathing (→ p. 86).

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. A defective glomerular filter may result in renal loss of plasma proteins, an impaired tubular reabsorption in renal loss of electrolytes, minerals, bicarbonate, glucose, or amino acids. Conversely, renal injury may lead to decreased **renal excretion** of useless or harmful substances (e.g., uric acid, urea, creatinine, vanadate [VnO_4], foreign substances [xenobiotics], and so-called uremic toxins) whose plasma concentrations then rise correspondingly (→ **A3**). 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. 94 ff, 132 ff.). Through its influence on water and electrolyte metabolism the kidney is also important for long-term **blood pressure regulation** (→ p. 222 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**]).

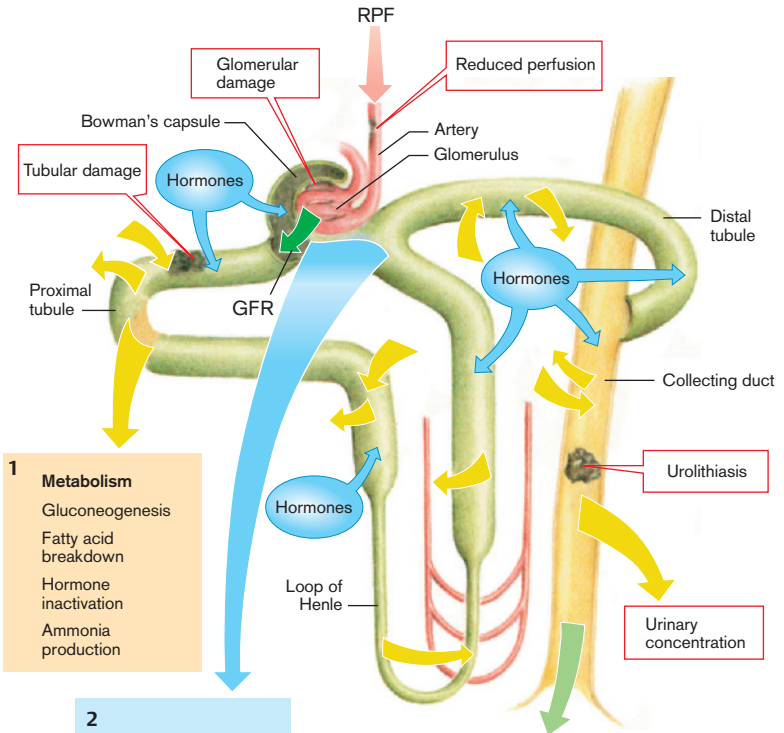
Renal excretion is regulated or governed by **hormones** (e.g., antidiuretic hormone [ADH] or [arginine] vasopressin [AVP], aldosterone, parathyroid hormone [PTH], calcitriol [$1,25(OH)_2D_3$], calcitonin, cortisol, prostaglandin E_2, insulin, progestogens, estrogens, thyroxine, growth hormone and natriuretic peptides [NP], such as ANP [atrial NP], LANP [long-acting NP], BNP [brain NP], CNP [C-type NP], DNP [dendroaspis NP], adrenomedullin, (uro)guanylin, vessel dilatator and kaliuretic peptide). 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. 36). The kidney produces KLOTHO, which participates in the regulation of calcium/phosphate metabolism and increases the life-span (→ p. 22).

Lastly, the kidney fulfills **metabolic tasks** (→ **A1**). Thus, for example, in acidosis it splits ammonia from glutamate (ammonia is excreted as NH_4^+; → p. 94) 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
- Klotho
- Renin, angiotensin
- Kinins
- Prostaglandins

3 Excretion

Regulation	Elimination	
	Loss of useful substances:	Retention of useless or harmful substances:
H_2O	Glucose	Uric acid
K^+	Amino acids	Urea
Na^+/Cl^-	Proteins	Creatinine
H^+/HCO_3^-		Xenobiotics
Ca^{2+}/HPO_4^{2-}		Uremia toxins
Mg^{2+}		

Erythropoiesis | **Water, electrolyte and mineral balance** | **Blood pressure**

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 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 (M_e) is identical to the filtered amount (M_f) and thus is equal to the product of plasma concentration (P) and the **GFR**: $M_e = M_f = P \cdot GFR$ (→ **B1**, green line). The clearance (M_e/P) is identical to the GFR and thus independent of the plasma concentration (→ **B2**, green line). If the production of creatinine is constant, a **reduction in GFR** transiently leads to a reduction in creatinine excretion (→ **B3a**). 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 (→ **B3b**) 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 (→ **B4**, green line).

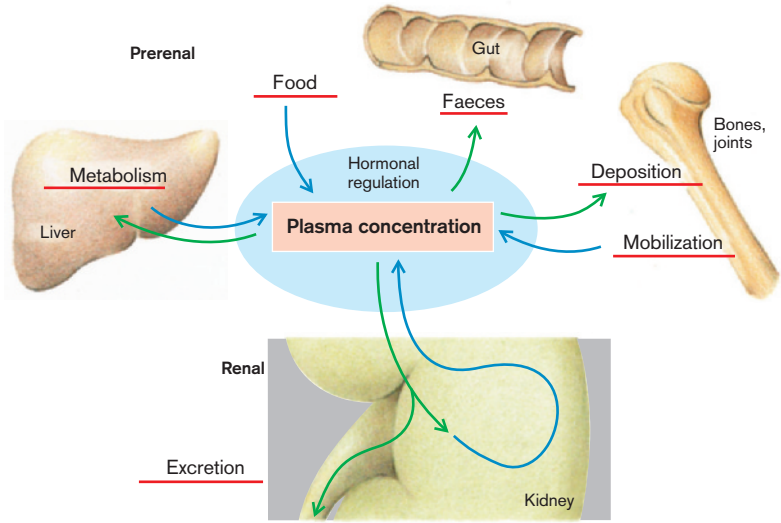
In **reabsorption by transport processes with high affinity** (e.g., glucose, most amino acids, phosphate, sulfate) practically the entire filtered amount is reabsorbed and nothing eliminated, as long as the plasma concentration is low (→ **B1**, blue curve). If the filtered amount exceeds the maximal 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* (→ **B1**, 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 (→ **B1**, orange curve).

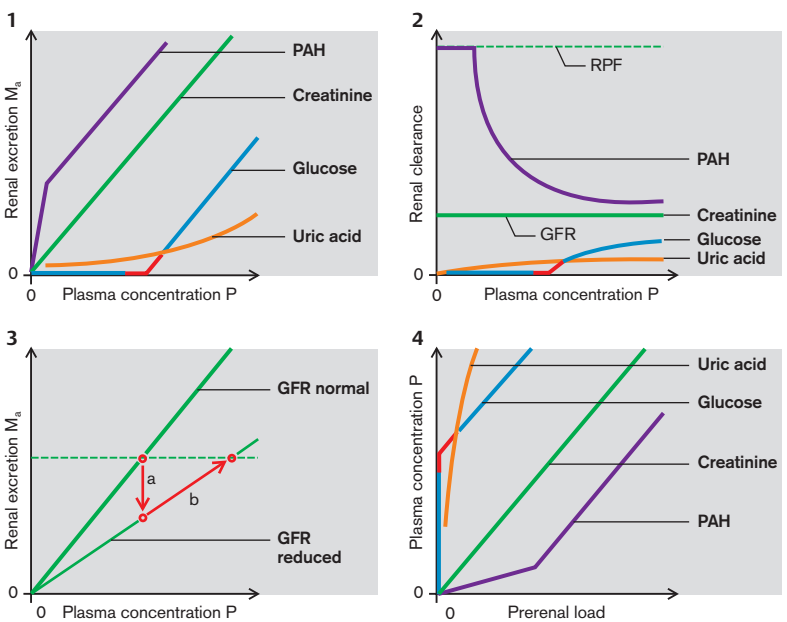
In **secretion** (e.g., of p-aminohippuric acid [PAH]) not only the filtered by also the secreted substance is excreted (→ **B1**, violet curve). In high affinity of the transport system and low plasma concentration, the entire amount reaching the kidney will be excreted. Renal clearance thus corresponds 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 (→ **B2**).

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 Ca^{2+} is prevented by the release of PTH which mobilizes Ca^{2+} from bone and increases enteric absorption of Ca^{2+} via the release of calcitriol (→ p. 138). The result is hypercalciuria but not hypocalcemia.

A. Determinants of Plasma Concentration



B. Plasma Concentration, Renal Excretion, Clearance



Pathophysiology of Renal Transport Processes

Genetic or toxic causes, drugs, or hormonal abnormalities can impair tubular transport processes (see also tubular proteinuria; → p. 114).

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 SGLT1 [SLC5A1] (→ **A1**) results in **glucose–galactose malabsorption** but to only slight glycosuria. A defect of the second renal glucose transporter SGLT2 [SLC5A2] leads to classical **renal glycosuria** in which either the maximal transport rate (type A) or the affinity (type B) is impaired (→ **D3**). At type 0 glucose resorption is completely lacking. Glucose leaves the cell across the basolateral cell membrane via the uniporter GLUT2 [SLC2A2]. A genetic defect of that carrier leads to glycosuria, hyper- and hypoglycemia, glycogen storage, and rickets (Fanconi–Bickel syndrome).

The Na^+-phosphate cotransporter (→ **A2**) is inhibited by fibroblast growth factor 23 (FGF23). Its action is supported by the renal hormone KLOTHO. Usually, FGF23 is degraded by the protease PHEX (phosphate regulating homology of endopeptidase on X chromosome). Genetic defects may result in inactive PHEX (X-linked hypophosphatemic rickets) or PHEX-resistant FGF23 (autosomal dominant hypophosphatemic rickets). In both cases renal tubular phosphate transport is impaired (**renal phosphate diabetes**). FGF23 and further phosphate transport-inhibiting "phosphatonines" are produced by some tumor cells. Renal phosphate reabsorption is further compromised at *calcitriol* deficiency. The renal loss of phosphate causes demineralization of bone via a deficiency of phosphate (rickets; → p. 142). **Increased renal phosphate reabsorption**, e.g., in PTH deficiency (*hypoparathyroidism*) or abnormal PTH action (*pseudohypoparathyroidism*), leads to hyperphosphatemia (→ p. 140).

A defect of Na^+ cotransport of certain neutral amino acids (B^0AT1 [SLC6A19]) in kidney and gut results in **Hartnup disease**, in which increased amino acid excretion occurs (→ **A3**). The renal loss of tryptophan impairs nicotinic acid synthesis, with nicotinic acid deficiency, and thus damage to the nervous system and the skin.

A defect of the amino acid exchanger for neutral and dibasic amino acids (B^{0+}AT-rBAT) increases the excretion of ornithine, lysine, arginine, and cystine (**cystinuria**) (→ **A4**). The poorly soluble cystine is precipitated and forms urinary stones (→ p. 130). In **familial protein intolerance** the reabsorption of dibasic amino acids is abnormal (Y^+LAT1-4F2hc [SLC3A2/SLC7A7]).

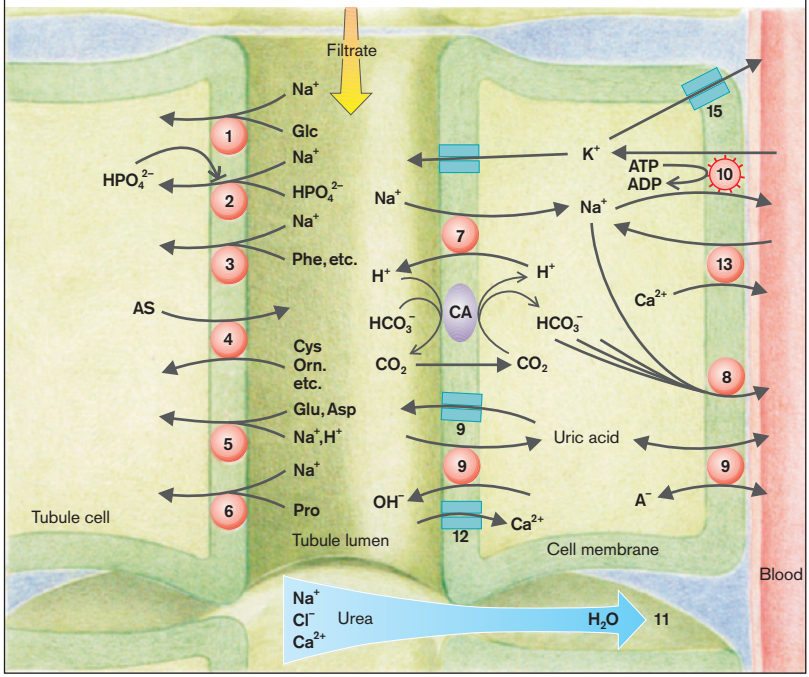
A defect of the Na^+ cotransporter for acidic amino acids (EAAT3 [SLC1A1]) leads to harmless **acid aminoaciduria** (→ **A5**); a defect of the carrier for cyclic amino acids such as proline (SIT1 [SLC6A20]), results in harmless **iminoglycinuria** (→ **A6**).

Decreased activity of the Na^+/H^+ exchanger NHE3 (→ **A7**) or of the Na^+-$3HCO_3^-$ cotransporter NBC1 (→ **A8**) results in **proximal-tubular acidosis** (→ p. 94 ff.). As the reduced HCO_3^- reabsorption in the proximal tubules cannot be compensated by the limited distal-tubular transport, bicarbonate is excreted in the urine even when the HCO_3^- load is normal (→ **E2**). If the plasma concentration of HCO_3^- is reduced, the proximal tubules can reabsorb the bulk of filtered bicarbonate, and the distal tubules will then produce urine of normal acidity. Defective carboanhydrase (CA) impairs proximal and distal tubular H^+ secretion (Typ III RTA). Na^+-$3HCO_3^-$ cotransport depends on the membrane potential. Hyperkalemia depolarizes the cell membrane and inhibits HCO_3^- reabsorption in the proximal tubules, while HCO_3^- reabsorption is increased by hypokalemia. The renal excretion of H^+ is thus a **function of the extracellular K^+ concentration** (→ p. 94 ff.).

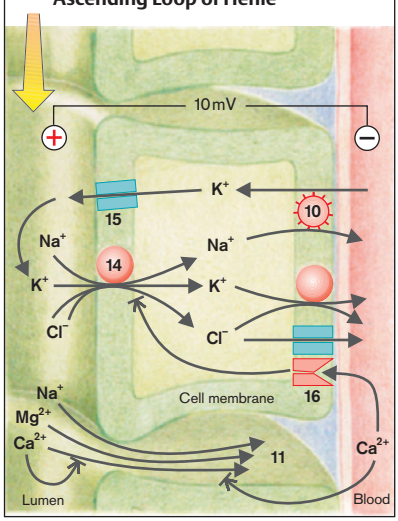
Volume depletion stimulates the Na^+/H^+ exchanger (→ **A7**) and thus proximal tubular HCO_3^- reabsorption. This results in a **volume depletion alkalosis**. Inhibition of the Na^+/H^+ exchanger or of carbonic anhydrase increases salt excretion (**natriuresis**). The inhibition of proximal tubular Na^+ reabsorption is, however, largely compensated by increased reabsorption in distal nephron segments such as 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 glycosuria, aminoaciduria, phosphaturia, proximal tubular acidosis, and hypokalemia (see below).

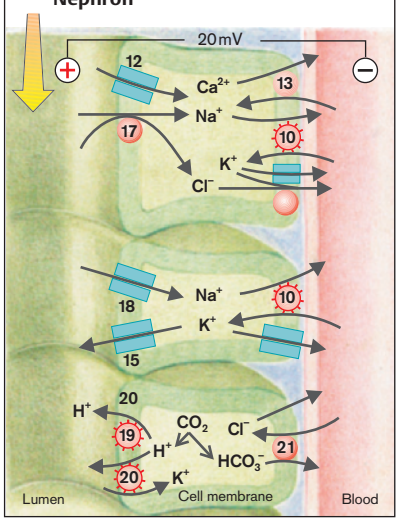
A. Transport Processes in Proximal Tubule



B. Transport Processes in Thick Ascending Loop of Henle



C. Transport Processes in Distal Nephron



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 (→ **A 9**). This causes hyperuricemia with deposition of poorly soluble uric acid in some joints (**gout**; → p. 268).

Energy deficiency (e.g., inadequate perfusion) leads to impaired **Na^+/K^+-ATPase** (→ **ABC 10**) reduced electrolyte reabsorption (salt-losing kidney), cellular swelling and cell death (→ p. 12).

The **Ca^{2+} reabsorption** is accomplished in the proximal tubules, loop of Henle and distal tubules, partially 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**). Parathyroid hormone (PTH) stimulates Ca^{2+} reabsorption; conversely, hypoparathyroidism results in hypercalciuria. High Ca^{2+} concentration (hypercalcemia) inhibits, via stimulation of the Ca^{2+} receptor (→ **B 16**), the Na^+-K^+-$2\,Cl^-$ cotransporter (NKCC2) and the paracellular shunt (→ **B 11**). 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. 108).

NKCC2 inhibition (→ **B 14**) by **loop diuretics** stops NaCl reabsorption in the loop of Henle and thus urinary concentration (→ p. 108). 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. NKCC2 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 NKCC2, 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. 124). The compensatory increase of distal-tubular Na^+ reabsorption is blunted by prostaglandins, which are formed due to the enhanced transport load. Inhibition of cyclo-oxygenase may ameliorate the life-threatening volume depletion of the affected patients.

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**).

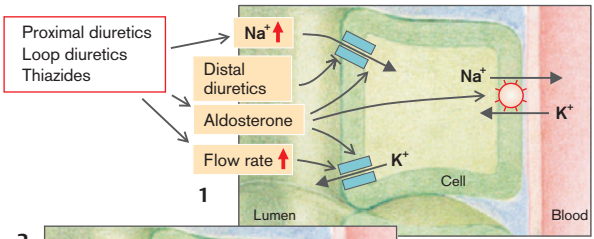
NaCl is reabsorbed in the early distal tubules via a Na^+-Cl^- cotransporter (→ **C 17**). **Thiazides** cause renal loss of sodium and potassium by inhibiting the carrier (see above). The volume depletion increases the proximal tubular reabsorption of Na^+ and Ca^{2+} resulting in anticalciuresis. A genetic defect of the transporter results in **Gitelman's syndrome**, a mild variant of Bartter's syndrome. A genetic defect of the kinases (WNK = with no K), which usually inhibits the carrier, leads to hypertension (Gordon syndrome).

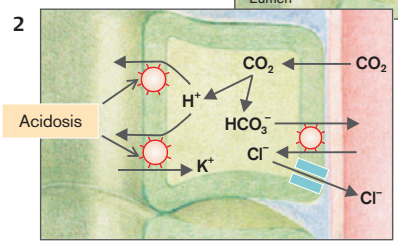
Na^+ is reabsorbed in the late distal tubules and the collecting ducts via luminal **Na^+ channels** (→ **C 18**) and the basolateral Na^+/K^+-ATPase. The influx of Na^+ depolarizes the luminal cell membrane and thus promotes the secretion of K^+ via luminal K^+ channels. If Na^+ reabsorption in the proximal tubules, loop of Henle, or early distal tubules is inhibited, more Na^+ reaches the late distal parts of the nephron and 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.

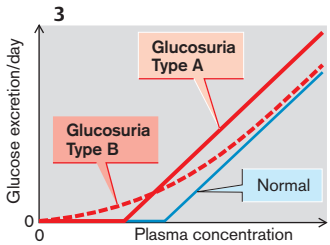
H^+ secretion in the late distal tubules and in the collecting duct is achieved by H^+-ATPases (→ **C 19**) and H^+/K^+-ATPases (→ **C 20**) and the anion exchanger AE1 (→ **C 21**). A defect results in **distal renal tubular acidosis** RTA1 (→ **D 2, E 4**). The affected person can produce only moderately 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. 123).

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. 108).

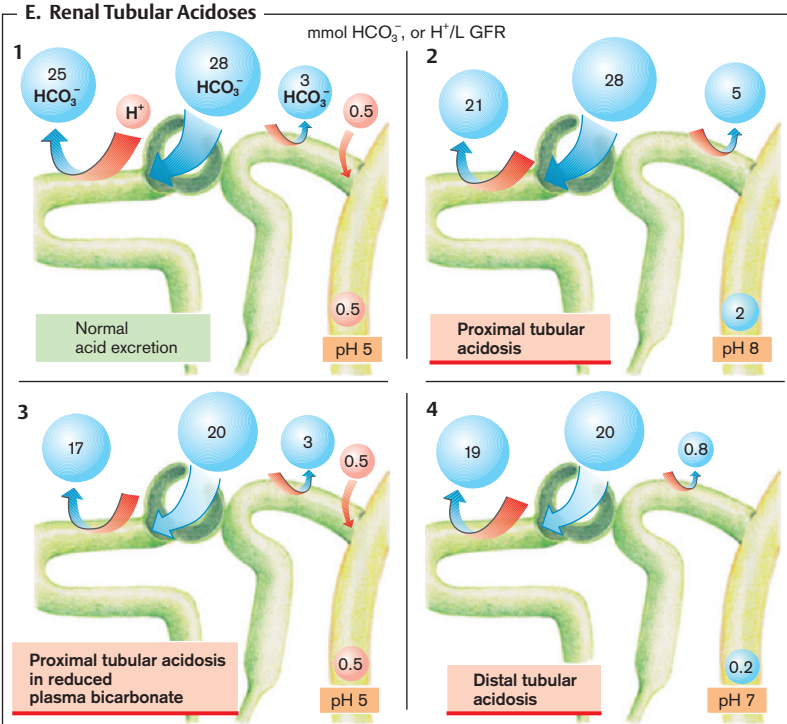
D. Mechanisms of Renal K^+ Loss, H^+ Secretion, Glucosuria Types







E. Renal Tubular Acidoses



Abnormalities of Urinary Concentration

Depending on requirements, the kidney can normally excrete hypotonic (< 100 mOsm/L) or hypertonic (> 1200 mOsmol/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. 104) 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 a 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 following its concentration gradient. 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 recycles to 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 (→ **A 1**). 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^+-2 Cl^- cotransport. Hypercalcemia inhibits the reabsorption via the Ca^{2+} 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^+-2 Cl^- cotransport (→ p. 105 B).

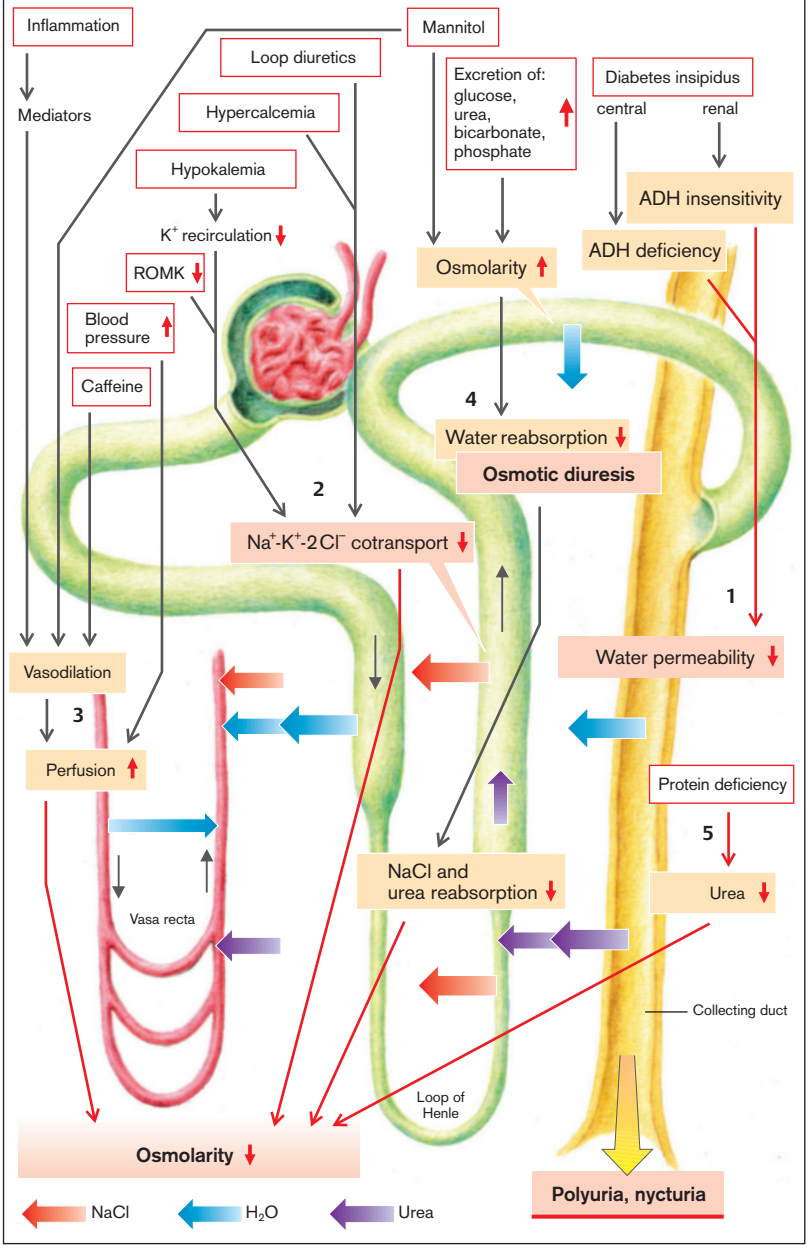
Raised perfusion through the renal medulla washes out medullary hyperosmolality (→ **A 3**). Mediators (e.g., kinins, prostaglandins) released during inflammation therefore lower medullary osmolality and thus reduce urinary concentration. Caffeine, too, acts as a dilator of the vasa recta. Raised blood 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 (→ **A 4**). 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 (diabetes mellitus), bicarbonate, urea, and phosphate are excreted.

A **low-protein diet** impairs the concentrating ability of the kidney because of reduced contribution of urea to the concentrating mechanism (→ **A 5**).

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

A. Abnormalities of Urinary Concentration



Polycystic Kidney Disease

Several genetic disorders lead to the appearance of fluid-filled cysts in the kidney and partially in other organs, such as liver, pancreas, and epididymis. Occasionally the affected patients suffer, in addition, from vascular aneurysms (→ p. 254), mitral valve prolapse, aortic valve insufficiency, and hernia of the abdominal wall. Renal cysts develop by extension of the tubular epithelium (particularly of the distal tubule and collecting duct). During the enlargement, the cysts loose contact with their nephron.

The relative common (0.2% of the total population) **autosomal dominant polycystic kidney disease** (ADPKD) is caused by a genetic defect of the cell membrane protein polycystin 1 (PKD1) or of the Ca^{2+}-permeable TRP (transient receptor potential) channel polycystin 2 (PKD2). The two interacting proteins are inserted into the apical epithelial cell membrane and allow the entry of Ca^{2+} into the cell whenever the luminal flow rate increases (→ **C1**). The two proteins influence a number of signaling pathways, which are deranged at a genetic defect of one of the two proteins.

The formation and extension of cysts results on the one hand from the proliferation of epithelial cells leading to an increase in the circumference of the epithelial layer and on the other hand from secretion of fluid into the lumen leading to the extension of the cyst (→ **A1**).

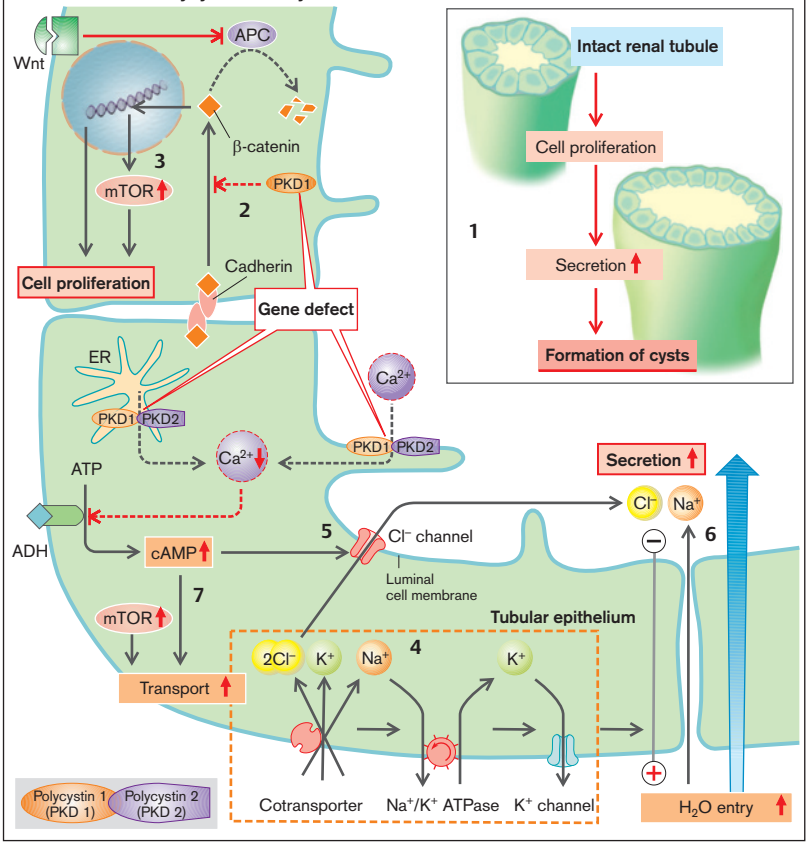
The **epithelial cell proliferation,** at least partially, results from a loss of the inhibitory effect of polycystin 1,2 on β-catenin-regulating Wnt signaling (→ **A2**; → p. 10). Polycystin 1 binds to cadherin and β-catenin. Overexpression of β-catenin and defective APC, which usually mediates the degradation of β-catenin (→ p. 10), may result even at intact polycystin in the appearance of renal cysts. ADPKD is further paralleled by enhanced activation of mTOR (→ **A3**), which fosters transport, protein synthesis, and cell proliferation (→ p. 10).

The **fluid secretion** is accomplished by insertion of the Na^+-K^+-2 Cl^- cotransporter NKCC2 (→ **A4**) into the basolateral cell membrane and of Cl^- channels (e.g., CFTR) into the luminal cell membrane (→ **A5**). Na^+, which enters via the Na^+-K^+-2 Cl^- cotransporter into the cell, is extruded by the Na^+/K^+-ATPase in the basolateral cell membrane. The K^+ thus accumulated by the pump leaves the cell via basolateral K^+ channels. Apical Cl^- channels and basolateral K^+ channels generate a lumen-negative transepithelial potential difference, which drives paracellular Na^+ transport into the lumen (→ **A6**). NaCl thus secreted into the lumen is followed by osmotically obliged water. In ADPKD the Cl^- secretion is stimulated by enhanced formation of cAMP (→ **A7**).

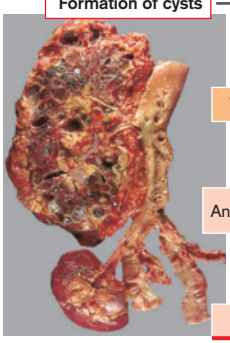
The growing cysts displace and distort normal renal tissue, increase the renal tissue pressure, compress vessels, and thus lead to local ischemia (→ **B**). The extension of the renal capsule generates **pain**, the compression of neighboring tubules interferes with urinary flow and predisposes to **urinary tract stones** (particularly calcium oxalate and uric acid stones). The urolithiasis is fostered by the decreased formation and secretion of citrate and ammonia in the injured proximal renal tubules: Lack of urinary citrate predisposes to precipitation of Ca^{2+} salts; decreased ammonia production requires an increase of urinary acidity to eliminate the daily acid load and thus favors the precipitation of uric acid, which is, by far, less soluble than urate prevailing in alkaline urine (→ p. 130). The ischemia stimulates the formation and release of renin, which triggers the renin-angiotensin-aldosterone mechanism and thus leads to fluid retention and **hypertension**. Ischemia further stimulates the formation of VEGF (vascular endothelial growth factor), which stimulates angiogenesis. The enhanced capillarisation may lead to bleeding into the cysts. Eventually the destruction of functioning renal tissue leads to renal insufficiency,

Less common cystic kidney diseases include ADPKD, medullary cystic kidney disease, medullary sponge disease, and nephronophthisis. The cause of type 2 nephronophthisis is a genetic defect of *inversin*, which normally suppresses Wnt-dependent signaling by stimulating the degradation of dishevelled (→ p. 10). Renal cysts are further observed in patients suffering from **tuberous sclerosis** (mutations of tuberin or hamartin, → p. 10) or from **von Hippel–Lindau disease** (mutations of vHLV, → p. 10). Both disorders are characterized by enhanced incidence of tumor growth. ADPKD is, however, not associated with enhanced risk to develop renal carcinoma.

A. Causes of Polycystic Kidney Disease



B. Consequences of Polycystic Kidney Disease



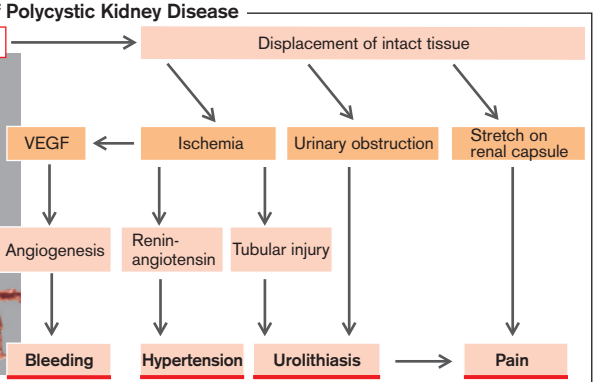


Photo: Riede, Werner, Schaefer Allgemeine und spezielle Pathologie. 5th ed. Stuttgart: Thieme; 2004.

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. 114) 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_f), and the filtering surface (F): $GFR = K_f \cdot F \cdot P_{eff}$. The **effective filtration pressure** is made up of the hydrostatic (ΔP) and the oncotic ($\Delta\pi$) pressure gradients across the filter (→ **A**): $P_{eff} = \Delta P - \Delta\pi$. Even if the filter is defective, π within the capsular space of the glomerulus can be ignored, i.e., $\Delta\pi$ practically equals the capillary 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 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. 52 ff.). This results in obstruction of the glomerular capillaries and destroys the filtering function (**immune complex nephritis**). Numerous drugs, allergens, and pathogens (particularly streptococci group A, type 12) may act as antigens. Antibodies include IgG, IgM, and commonly IgA (IgA nephritis).

Glomerulonephritis may, less commonly, be caused by an immune reaction against the basement membrane. Glomeruli may further be affected by infections. 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 capsular epithelial cells to proliferate and ultimately produce excess mesangial matrix (sclerosis) and/or collagen fibers (fibrosis).

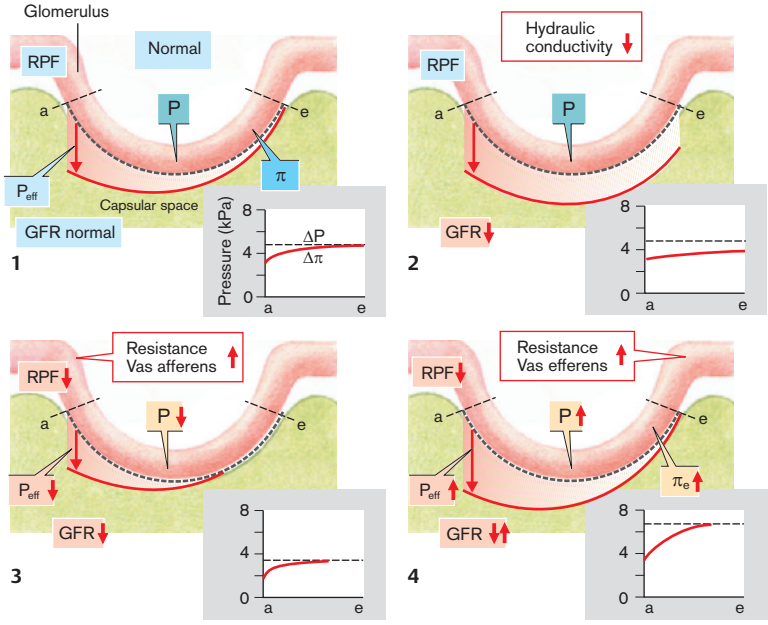
The glomeruli may also be damaged without any local inflammation, e.g., by **high pressure** in the glomerular capillaries (e.g., in arterial hypertension, renal vein thrombosis, venous back pressure in right heart failure, and hyperfiltration in diabetic nephropathy or chronic renal failure), by **reduced perfusion** (e.g., in atherosclerosis, arteriosclerosis), by **toxic injury**, by thrombotic microangiopathy, by increased concentrations of filterable plasma proteins (e.g., multiple myeloma), by **deposition** of amyloid in amyloidosis, by deposition of glycosphingolipid in Fabry disease, or by **genetic defects** of glomerular proteins (→ p. 114).

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 H_2O, brought about by the decrease in GFR (→ p. 124).

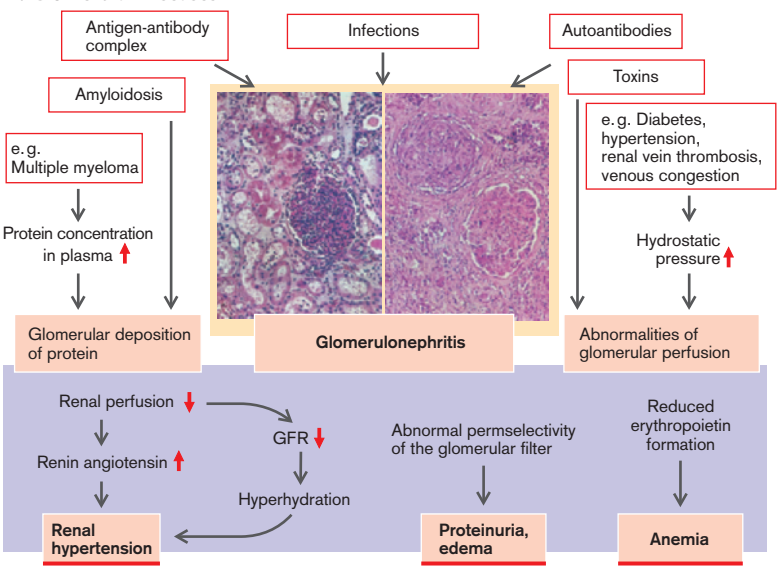
Selective permeability is lost by damage to the glomerular filter, thus leading to **proteinuria** and **edema** (→ p. 114).

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



B. Glomerular Diseases



Photos from: Doerr, W. ed. Organpathologie. Stuttgart: Thieme; 1974

Disorders of Glomerular Permselectivity, Nephrotic Syndrome

The **glomerular filter** (fenestrated endothelium, basement membrane, slit membrane between podocytes, → **A1**) is permselective, i.e., it prevents the passage of some blood components. The filtration of molecules at the glomerular filter depends on their size, shape, and charge. Normally, macromolecules with a diameter of > 4 nm cannot pass the basement membrane and the slit membrane. Negatively charged macromolecules (e.g., albumins) are repelled by the negative charge at the fenestrated endothelium (→ **A1**). The matrix of the basement membrane includes collagen type IV 3α, 4α, and 5α as well as lamina β_2. genetic defects of 3α (IV), 4α (IV), or 5α (VI) (Alport syndrome and "thin basement membrane" disease) and of lamina β_2 (Pierson syndrome) lead to glomerulosclerosis. Antibodies against 3α (IV) are found in Goodpasture syndrome, an autoimmune disease affecting the basement membrane, leading, among others, to glomerulonephritis.

The podocytes are connected to each other by nephrin, a transmembrane protein with a large extracellular domain. Nephrin binds the adaptor protein CD2AP (CD2-associated protein) and the membrane protein podocin. Podocytes further express the Ca^{2+}-permeable cation channel TRPC6 (transient receptor potential channel 6), and the cytoskeletal proteins α-actinin-4 and NMMHC-IIA (nonmuscle myosin heavy chain IIA). Regulation of gene expression in podocytes involves WT1, which suppresses the expression of several growth factors (→ p. 16). Genetic defects of nephrin (nephrotic syndrome Finnish type), CD2AP, podocin (autosomal recessive steroid resistant nephrotic syndrome), TRPC6, α-actinin-4, NMMHC-IIA or WT1 (Danys–Drash syndrome, Frasier syndrome) may lead to glomerulosclerosis. Genetic defects are further responsible for the glomerular lesions in the "Nagel–Patella" syndrome.

By far more frequent than the genetic defects affecting glomerular function are glomerular lesions due to **glomerulonephritis** or due to systemic disease, such as hypertension and diabetes mellitus (→ p. 112).

If the integrity of the glomerular filter is disrupted, plasma proteins and even erythrocytes gain access to the Bowman space with resulting proteinuria and hematuria. Electrophoresis reveals that the defective filter preferably allows the passage of the small, **negatively charged albumins** (→ **A3**).

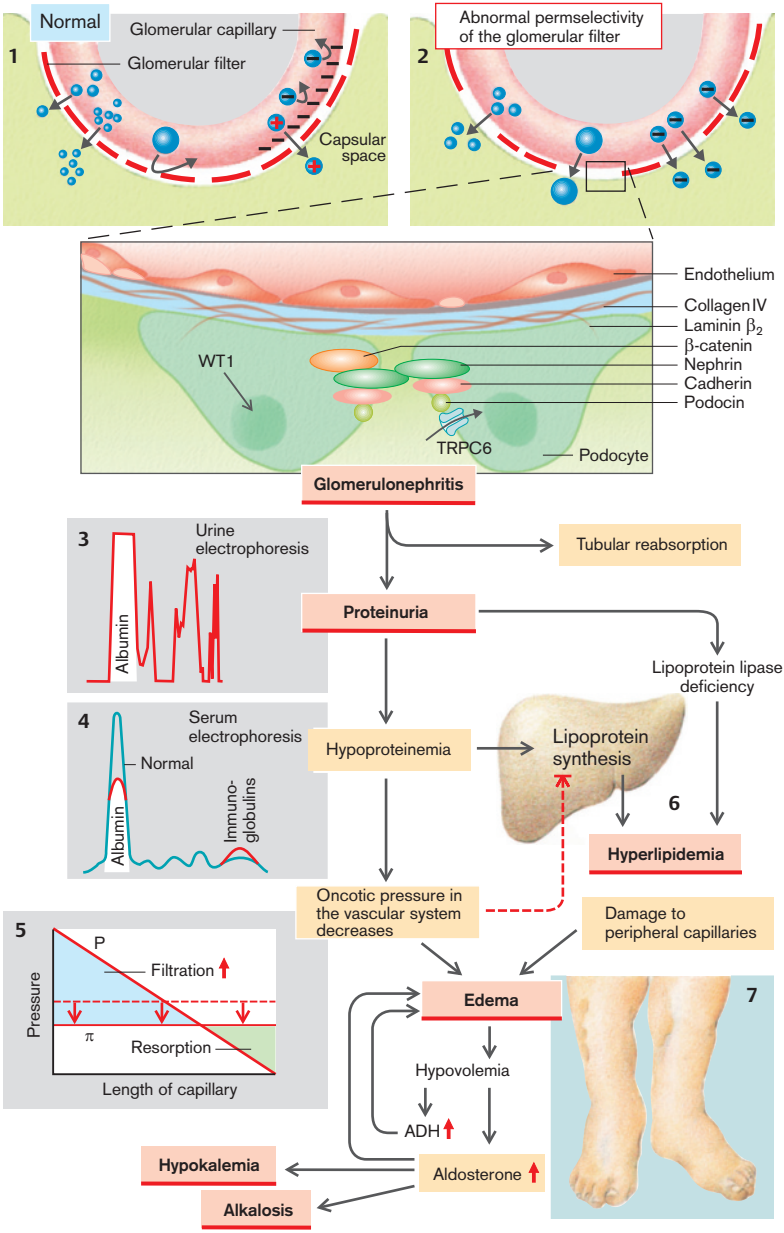
Even an intact glomerular filter allows the passage of small proteins, which are then reabsorbed in the proximal tubule. The limited transport capacity of the tubular epithelium cannot cope, however, with the massive load of filtered proteins, if the glomerular filter is defective, which thus leads to **proteinuria**. A defective reabsorption of proteins in the proximal tubule leads to excretion of moderate amounts of small sized proteins (*tubular proteinuria*).

Renal loss of proteins due to glomerular damage leads to **hypoproteinemia**. Serum electrophoresis demonstrates that it is largely due to a loss of albumin (→ **A4**). The reduced oncotic pressure in the vascular system leads to increased filtration of plasma water in the periphery. Filtration in the peripheral capillaries is facilitated 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**). The peripheral filtration increases the concentration of larger proteins, which are not filtered at the defective glomerular filter (e.g., lipoproteins).

If proteinuria, hypoproteinemia, and peripheral edema occur together, this is termed **nephrotic syndrome**. The increase of the lipoproteins result in hyperlipidemia and hypercholesterolemia (→ **A6**). The hyperlipidemia is confounded by decreased lipoprotein lipase activity.

Hypoproteinemia favors 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. 132). 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. 106), *hypokalemia* and *alkalosis* develop.

A. Abnormalities of Glomerular Permselectivity and Nephrotic Syndrome



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 partially vulnerable, 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. 130], pregnancy [→ p. 126], prostatic hypertrophy, tumor) and by reduced immune defenses (e.g., diabetes mellitus [→ p. 312]).

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. 268). 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. 142).

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 O_2 diffuses from the descending to the ascending limb of the vasa recta. In **sickle cell anemia** (→ p. 40) deoxygenation therefore leads to aggregation 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.

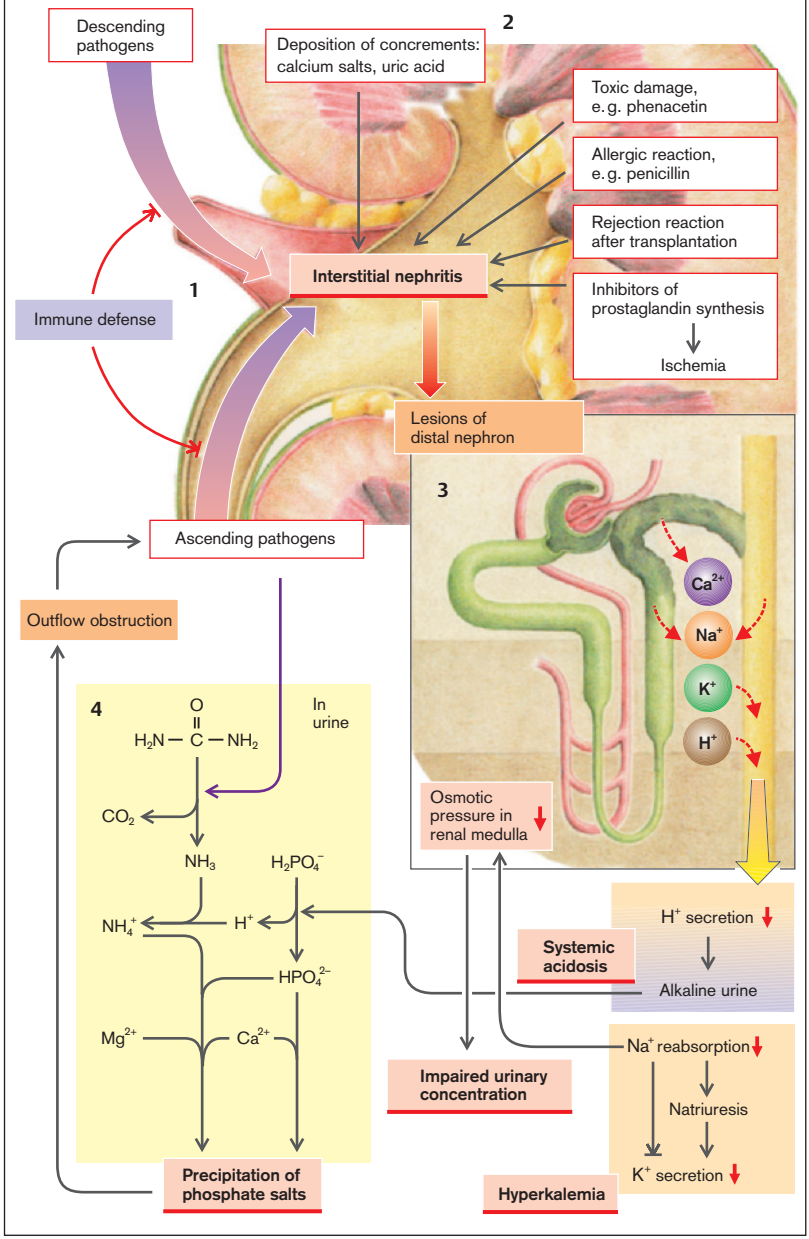
In accordance with the site of the inflammatory processes, the first **effects** are caused by lesions in the segments of the nephron that lies within the renal medulla (loop of Henle and collecting duct). A relatively early occurrence is **reduced urinary concentration,** caused by damage to the ascending part, by flushing out of the medulla as a result of inflammatory hyperemia as well as by a lack of ADH sensitivity of the damaged distal nephron. The increased urine volume causes nocturnal diuresis (nycturia). 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. 288).

Renal acid excretion can be impaired, resulting in formation of an alkaline urine 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. 130) 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



Acute Renal Failure

Diverse prerenal, intrarenal, and postrenal disorders can lead to sudden impairment of renal function (→ **A 1**):

Obstruction of the urinary tract, for example, by urinary stones (→ p. 130) can stop urinary excretion, even though the kidney remains intact—at least at first (postrenal).

Following **hemolysis** and 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 disrupts urine formation. Similarly intrarenal precipitations of uric acid and calcium oxalate may obstruct tubules. Renal function can also cease as a result of rapidly progressing renal diseases (e.g., **glomerulonephritis**; → p. 112) or **toxic damage** to the kidney (intrarenal).

Loss of blood and fluid, compromised cardiac pump function, or peripheral vasodilation requires centralization of the circulation to maintain blood pressure (→ p. 246). The activation of the sympathetic nerve system with subsequent activation of α-receptors thereby leads to renal vascular vasoconstriction, which may cause acute ischemic renal failure despite the release of vasodilating prostaglandins (prerenal).

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 (→ **A 1**):

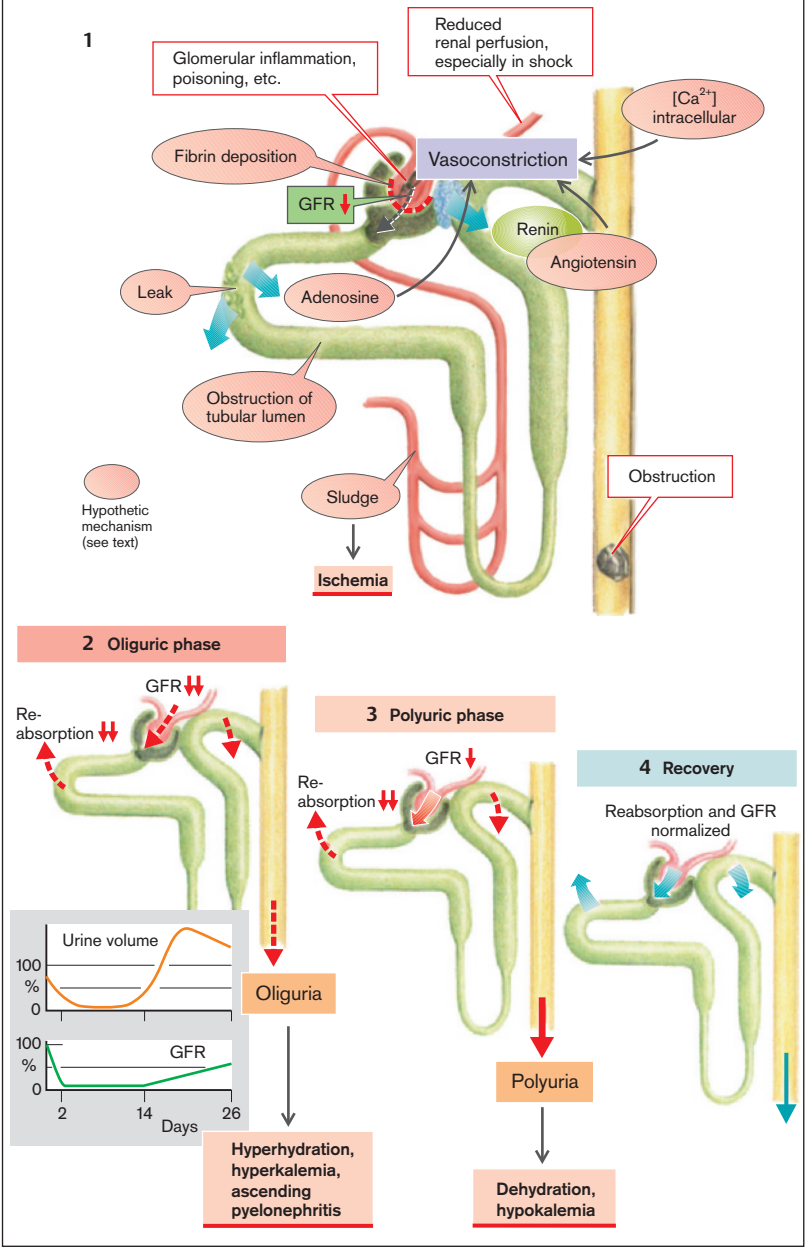
- **Constriction of the vasa afferentia**:
  - **Energy deficiency** impairs Na^+/K^+-ATPase; the resulting increase in intracellular concentration of Na^+ also causes, via the $3Na^+/Ca^{2+}$ exchanger, a rise in intracellular **Ca^{2+} concentration** (→ p. 12, 114) and thus vasoconstriction.
  - The 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 generated 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** by thrombosis or adhesion of suicidal erythrocytes at the vascular wall ("sludge"). Thrombosis and erythrocyte death is fostered by injury to endothelial cells and subsequent decrease of NO formation. The blood cells cannot be flushed out of the network between renal medulla and cortex, even if the perfusion pressure rises. In humans, the enhanced formation of vasoconstrictory endothelin presumably plays only a minor role.

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**; → **A 2**). 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. Accordingly, a relatively large fraction of filtered fluid is excreted.

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; → **A 3**). 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



Chronic Renal Failure

A number of renal diseases (→ p. 112 ff.), diabetes mellitus (→ p. 312) and/or hypertension (→ p. 124, 222 ff.) can ultimately lead to the destruction of renal tissue (→ p. 112 ff., 124). If the residual renal tissue is not in a position to adequately fulfill its tasks, the picture of renal failure evolves.

Reduced renal excretion plays a decisive role for the course of the disease. The loss of nephrons increases the filtration in the remaining glomerula. The decreased GFR leads to an inversely proportional rise in the plasma level of **creatinine** (→ **A**, top; see also p. 102). 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, including natriuretic peptides and PTH (→ p. 122). The reduced reabsorption of Na^+ in the proximal tubules also decreases the reabsorption of other substances, such as phosphate, uric acid, HCO_3^-, Ca^{2+}, 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. 108). 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 to adequately increase the excretion of water, Na^+, K^+, H^+, phosphate, etc. (e.g., if oral intake is increased).

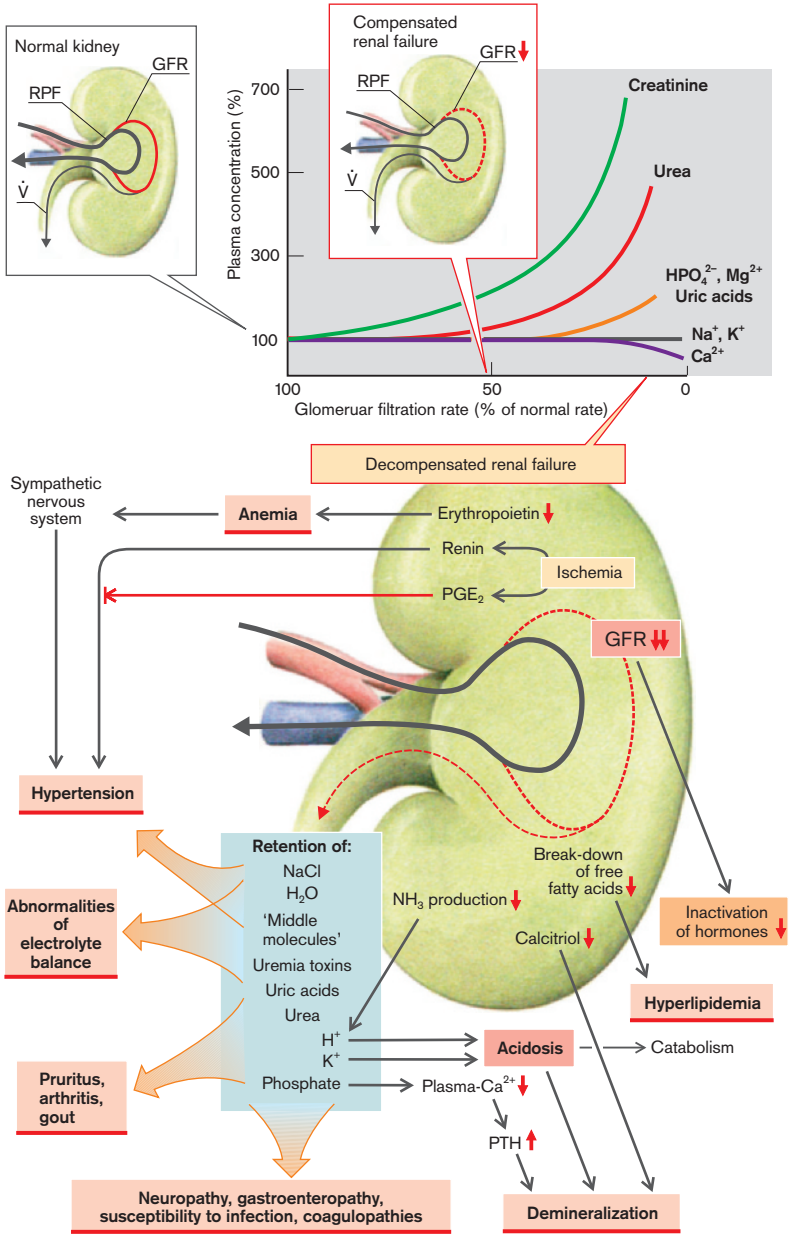
Uric acid can be precipitated at high concentrations, especially in the joints, and thus cause **gout** (→ p. 268). The renal retention of oxidants increases oxidative stress and inflammation. Oxidative stress and decreased renal elimination increase the plasma concentrations of "*uremia toxins*" (e.g., acetonine, dimethlyl-arginine, 2,3-butyleneglycol, hippurate, guanidinosuccinic acid, methylguanidine, methylglyoxal, indoles, phenols, dimethyl-arginine [ADMA], aliphatic and aromatic amines, homocysteine, etc.) as well as of "middle molecules" (lipids or peptides with a molecular weight of 300–2000 Da). The substances exert their toxic action via different mechanisms. ADMA, for instance, inhibits the NO synthesis, the decreased formation leads to ischemia and blood pressure increase. Methylglyoxal triggers suicidal cell death and contributes to the pathophysiology of blood cells (accelerated degradation of erythrocytes and impairment of leukocyte function). 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 bacterial degradation of urea yields ammonia, which causes halitosis (foetor uraemicus), and contributes to the derangement of **gastrointestinal function** (nausea, peptic ulcer, diarrhea). Urea and several uremia toxins are products of protein metabolism and their concentration can be decreased by dietary protein restriction.

The impaired renal production of *erythropoietin* leads to the development of renal **anemia** (→ p. 34 ff.), which leads to activation of the sympathetic nerve tone. The intrarenal formation of renin and of prostaglandins can be increased (e.g., in ischemia) or reduced (death of renin- or prostaglandin-producing cells). Increased formation of *renin* promotes, while its reduced formation of renin or increased formation of prostaglandins (→ p. 318) inhibit the development of **hypertension**, a frequent occurrence in renal failure (→ p. 124 ff.). The hypertension contributes to further renal injury. Accordingly, the progression of chronic renal failure is accelerated by genetic increase of angiotensin converting enzyme.

The loss of renal *inactivation of hormones* (→ p. 100) may slow hormonal regulatory cycles. Delayed elimination of insulin, for instance, may lead to **hypoglycemia.** Hyperprolactinemia inhibits the release of gonadotropins and thereby reduces the plasma levels of estrogens (♀) and testosterone (♂). Consequences include **amenorrhea** (♀) and **impotence** (♂).

The reduced consumption of fatty acids by

A. Chronic Renal Failure



the kidney contributes to **hyperlipidemia**, while reduced gluconeogenesis favors the development of **hypoglycemia**.

The decreased formation and excretion of ammonia leads to acidosis, which in turn stimulates the protein catabolism.

The extracellular volume expands if there is an excess of NaCl and water (→ **B**), and **hypervolemia** as well as **edemas** develop (→ p. 132); *pulmonary edema* being the most dangerous complication (→ p. 84). 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. 380).

The hypervolemia results in the release of natriuretic factors (→ p. 132), which partially inhibit the Na^+/K^+ATPase (→ **B 1**). **Inhibition of Na^+/K^+-ATPase** causes a decrease of the intracellular K^+ concentration leading to depolarization in cells from diverse tissues. The intracellular concentration of Na^+ rises. This impairs $3Na^+/Ca^{2+}$ exchange (→ **B 2**), and thus the intracellular concentration of Ca^{2+} also increases. The consequences of depolarization are **abnormal neuromuscular excitability** (polyneuropathy, confusion, coma, convulsions), cellular accumulation of Cl^-, and **cell swelling** (→ **B**; see also p. 12). The increased intracellular Ca^{2+} concentration causes **vasoconstriction** as well as an increased **release of hormones** (e.g., gastrin, insulin) and increased hormonal effects (e.g., epinephrine).

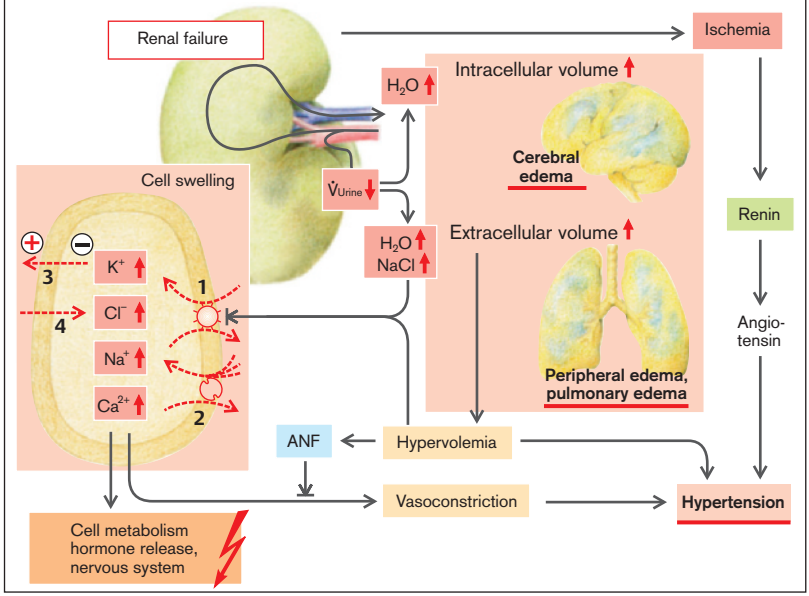
Abnormalities of **mineral metabolism** also contribute greatly to the symptoms of renal failure (→ **C**). If the GFR is reduced to less than 20% of normal rate, less *phosphate* is filtered than is absorbed through the gut. Even if the entire amount of filtered phosphate is eliminated, i.e., there is no reabsorption, renal elimination cannot keep up with intestinal absorption, and the plasma concentration of phosphate rises. Phosphate may combine with Ca^{2+} to form poorly soluble calcium phosphate. The precipitated calcium phosphate (calciphylaxis) is deposited in the joints (arthritis) and skin. The deposition in the vascular wall leads to vascular calcification. $CaHPO_4$ is less soluble than $Ca(H_2PO_4)_2$. Acidosis favors the formation of $Ca(H_2PO_4)_2$ and thereby counteracts precipitation of $CaHPO_4$. Correction of acidosis at continued hyperphosphatemia thus favors vascular calcification.

When Ca^{2+} forms a complex with phosphate, the concentration of Ca^{2+} is lowered. The *hypocalcemia* stimulates the release of **PTH** from the parathyroid gland, mobilizing calcium phosphate from bone (→ **C**). The result is accelerated degradation of bone (**osteitis fibrosa**). Normally PTH decreases, by simultaneous inhibition of renal reabsorption of phosphate, the plasma concentration of phosphate so that, despite mobilization of calcium phosphate from bone, the solubility product in plasma is not exceeded and Ca^{2+} concentration can increase. In renal insufficiency, however, renal excretion cannot be enhanced, plasma phosphate concentration increases, $CaHPO_4$ is precipitated, and plasma Ca^{2+} 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.

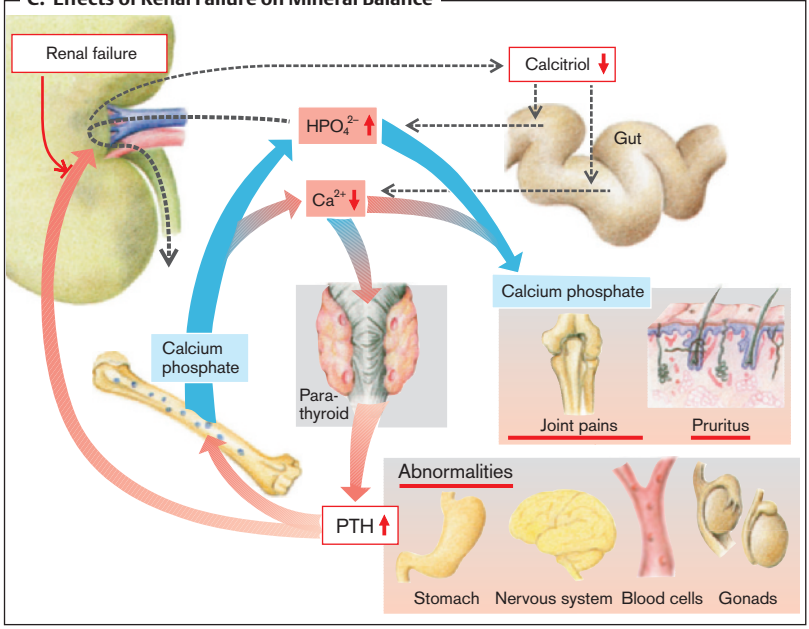
As the receptors for PTH are, in addition to those in the kidney and bones, expressed in many other organs (nervous system, stomach, blood cells, gonads) PTH presumably plays a role in the development of abnormalities in these organs.

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 (→ **C**). Although calcitriol deficiency reduces the intestinal absorption of phosphate, it aggravates the hypocalcemia. Calcitriol deficiency fosters the development of a dynamic bone disease and osteomalacia. There are receptors for calcitriol in various organs. The effects of calcitriol include immunosuppression, and calcitriol deficiency could contribute to the enhanced inflammation in renal insufficiency. Calcitriol substitution may, however, endanger the patient with renal failure by stimulating the intestinal absorption of phosphate.

B. Disorders of Salt and Water Balance in Renal Failure



C. Effects of Renal Failure on Mineral Balance



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. 222 ff.).

Renal ischemia is an important **cause** of hypertension brought about by renal disease. This happens regardless of the site where renal blood flow is decreased, whether intrarenally in the course of renal disease (e.g., glomerulonephritis [→ p. 112], pyelonephritis [→ p. 116], polycystic kidney disease [→ p. 110]), in the renal artery (renal artery stenosis), or in the aorta above the origin of the renal arteries (aortic coarctation) (→ **A 1**).

Reduced perfusion of the kidney results, among others, in hypertension via stimulation of the **renin–angiotensin mechanism** (→ **A 2**), 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 (ACE) 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 (→ **A 3**).

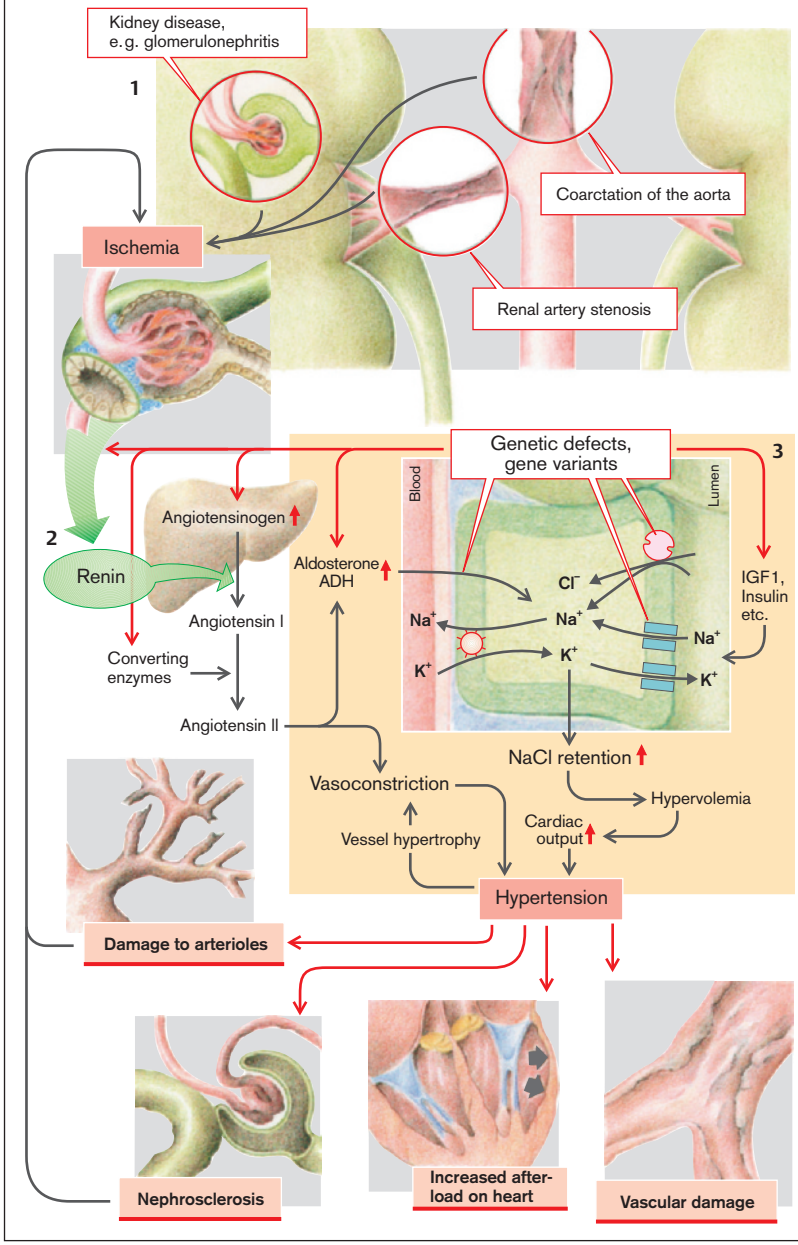
A renin-producing renal tumor may similarly result in hypertension. The plasma concentration of the angiotensinogen formed in the liver does not saturate renin, i.e., an increase in angiotensinogen concentration can raise the blood pressure further. Thus, overexpression of angiotensinogen favors the development of hypertension as does overexpression of renin.

Hypertension is caused by the **retention of sodium and water** even without the renin–angiotensin mechanism as in primary increase of aldosterone release (hyperaldosteronism; → p. 106). Several rare genetic defects affecting renal tubular Na^+ transport lead to hypertension, including Liddle's syndrome (overactive Na^+ channel), Gordon syndrome (lacking inhibition of the NaCl cotransporter by defective WNK kinase), "hypertension exacerbated by pregnancy" (mutation of the mineralocorticoid receptor, which allows stimulation of the receptor by progesterone) and "apparent mineralocorticoid excess" (AME, defective 11-β-hydroxysteroid dehydrogenase and thus lacking inactivation of cortisol, which then stimulates the mineralocorticoid receptor, → p. 288).

A variety of more common gene variants increase blood pressure only moderately, but predispose a large proportion of the common population to the development of hypertension. The genes associated with hypertension include those encoding renin, angiotensinogen, angiotensin converting enzyme, 11β-hydroxylase (aldosterone synthesis), prostacyclin synthase, growth hormone, IGF1, CRH (corticotrophin releasing hormone), several receptors (angiotensin, ANP, insulin, glucocorticoids, dopamine, epinephrine, leptin), or signaling molecules (G proteins, guanylate cyclase A, serum and glucocorticoid inducible kinase, adducin). The gene variants are, at least partially, effective through influence on renal salt excretion.

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. 222 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



Kidney Disease in Pregnancy

Normal pregnancy (→ **A**) is paralleled by release of gestagens and relaxin, which stimulate the endothelial formation of NO and thereby cause vasodilatation. 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. The hyperfiltration predisposes to albuminuria. Na^+ reabsorption in the proximal tubules does not keep in step with a high GFR. In addition, *estrogens* inhibit K^+ channels in the proximal tubules. The resulting depolarization retains HCO_3^- in the cell, and the intracellular acidosis inhibits the Na^+/H^+ exchanger (→ p. 105 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).

Enhanced delivery of Na^+ to the distal nephron stimulates distal tubular reabsorption, which increases the formation of prostaglandin E_2 (PGE_2) (→ p. 318). Estrogens and PGE_2 both stimulate the release of renin, which raises the plasma concentrations of angiotensin II and aldosterone. Angiotensin II elicits thirst and increases ADH release. ADH stimulates the renal H_2O reabsorption, aldosterone the renal Na^+ reabsorption and the salt appetite. 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.

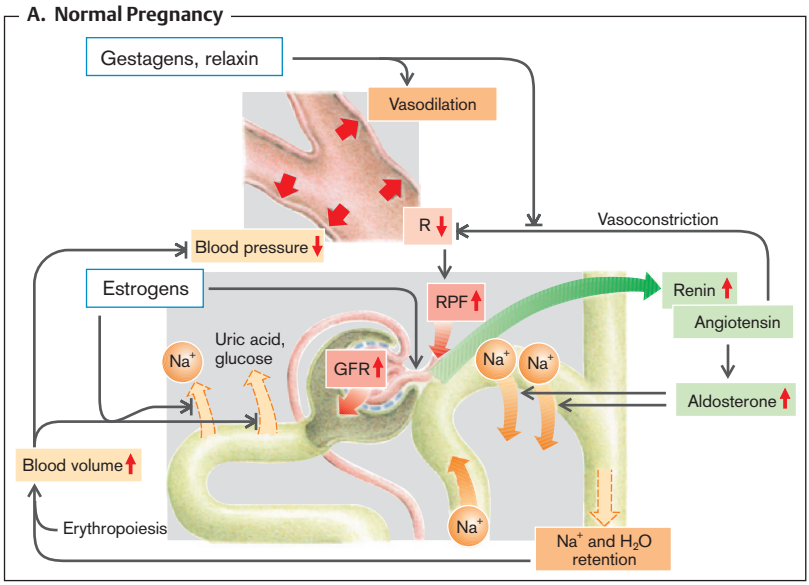
Edema, proteinuria, and hypertension (EPH) occur in ca. 5% of all pregnant women (**preeclampsia, toxemia of pregnancy,** or **EPH-gestosis**). The symptoms point to renal damage, hence the term **nephropathy of pregnancy** (→ **B**).

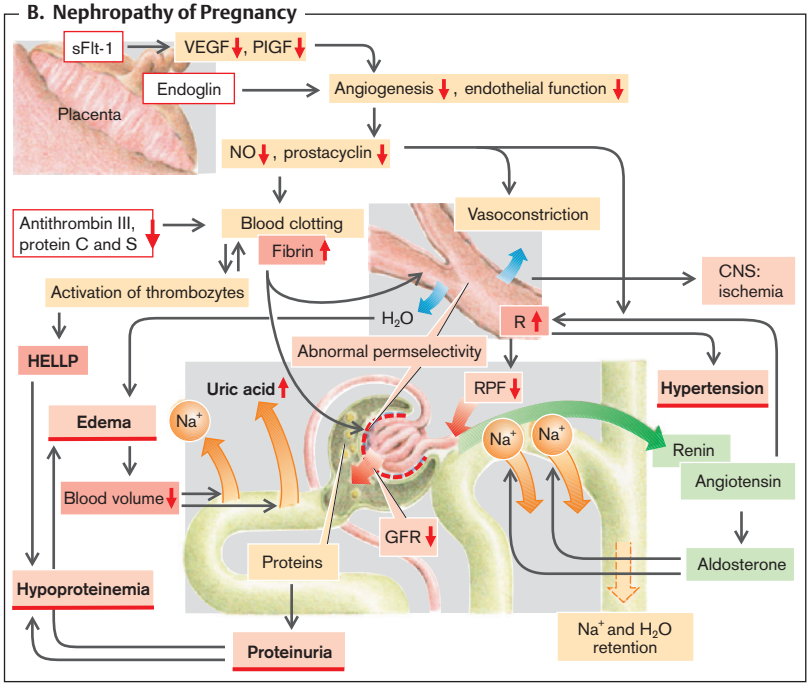
In patients who are suffering from EPH gestosis, the (ischemic) placenta produces enhanced levels of sFlt-1 (soluble fms-like tyrosine kinase-1), a truncated soluble VEGF receptor (vascular endothelial growth factor receptor). The soluble receptor binds VEGF and PlGF (placental growth factor) and thereby lowers the concentration of free VEGF and PlGF. The placenta further produces endoglin. Both sFlt-1 and endoglin counteract the angiogenesis and endothelial function. In patients suffering from EPH gestosis the formation of NO and prostacyclin are decreased, the release of vasoconstricting endothelin enhanced, and the reagibility of vascular smooth muscle cells to vasoconstrictive agents (e.g., angiotensin II) increased. By virtue of their effect on the vascular smooth muscle cells, sFlt-1 and endoglin lead to hypertension, glomerular injury, and proteinuria. The patients experience hypoalbuminemia. The resulting decrease of the oncotic pressure and the damage to the peripheral vessels leads to peripheral **edema** at the expense of the plasma volume. Occasionally the disorder leads to lung edema.

In EPH gestosis the formation of thrombosis-inhibiting proteins (antithrombin III, protein C, protein *S*; → p. 68) is decreased. Deficiency of those proteins and absent formation of prostacyclin (see above) foster the coagulation. The sensitivity of thrombocytes to activators is enhanced and their number decreased. Massive activation of thrombocytes may damage erythrocytes and the liver (HELLP syndrome, **H**emolysis, **E**levated **L**iver enzymes, **L**ow **P**latelets). The impairment of the hepatic albumin synthesis contributes to the hypoalbuminuria.

The increase of the renal vascular resistance (→ **B 3**) lowers the renal plasma flow (RPF) and, even more so, the GFR. As a consequence of the volume depletion, the Na^+ reabsorption in the proximal renal tubule is enhanced and the luminal flow rate is decreased. As a result, the contact time of luminal fluid with the reabsorbing epithelium is enhanced, which increases the renal tubular reabsorption of uric acid. The plasma concentration of uric acid increases, a valuable diagnostic parameter.

The deranged coagulation may lead to fibrin deposits in the cerebral circulation on the one hand and to bleeding on the other. Patients may develop brain edema with subsequent severe headache, sensory loss, convulsions, and coma (eclampsia).





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.

In liver cirrhosis, the narrowing of the vascular bed within the liver (→ p. 184) leads to congestion in the portal venous system. The hydrostatic pressure in the capillaries rises and excessive amounts of fluid are filtered into the abdominal cavity (**ascites**, → p. 184). Because of the high protein permeability of the liver sinusoid, plasma proteins are also lost into the extravascular 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** (→ p. 250). The formation of ascites and peripheral edemas occurs at the expense of the circulating plasma volume with decrease of central venous pressure, of right ventricular filling, and of cardiac stroke volume.

The disease further leads to **peripheral vasodilation**. 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. 184), 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. The stimulation of the renal sympathetic nerves 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. 288). ADH and aldosterone increase the tubular reabsorption of water and sodium chloride (leading to loss of potassium! → p. 134), and the kidney excretes small volumes of highly concentrated urine (**oliguria**).

Administration of vasoconstrictive drugs (e.g., vasopressin or related substances and α-adrenergic agonists) in combination with albumin are effective in two-thirds of the patients with hepatorenal syndrome. In those patients the decrease of the effective plasma volume is the major cause for the hepatorenal syndrome. Nevertheless, further mechanisms may contribute to this life-threatening complication of liver insufficiency.

Renal vasoconstriction may be fostered by **hepatic encephalopathy** (→ p. 188). The compromised hepatic metabolism alters plasma amino acid concentrations and increases the NH_4^+ concentration in blood and cerebral fluid. The consequences include glial cell swelling and profound derangement of transmitter metabolism, which may, through activation of the sympathetic nerve tone, lead to renal vasoconstriction.

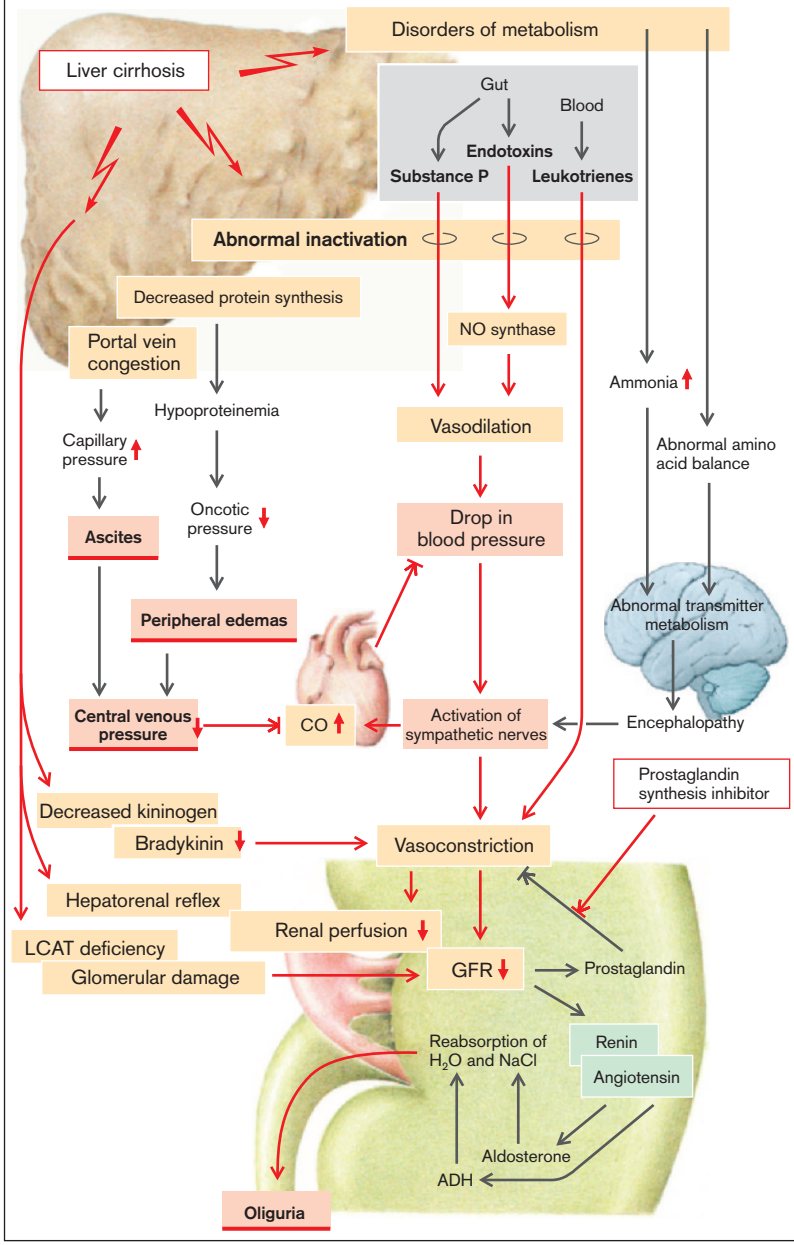
Incomplete hepatic inactivation of mediators that exert a direct vasoconstrictor effect on the kidney (e.g., **leukotrienes**) also contributes to renal vasoconstriction. Due to impaired hepatic metabolism, the **kininogen** production is decreased leading to reduced formation of vasodilating kinins, such as bradykinin. Moreover, hepatorenal syndrome may be paralleled by a decreased ability to form vasodilating prostaglandins.

Renal ischemia normally stimulates the release of vasodilating **prostaglandins** that prevent further reduction in renal perfusion (→ p. 318). 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.

A decrease in GFR may further result from a hepatorenal reflex, triggered by hepatocyte swelling.

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. 264) and plays an important part in breaking down or transforming lipoproteins. Complete familial LCAT deficiency leads to glomerular injury and thus to renal failure.

A. Hepatorenal Syndrome



Urolithiasis

Concrement-forming urinary components (→ **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 Ca^{2+} and, by reducing the Ca^{2+} 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. 102). 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 *de novo* 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. 104). The Ca^{2+} 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. Urolithiasis may further be precipitated by decreased urinary excretion of citric acid due to enhanced proximal tubular reabsorption.

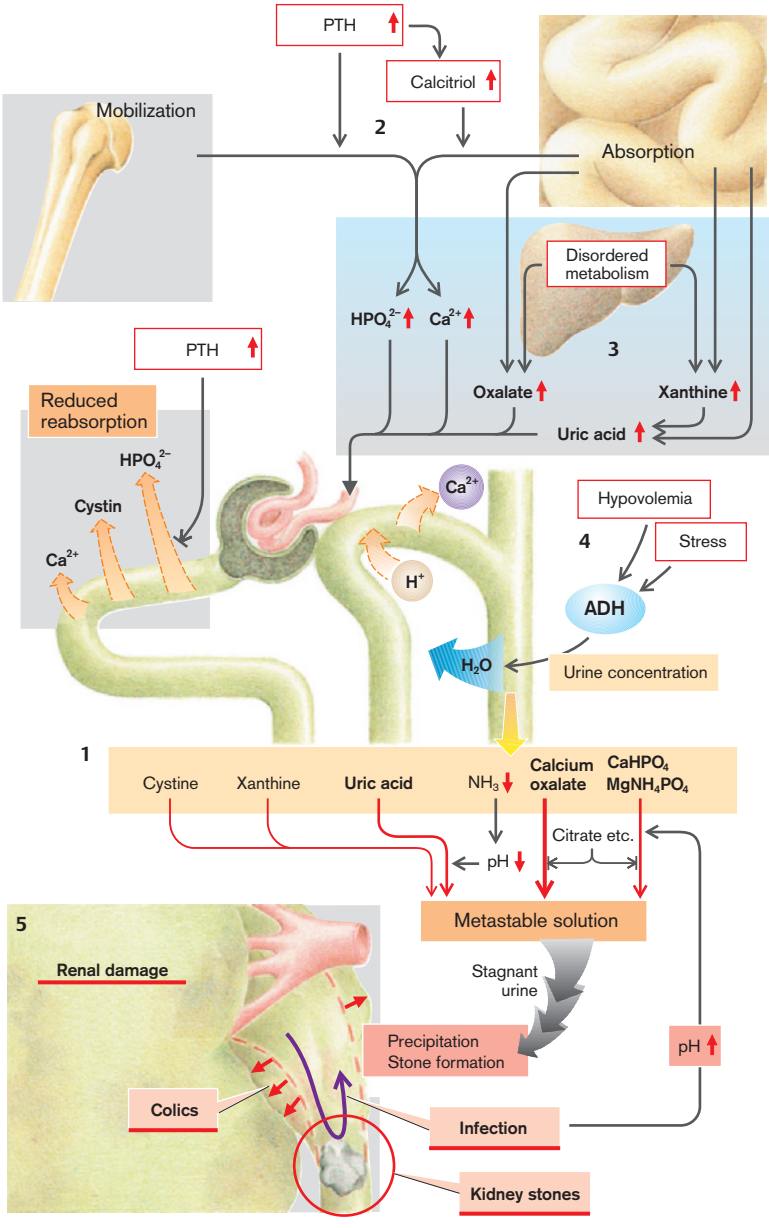
Release of ADH (in volume depletion, stress, etc.; → p. 282) increases the concentrations of stone-forming substances via enhanced **urine concentration** (→ **A4**).

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. The inability to generate an acidic urine increases the incidence of urolithiasis in distal renal tubular acidosis. 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 NH_3 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. 116). Urea-splitting pathogens form NH_3 from urea, thus alkalinizing 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



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. 108). The blood pressure, raised by the hypervolemia, inhibits the renin–angiotensin–aldosterone system. At the same time the release of natriuretic factors is stimulated (→ p. 100). 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/or NaCl** (→ **A**) occurs, for example, when fluid with greater osmolality than the maximum osmolality of urine is ingested (e.g., ship-wrecked people *drinking seawater*). 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 ADH or mineralocorticoids* is inappropriately increased (e.g., by hormone-producing tumors, → p. 282, 288). If the filtration balance in the peripheral vasculature is tipped, *edemas* occur at the expense of plasma volume (→ p. 250). 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 following excessive sweating (fever, heat), vomiting, diarrhea, blood loss, burns, osmotic diuresis (e.g., glucosuria), diuretic treatment, hypoaldosteronism, or salt-losing kidney (→ p. 118). Renal water loss can occur in ADH deficiency (central diabetes insipidus; → p. 282) and in lack of responsiveness of the kidney to ADH (renal diabetes insipidus; → p. 108). 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. 168), into the abdominal cavity (ascites; → p. 184) or in the periphery (edema; → p. 250).

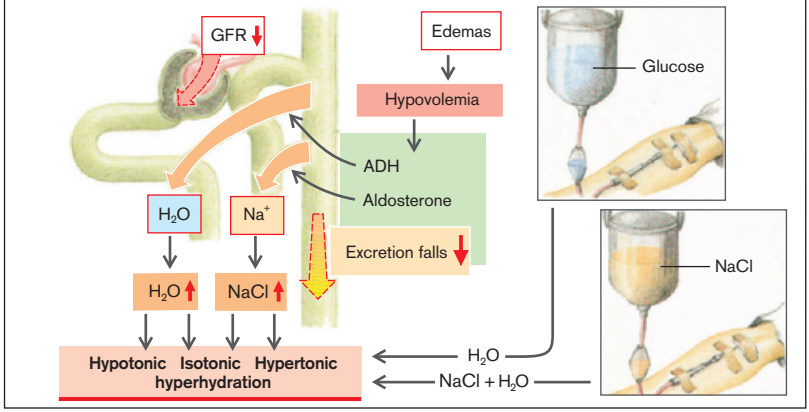
An excess of water (**hyperhydration**) necessarily leads to the enlargement of one body compartment (→ **C**). If there is NaCl excess at the same time (isotonic or hypertonic hyperhydration), the extracellular space is increased. In *hypertonic hyperhydration* the extracellular space is increased, 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).

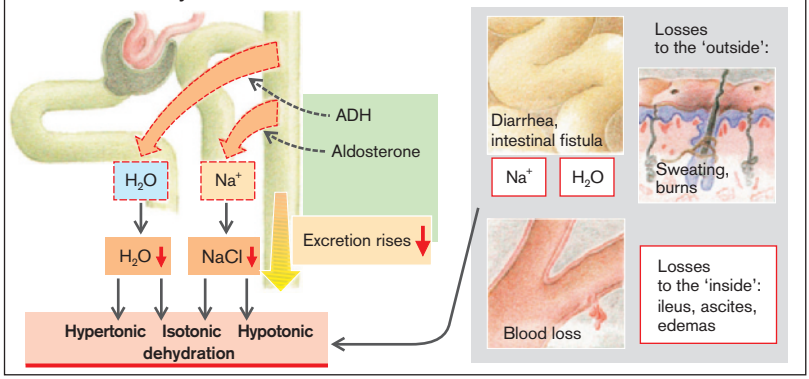
Any *reduction in extracellular space* is especially dangerous because of the decrease in plasma volume (**hypovolemia**). Signs of this are reduced central venous pressure, tachycardia, and a tendency to faint. If there is a drop in blood pressure, renal function is impaired and the release of ADH and 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. 124). On the other hand, the dilution of intravascular proteins promotes filtration in the peripheral capillaries and **edema** formation (→ p. 250) and, in the worst case, pulmonary edema (→ p. 84).

If the *intracellular volume* is enlarged, there is a particular danger that **cerebral edemas** will develop (→ p. 380). 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.

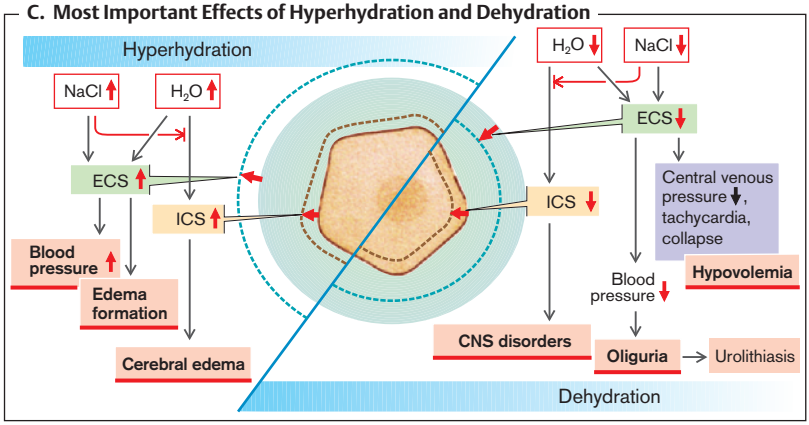
A. Causes of Hyperhydration



B. Causes of Dehydration



C. Most Important Effects of Hyperhydration and Dehydration



Abnormalities of Potassium Balance

An abnormal potassium level results from a disorder of K^+ balance or of its redistribution 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 enters into a compartment, namely plasma, that has a relatively low potassium content, too rapid K^+ administration can lead to dangerous hyperkalemia even at 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. 104 ff.). Renal loss of K^+ occurs, for example, in hyperaldosteronism (→ p. 288) or if there is an increased availability of Na^+ in the distal tubules (→ p. 107 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**). In hyperaldosteronism or at increased delivery of Na^+ to the colon K^+ may be lost in exchange for Na^+. Significant amounts of K^+ may further be lost in sweat.

Even minor **shifts of K^+ between intracellular and extracellular fluid** may 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 may result from cellular energy deficiency (→ **A5**), during severe physical work (muscular K^+ loss), cell death (e.g., in hemolysis, myolysis), and in transfusion of stored blood (loss of K^+ from erythrocytes). Furthermore, hemolysis venopuncture 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) (→ **A6**). 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 cellular uptake of K^+. In insulin deficiency or hypoglycemia (when fasting), the cells lose K^+. The administration of insulin in diabetic hyperglycemia (→ p. 308 ff.) or food intake following starvation may lead to dangerous hypokalemia because the cells will be taking up K^+.

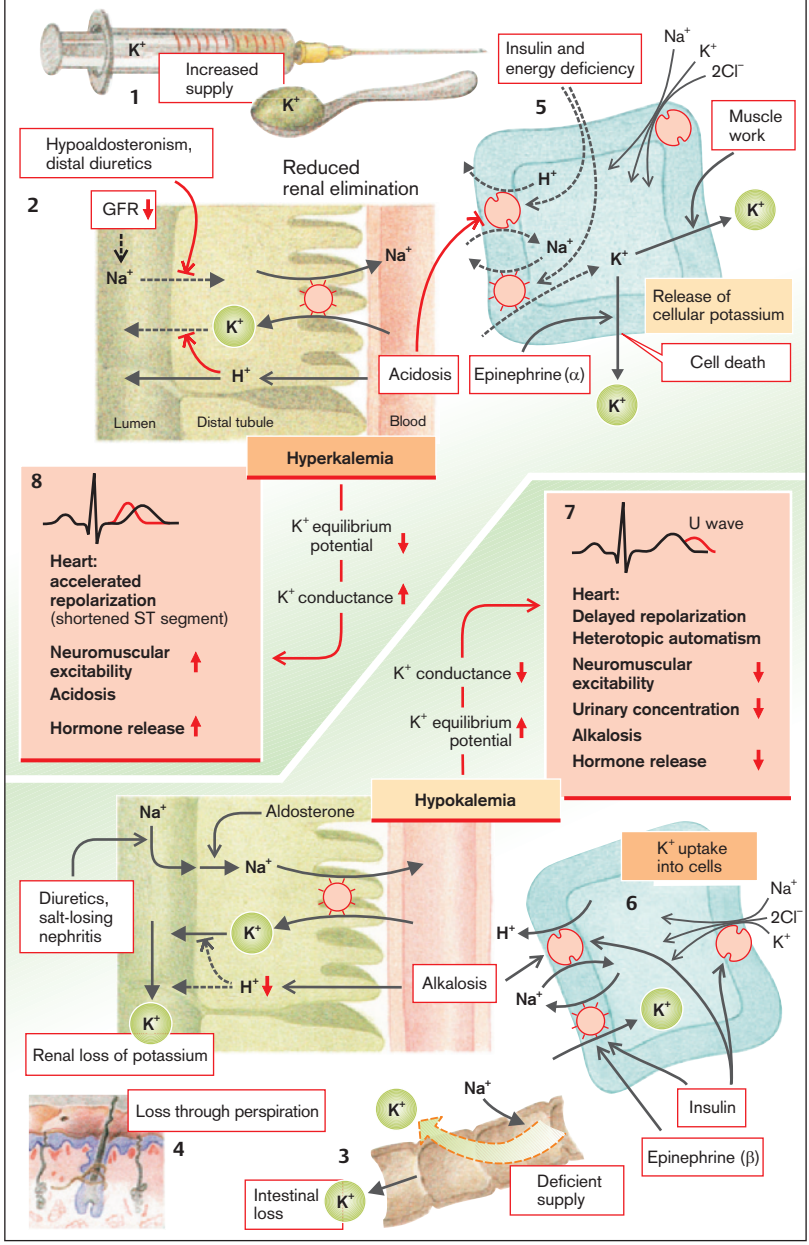
Catecholamines promote the uptake of K^+ by the cells via β-receptors and the cellular release of K^+ from the cells via α-receptors. At massive new formation of cells (e.g., at stimulated erythropoiesis) significant amounts of K^+ are accumulated in the newly formed cells. Moreover, intoxication with K^+ channel blockers (e.g., Ba^{2+}) may lead to hypokalemia.

The **effects** of changed plasma K^+ concentration are mainly due to 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**). Consequences include the life-threatening intestinal paralysis (→ **A7**). Conversely, hyperkalemia can increase the excitability of the nervous system (hyperreflexia), smooth muscles (→ **A7**), and skeletal muscles (→ p. 328).

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. 202 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**).

K^+ deficiency promotes the cellular retention of H^+ and its secretion in the distal tubules. This results in an alkalosis (→ p. 94). Conversely, K^+ excess leads to acidosis (→ p. 96). Hypokalemia also causes polyuria (→ p. 108) 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. 308] and aldosterone [→ p. 288]).

A. Deranged Potassium Metabolism



Abnormalities of Magnesium Balance

Half of the body's magnesium is bound in bone, almost one-half is intracellular. Mg^{2+} concentration in extracellular fluid is relatively low (approx. 1 mmol/L) and the plasma concentration is not a reliable indicator for the Mg^{2+} balance. Mg^{2+} binds to ATP and is essential for the activity of numerous enzymes. It acts in part antagonistically to Ca^{2+}, which it can displace from its binding to proteins. In this way Mg^{2+} can inhibit the release of neurotransmitters and thus inhibit synaptic transmission. Intracellular Mg^{2+} inhibits Ca^{2+}-permeable neuronal NMDA channels. Extracellular Mg^{2+} stimulates the Ca^{2+}-sensing receptor and thus inhibits PTH release.

Magnesium deficiency occurs mainly when there is an inadequate supply or a loss via the gut (*malabsorption*; vomiting, diarrhea, fistulas, vitamin D deficiency, primary infantile hypomagnesemia; → **A1**; see also p. 164 ff.) or the kidneys. In the kidneys, paracellular Mg^{2+} transport requires claudin-16/paracellin-6, and transcellular Mg^{2+} transport requires the Mg^{2+} channel TRPM6 (→ p. 104). The driving force is provided by the cell membrane potential, which depends on the Na^+/K^+ ATPase activity. The paracellular reabsorption is driven by the transepithelial potential that is indirectly created by NaCl reabsorption (→ **A2**). The permeability of the tight junctions is reduced in *hypercalcemia* and *acidosis*. Ca^{2+} further inhibits, via the Ca^{2+} sensing receptor, the Na^+-K^+-2 Cl^- cotransport, causing a decrease in the transepithelial potential and thus of Mg^{2+} reabsorption. Magnesuria may further be the consequence of very rare genetic defects (→ p. 104) such as Bartter's syndrome (Na^+-K^+-2 Cl^- cotransporter, Cl^- channel or luminal K^+ channel), Gitelman's syndrome (NaCl cotransporter), hypomagnesemia with secondary hypocalcemia (TRPM6), autosomal dominant renal hypomagnesemia with hypercalciuria (claudin-16/paracellin-1), and autosomal dominant renal hypomagnesemia with hypocalciuria (Na^+/K^+ ATPase).

The reabsorption of Mg^{2+} is also reduced in *salt-losing nephropathy*, in osmotic diuresis (e.g., glycosuria in diabetes mellitus), and due to the effect of *alcohol* and *loop diuretics*. *Hyperaldosteronism* leads to volume expansion and thus decreases Na^+ and Mg^{2+} reabsorption in the proximal tubules and the ascending limb (→ **A2**). Mg^{2+} may further be lost in sweat or during lactation.

Even when the Mg^{2+} balance is in equilibrium, **shifts of Mg^{2+} between the extracellular and intracellular spaces** or bone can change the plasma concentration of Mg^{2+}. Insulin stimulates the cellular uptake of both K^+ (→ p. 134) and Mg^{2+} (→ **A3, A7**), and loss of Mg^{2+} may occur in diabetes mellitus or prolonged fasting. Substitution of insulin or resumption of food intake may then bring about hypomagnesemia. Alkalosis or correction of acidosis similarly stimulates cellular Mg^{2+} uptake, acidosis stimulates the cellular Mg^{2+} release. Enhanced Mg^{2+} uptake in bone is observed after parathyroidectomy.

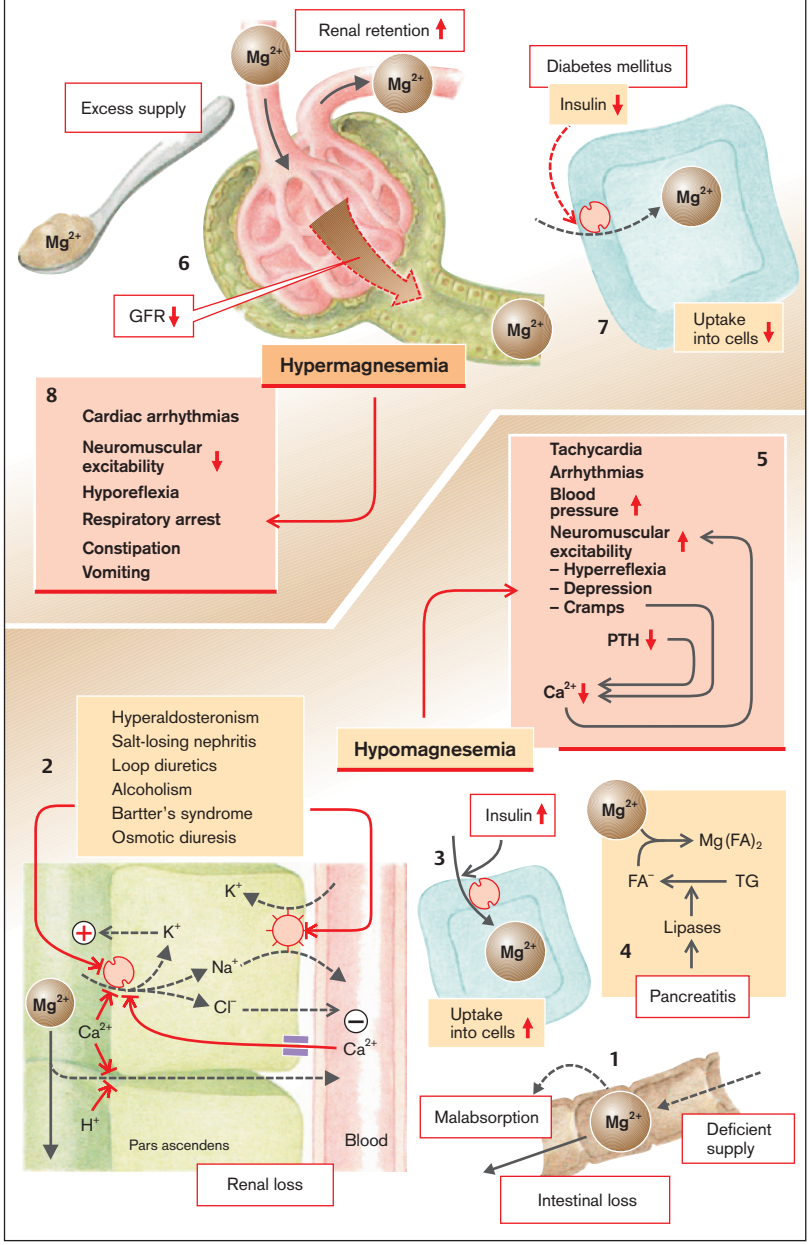
In acute **pancreatitis** (→ **A4**) activated lipases from the damaged pancreas split triglycerides (TGs) in the fat tissue. The liberated fatty acids (FAs) bind Mg^{2+} and thus lower the plasma Mg^{2+} concentration.

The **effects of Mg^{2+} deficiency** include an increased neuromuscular excitability, hyperreflexia, cramps, depression, and psychosis (→ **A5**). The cramps sometimes resemble those after damage to the basal ganglia (→ p. 334 ff.). Cardiovascular signs include tachycardia and arrhythmias, even ventricular fibrillation, and a rise in blood pressure. These symptoms are accentuated by hypocalcemia. Usually Mg^{2+} deficiency coexists with K^+ deficiency (common causes; → p. 134) so that the symptoms of hypokalemia are accentuated.

Mg^{2+} excess is caused by *renal failure* (→ **A6**). If the glomerular filtration rate (GFR) drops below ca. 30 mL/min a decrease of filtration can no longer be compensated by decreased renal tubular reabsorption. The renal Mg^{2+} reabsorption is enhanced in patients with a genetic defect of the Ca^{2+}-sensing receptor (familial hypocalciuric hypercalcemia). Hypermagnesemia (without excess Mg^{2+}) can also occur in *diabetes mellitus* (→ **A7**). Lastly, *excessive supply of Mg^{2+}* (Mg^{2+}-containing infusions, parenteral feeding, or therapeutic Mg^{2+} administration to reduce neuromuscular excitability) can cause hypermagnesemia.

The **effects of Mg^{2+} 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



Abnormalities of Calcium Balance

Ca^{2+} regulates as "intracellular transmitter" (→ p. 6 ff) the electromechanical coupling, the release of neurotransmitters (synaptic transmitters) and hormones, the secretory activity of exocrine glands as well as the activity of a number of enzymes (e.g., glycogenolysis, phospholipase A, adenylylcyclase, phosphodiesterases) and of several ion channels, such as K^+ channels in the heart. Extracellular Ca^{2+} stabilizes Na^+ channels, reduces the permeability of the basement membranes and the tight junctions, plays a role in blood clotting, and stimulates the Ca^{2+} sensing receptor, which governs a variety of functions including PTH release, activity of the renal tubular Na^+–K^+–2 Cl^- cotransporter, gastric acid secretion, and cell proliferation.

The **regulation of the extracellular Ca^{2+} concentration** is, in the first instance, the task of PTH. It is released in hypocalcemia (and hypomagnesemia) and its action increases the plasma concentration of Ca^{2+} (→ **A1, A2**). PTH stimulates the mobilization of calcium phosphate from bone, decreases the plasma concentration of phosphate and HCO_3^- by inhibiting their renal tubular reabsorption, and stimulates the formation of calcitriol, which promotes the enteric absorption of Ca^{2+} and phosphate.

Hypocalcemia (→ **A1**) 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 (→ p. 142). In *renal failure* phosphate elimination by the kidney is reduced, the plasma phosphate level rises, and calcium phosphate is deposited in the body (→ p. 120). One of the consequences is hypocalcemia. *Mg^{2+} deficiency* decreases the PTH release and may thus similarly lead to hypocalcemia. A rare genetic defect of claudin-16/paracellin-1 impedes the paracellular Ca^{2+} reabsorption (→ p. 106) and thus similarly causes hypocalcemia.

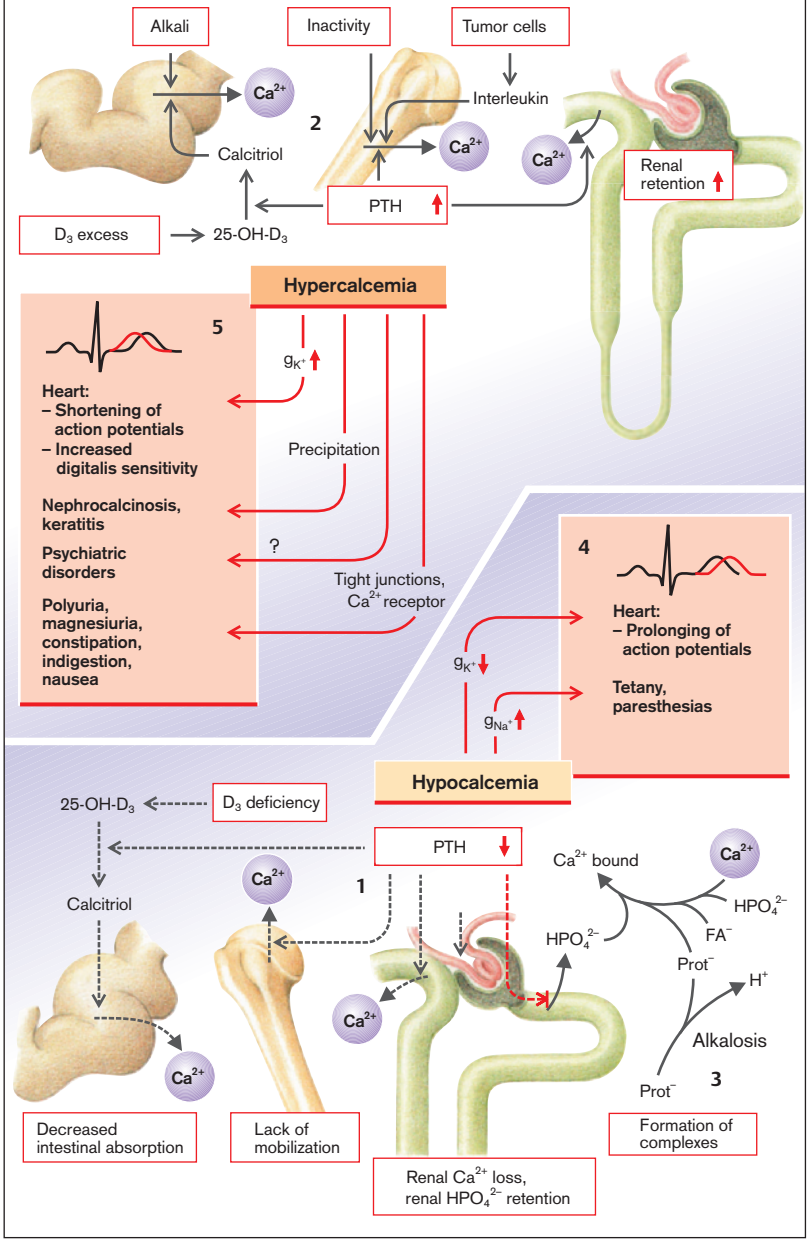
Even when the total Ca^{2+} concentration in blood is normal, the concentration of the physiologically relevant ionized Ca^{2+} may be reduced because of increased *formation of complexes* with proteins (in alkalosis), bicarbonate (in metabolic alkalosis), phosphate (in renal failure, see above), and fatty acids (in acute pancreatitis; → p. 136, 172) (→ **A3**).

Hypercalcemia (→ **A2**) occurs in *hyperparathyroidism* and *vitamin D excess*. Malignant *tumors* may, even in the absence of skeletal metastases, produce bone-mobilizing hormones such as PTHrP (PTH related protein) or osteoclast-activating factor (OAF). Bone minerals are mobilized on acute *immobilization* associated with atrophy of inactivity. Increased (partially paracellular) enteric Ca^{2+} absorption may result from an *excessive supply* of Ca^{2+} and of alkaline anions (milk-alkali syndrome). Several rare genetic defects lead to disorders of bone metabolism and hypercalcemia (→ p. 132).

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 (→ **A4**). The increased excitability results from a lowered threshold of Na^+ channels in hypocalcemia. In severe cases epileptic seizures may occur (→ p. 360). Hypocalcemia delays the activation of repolarizing cardiac K^+ channels and thus lengthens the cardiac action potential, which is apparent from a prolongation of the ST segment and QT interval in the ECG.

The **effects of hypercalcemia** (the condition is often asymptomatic) may include *gastrointestinal symptoms* (activation of 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* (→ **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 (→ p. 196).

A. Deranged Calcium Metabolism



Abnormalities of Phosphate Balance

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

PTH and calcitriol are critically important 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 (relationship between enteric absorption and renal excretion) or by changes in distribution within the body (intracellular and extracellular spaces; bone).

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 drugs (→ **A1**). *Renal loss* of phosphate occurs in hyperparathyroidism, vitamin D deficiency, certain transport defects in the proximal tubules (phosphate diabetes, Fanconi's syndrome; → p. 104), and, to a lesser extent, in salt-losing nephritis, in expansion of the extracellular space, during diuretic treatment, in osmotic diuresis (e.g., glucosuria of diabetes mellitus) and in glucocorticoid excess. Some tumors produce phosphatonins with phosphaturic action, such as PTHrP (PTH related peptide, → p. 104).

Phosphate excess can be caused by excessive oral phosphate intake, vitamin D intoxication (→ p. 142), lack of PTH (hypoparathyroidism), decreased efficacy of PTH (pseudohypoparathyroidism), or renal failure (→ **A2**).

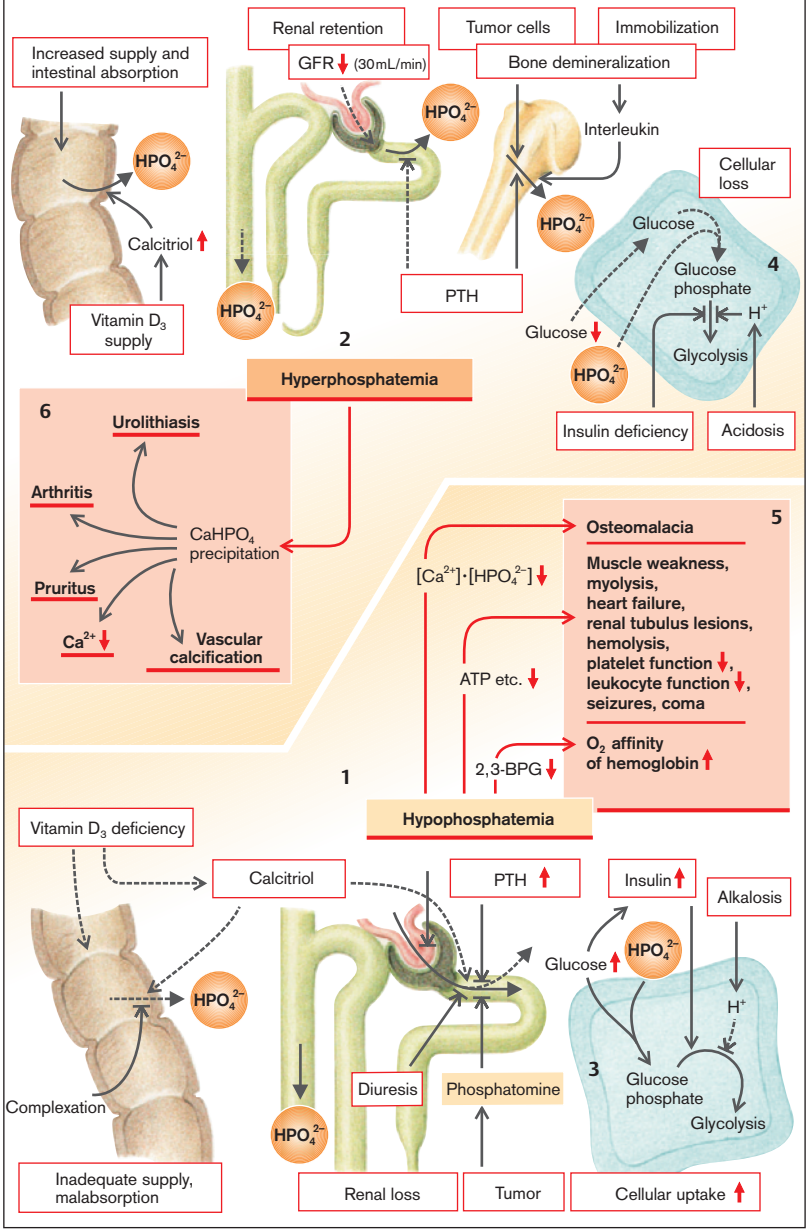
The phosphate concentration is markedly higher in the cells than in the extracellular space (see also potassium; → p. 134). For this reason **shifts between intracellular and extracellular space** play an important role in determining the plasma phosphate level. Cellular phosphate uptake occurs when phosphate is utilized for metabolism (e.g., for the formation of glucose phosphate from free glucose). A dramatically increased cellular uptake occurs after food intake following starvation and in 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, such as severe hemolytic anemia (→ **A4**).

Hyperphosphatemia may 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. 142). Conversely, excessive bone mineralization (e.g., following parathyroidectomy or treatment of rickets with vitamin D) may result in hypophosphatemia.

Effects of hypophosphatemia include myopathy (muscular weakness, myolysis), heart failure, respiratory failure, hemolysis, dysfunction of platelets and leukocytes, renal tubular lesions, and nervous system dysfunction (e.g., weakness, sensoric and motoric disorders, confusion, coma). 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. 142).

Effects of hyperphosphatemia include precipitation of calcium phosphate with the development of soft-tissue calcifications in tissues of low metabolic turnover (e.g., mucous bursae, joints, skin). Corresponding symptoms are itching (pruritus), joint pain (arthritis), etc. Vascular Ca^{2+} precipitations lead to vascular calcification. The plasma Ca^{2+} concentration falls and the release of PTH is stimulated. In renal failure a vicious circle develops (→ p. 120 ff.).

A. Deranged Phosphate Metabolism



Pathophysiology of Bone

Bone consists of connective tissue or bone matrix (including type I collagen [> 90%], thrombospondin, osteopontin, fibronektin, osteocalcin, proteoglykanes), minerals (alkaline salts of Ca^{2+}, phosphate, Na^+, CO_3^{2-}, Mg^{2+}, K^+, and F^-) and cells (osteocytes, osteoblasts, and osteoclasts).

Osteocytes are mechanosensitive and adjust the bone architecture to the mechanical requirements by influencing osteoblasts and osteoclasts.

Osteoblasts develop under the influence of BMPs (bone morphogenetic proteins) from mesenchymal progenitor cells. BMPs stimulate through the transcription factor CBFA1 (cor binding factor A1) the expression of, among others, type I collagen, osteocalcin, osteopontin, and RANKL (receptor activator of NFκB ligand). Osteoblasts are stimulated by growth factors (TGF-β, FGF, PDGF, IGF) and form alkaline phosphatase, which fosters the mineralization by cleaving pyrophosphate. The plasma concentration of alkaline phosphatase reflects the osteoblast activity (→ **A**).

The osteoblasts release RANKL, a mediator that stimulates the formation of **osteoclasts** from hematopoietic progenitor cells. The development of osteoclasts is inhibited by RANKL-binding osteoprotegerin and is fostered by the antiapoptotic M-CSF (macrophage colony-stimulating factor). The osteoclasts are inhibited by calcitonin. Osteoclasts degrade bone by proteolysis (proteinases such as kathepsin K) and by H^+ secretion (H^+ ATPase, carbonic anhydrase II [Ca II], Cl^- channel). The osteoclast activity is apparent from the plasma concentrations of type I collagen degradation products (peptides).

In children bone develops from cartilage, which is generated by **chondrocytes**. Those cells are under the control of parathyroid hormone (PTH), PTHrP (PTH-related peptide), FGF (fibroblast growth factor), growth hormone, glucocorticoids, and estrogens. High phosphate concentrations stimulate the apoptosis of chondrocytes.

Bone is constantly remodeled to meet the mechanical requirements. Following bone fractures, infections, and ischemia, dead bone is degraded, the blood supply improved by angiogenesis, and new bone is synthesized. Unstable links stimulate the formation of connective tissue and of cartilage.

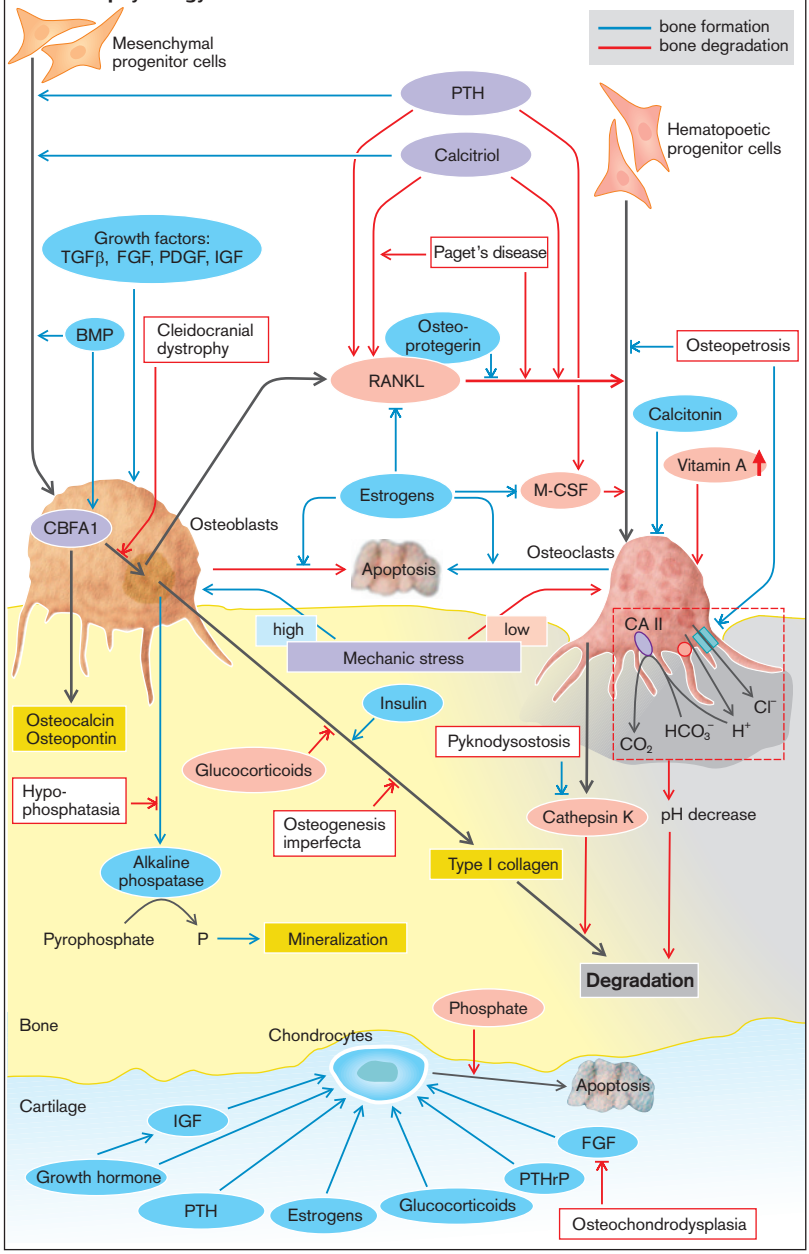
The **regulation of bone structure and mineralization** is a function of *mechanical use*, plasma Ca^{2+} and phosphate concentrations as well as of PTH and calcitriol.

The release of **PTH** is stimulated by hypocalcemia (→ p. 138) and inhibited by calcitriol (→ **B**). PTH stimulates the remodeling of bone and increases the number of osteoblasts and (via RANKL and M-CSF) of osteoclasts. Intermittent administration of PTH stimulates bone formation; continuous increase of PTH leads to bone resorption.

PTH further influences bone metabolism by stimulation of **calcitriol** ($1,25(OH)_2D_3$) formation (→ **A 1**, → p. 138): Exposure of the skin to UVB radiation stimulates the generation of vitamin D_3 from 7-dehydrocholesterin. Vitamin D_3 is converted to $25(OH)D_3$ in the liver and by the enzyme 1α-hydroxylase to the active hormone $1,25(OH)_2D_3$ mainly in the kidney. The enzyme is stimulated by PTH and growth hormone and inhibited by excess of Ca^{2+} and phosphate, by FGF23 and by KLOTHO (→ p. 100). $1,25(OH)_2D_3$ is further produced in macrophages and lymphocytes, which synthesize the hormone irrespective of PTH and calcium phosphate metabolism. Stimulation of macrophages (e.g., at sarcoidosis and tuberculosis) or lymphocytes (e.g., lymphomas) thus leads to inadequate formation of $1,25(OH)_2D_3$. A vitamin D-24-hydroxylase inactivates $1,25(OH)_2D_3$. Calcitriol stimulates via the vitamin D receptor (VDR) the formation of bone matrix proteins, osteocalcin, osteopontin, and RANKL. Calcitriol stimulates via RANKL and M-CSF the formation of mature osteoclasts. Calcitriol thus stimulates both bone formation and bone resorption. The VDR is stimulated not only by $1,25(OH)_2D_3$ but also by excessive $25(OH)D_3$ concentrations.

Glucocorticoids inhibit the formation and action of calcitriol and thus foster bone resorption. **Insulin** stimulates the formation of bone matrix. **Estrogens** (mainly estradiol) inhibit the apoptosis of osteoblasts and stimulate the apoptosis of osteoclasts. They inhibit via RANKL and M-CSF the formation of mature osteoclasts and thus the bone resorption. **Thyroid hormones** increase the bone remodeling. Bone

A. Pathophysiology of Bone – Local Mechanisms



resorption is stimulated by excessive concentrations of **vitamin A**.

Disorders of bone metabolism may affect the bone matrix or the mineralization of bone.

In **Paget's** disease the overactivity of osteoclasts with subsequent stimulation of osteoblasts leads to enhanced bone turnover with formation of structurally disorganized bone, which is particularly susceptible to deformities and fractures. Putative causes include enhanced sensitivity of osteoclast progenitor cells to 1,25 $(OH)_2 D_3$ or enhanced formation or activity of RANKL. Mutations of RANK lead to a similar clinical condition. Juvenile Paget's disease results from a genetic defect of osteoprotegrin.

The very common **osteoporosis** results from a longstanding disequilibrium between bone formation and bone resorption, which decreases the bone density. Causes include glucocorticoid excess, estrogen deficiency (postmenopausal), insulin deficiency (diabetes mellitus), calcium-deficient diet, smoking, and inactivity (rigid cast, tetraplegia, microgravity). However, most often the cause remains unknown (primary osteoporosis). Effects of osteoporosis include skeletal pain even at rest and bone fractures (e.g., spine, lower arms, femoral neck). Hypercalcemia may be present in extreme cases. Depending on its cause, 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. 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). Hereby hypophosphatemia fosters the survival of chondrocytes in the growth plates. 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 dietary depletion or intestinal malabsorption of vitamin D coinciding with lack of ultraviolet light in liver insufficiency, estrogen deficiency (postmenopausal), or in chronic renal failure (→ p. 120 ff.). Even without calcitriol deficiency, hypophosphatemia (phosphate diabetes, Fanconi's syndrome; → p. 104, 120 ff.) or chronic renal tubular acidosis can result in osteomalacia.

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 (craniotabes). **Osteomalacia** leads to bone pain (pain on movement), translucent bands of demineralization in bone (pseudofractures or Looser's zones), and muscular weakness (Ca^{2+} deficiency).

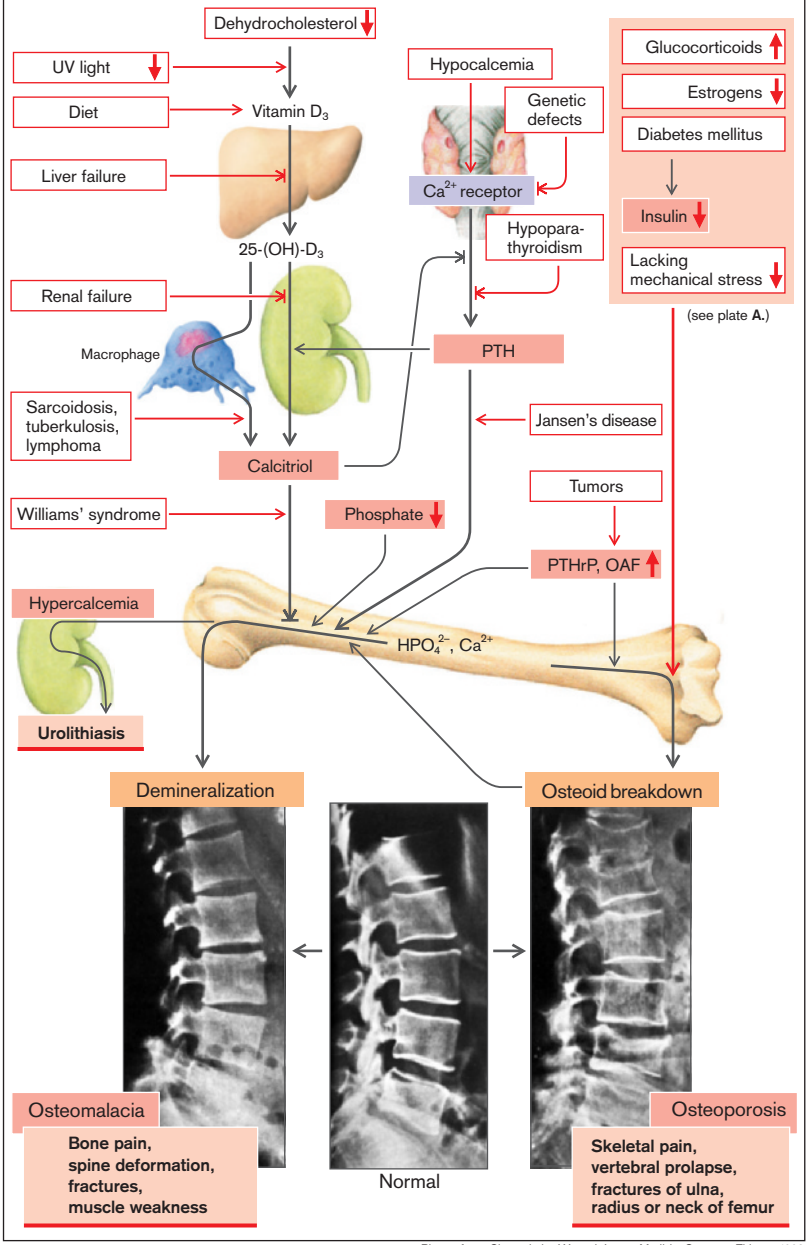
The demineralization of bone may increase renal Ca^{2+} and phosphate excretion and thus result in urolithiasis. Bone resorption may further be stimulated by **tumors** (formation of PTHrP and osteoclast-activating factor OAF). In primary **hyperparathyroidism** (by uncontrolled proliferation of PTH-producing cells; → p. 18) normal bone is replaced by fibrous tissue.

Disorders of bone formation and resorption may result from rare **genetic defects**, as in mutations of type I collagen (*osteogenesis imperfecta*) or inactivating mutations of CBFA1 (*cleidocranial dysplasia*). A defect of the alkaline phosphatase (*hypophosphatasia*) impairs the bone mineralization. The osteoclast function is compromised by defects of the H^+ pump subunit TC1RG1, the Cl^- channel ClCN7, the carbonic anhydrase II, or the RANK (*osteopetrosis*). Bone resorption is further impaired at a genetic defect of the protease cathepsin K (*pyknodysostosis*, the likely disease of Toulouse-Lautrec).

Genetic defects of the Ca^{2+}-sensing receptor (CaSR) lead to the *familiary benign hypercalcemia*, activating mutations of the PTH receptor to *Jansen's disease* (hypercalcemia, hypophosphatemia, skeletal malformations, dwarfism). Genetic defects affecting PTH release (hypoparathyroidism) or the PTH effect (pseudohypoparathyroidism, e.g., by a defective G protein) similarly lead to hypercalcemia and partially to bone malformations. Hereditary PTH deficiency may further result in calcification and subsequent damage of basal ganglia. A genetic defect of the 1α-hydroxylase leads to *pseudo-vitamin D-deficiency rickets*, a hereditary increase of calcitriol sensitivity to the hypercalcemia of *Williams' syndrome*.

A wide variety of distinct, rare, genetic defects (e.g., of FGF3) lead to defective cartilage formation (*osteochondrodysplasia*).

B. Pathophysiology of Bone



Photos from: Siegenthaler, W. et al. Innere Medizin. Stuttgart: Thieme; 1992

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 cobalamines (vitamin B_{12}).

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 HCO_3^- 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.

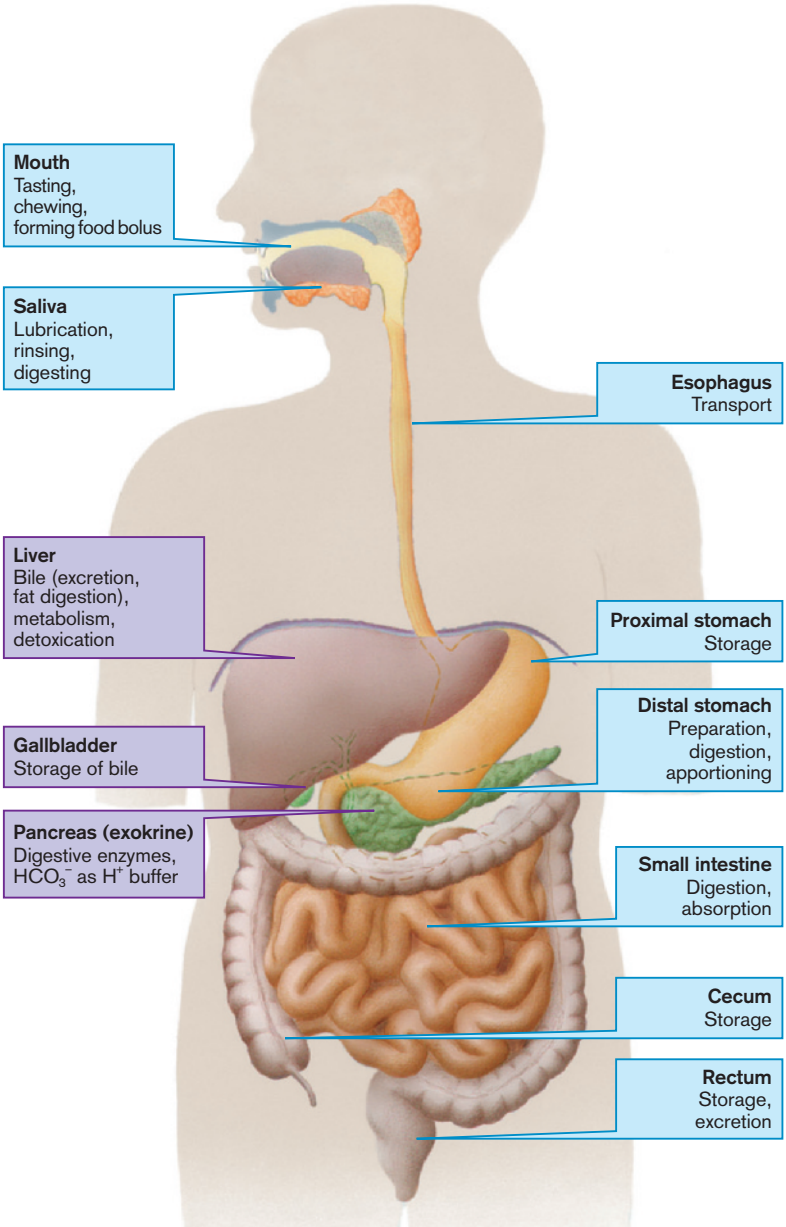
Together with the bile secreted by the **liver,** *excretory products* (e.g., bilirubin) reach the stool. The liver has numerous additional metabolic functions: it is the obligatory intermediate station for almost all substances absorbed from the small intestine, and it is able to *detoxify* numerous 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* (intestinal flora) 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 m^2) 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 its 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. The intestinal defense mechanisms recognize the physiological intestinal flora, which are thus protected against the immune response. **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



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 in 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 (→ **A**).

Esophageal motility, for example, the progression of the peristaltic wave, is usually tested by **pressure measurements** in the various segments of the esophagus (→ **A 1, 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 (→ **A 3**), 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 (→ **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, $PGF_{2\alpha}$), 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 phrenicoesophageal ligament (→ **E 1**) 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*.

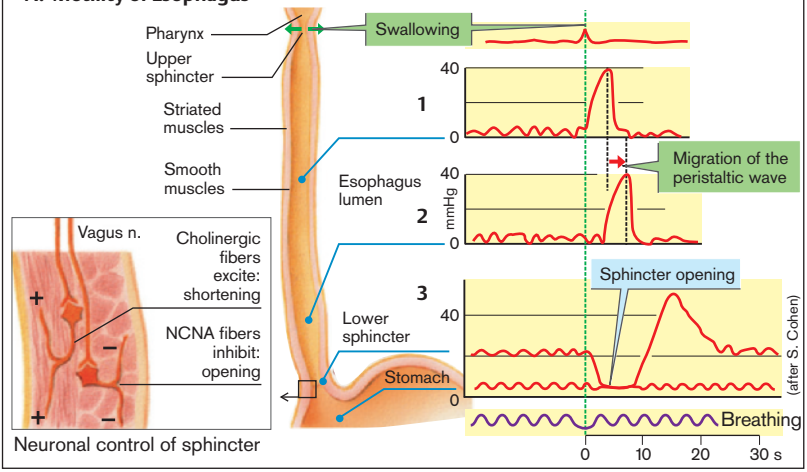
Factors that lower sphincter pressure will **promote reflux**. Among these are vasoactive intestinal polypeptide (VIP) and ATP, the transmitters of the inhibitory *NCNA neurones* as well as dopamine and β-adrenergic agonists, *hormones* such as secretin, cholecystokinine (CCK), progesterone, and **g**lucose–dependent **i**nsulinotropic **p**eptide (GIP = formerly: gastric inhibitory polypeptide), *paracrine substances* (NO, PGI_2, PGE_2), a progesterone effect during pregnancy, food with a high fat content, and many others.

Sporadic reflux 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; → **B 5**, right), or during **transient openings of the sphincter** (→ **B 5**, 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 (→ **B 4**).

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

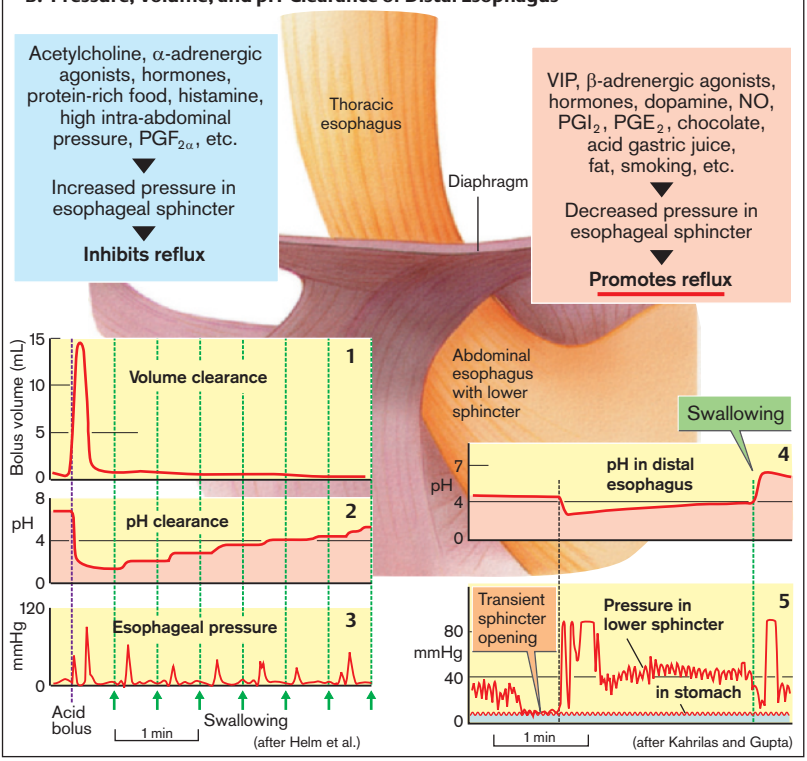
- **Volume clearance**, i.e. the rapid replacement of reflux volume into the stomach by the esophageal peristalsis reflex. Reflux volume of 15 mL, except for a small residual amount, normally remains in the esophagus for only five to 10 seconds (→ **B 1**).
- **pH clearance**. Residual gastric juice, left behind by the volume clearance, has an unchanged, low pH. It only rises, step by step (→ **B 2**), with each act of swallowing (→ **B 3**), i.e., the *swallowed saliva buffers* the residual 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

A. Motility of Esophagus



Neuronal control of sphincter

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



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. 156), 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 HCO_3^- 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 esophageal 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 enormous *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 dysphagia (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).

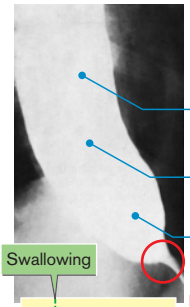
Hypomotility of the esophagus is caused by factors that are the opposite of those described above. In **scleroderma** (→ **D**), an autoimmune disease, hypomotility in its early stages is due to neuronal defects that later result in atrophy of the smooth muscles of the esophagus, so that peristalsis in the distal portion ultimately ceases altogether. Contrary to achalasia, the *lower sphincter pressure is reduced*, so that gastroesophageal reflux disease develops.

Gastroesophageal reflux disease (→ **E**). Reflux 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 CO_2);
- decreased volume clearance (abnormal distal esophageal peristalsis);
- slowed pH clearance, for example, due to decreased salivary flow (sleep, chronic saliva deficiency [xerostomia]), or decreased 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 mechanism of sphincter closure, increased intra-abdominal pressure, is absent;
- direct irritation and damage to the esophageal mucosa, for example, by citrus fruits, tomato-based foods, hot spices, high-proof alcohol, and nonsteroid anti-inflammatory drugs (NSAIDs; → p. 154).

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



Swallowing

mmHg 40 0 40 0 40 0

20 s

Swallowing

Distal esophagus

mmHg 40 0

Lower sphincter

80

Stomach

40 0

20 s

Excitation of the NCNA neurons

Sphincter pressure too high

Weight loss
Trouble swallowing
Pain

Esophagitis

Pneumonia

D. Scleroderma

Swallowing

mmHg 40 0 40 0 40 0

20 s

Neuronal defects

Muscle atrophia

no peristalsis in smooth muscles

Hypomotility

Sphincter pressure too low

Gastroesophageal reflux disease

E. Gastroesophageal Reflux Disease

Transient sphincter opening (air, CO_2)

Saliva production (in sleep, xerostomia)

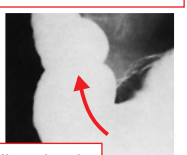
Buffering capacity of saliva (e.g. through smoking)

Sphincter pressure

Abnormal peristalsis

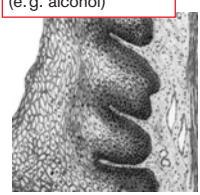
Volume clearance

pH clearance



Hiatus hernia

Defective mucosal protective mechanism (e.g. alcohol)



Phrenico-esophageal ligament

Diaphragm

Angle of His

Esophago-gastric border

Reflux

Reflux esophagitis

Epithelial metaplasia

Carcinoma

Photo in C.: Thurn P., et al. Einführung in die radiologische Diagnostik. 10th ed. Stuttgart: Thieme; 1998
Photo in E.: Treichel J. Doppelkontrastuntersuchung des Magens. 2nd ed. Stuttgart: Thieme; 1990

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 **chemosensors** of the area postrema on the bottom of the 4th ventricle (*chemosensor 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. 168);
- by *overdistension* and *inflammation* of the peritoneum, biliary tract, pancreas, and intestine.

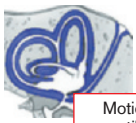
Finally, visceral afferents from the **heart** may also cause nausea and vomiting, for example, in coronary ischemia. Nausea and vomiting are common during the first trimester of **pregnancy** (*vomitus matutinus*). Exceptional disturbances (see below) due to the vomiting may occur (*hyperemesis gravidarum*). **Psychogenic vomiting** occurs mostly in (nonpregnant) 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. 30) 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 H_2O leads to *hyponatremia* which is exacerbated by increased excretion of $NaHCO_3$. The latter is a response to a *nonrespiratory alkalosis*. This situation results from the parietal cells of the stomach passing one HCO_3^- 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 HCO_3^- to buffer them in the duodenum, HCO_3^- 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^+ [→ pp. 106 and 132 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)

'Vomiting center' (reticular formation)

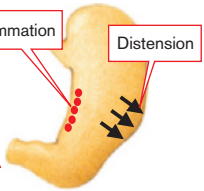
Motion sickness, vestibular disease

Intracranial pressure

Exposure to radiation

Psychogenic

Pregnancy



Inflammation

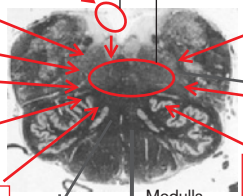
Distension

Delayed gastric emptying

'Heavy' meal

Intestinal obstruction

Inflammation and overtension of peritoneum, bile passages, pancreas, intestine, etc.



Medulla oblongata

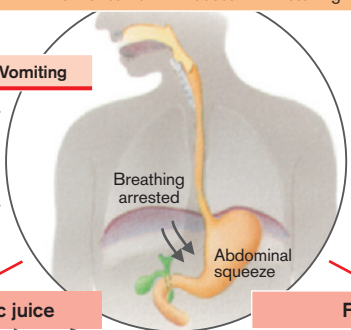
ADH (see below)

Warning signs

Outbreak of sweat — Wide pupils — Pallor

Flow of saliva — Nausea — Retching

Vomiting



Breathing arrested

Abdominal squeeze

HCl → Damage of teeth

Aspiration of HCl, pepsin → Pneumonia

Gastric rupture

Mallory-Weiss syndrome

Esophageal rupture

Loss of gastric juice

Food uptake ↓

Chronic

Loss of K^+ — **Loss of Na^+** — **Loss of H^+**

Hypovolemia → Renin → Angiotensin II → Aldosterone → K^+ excretion ↑ → Hypokalemia

ADH ↑ (see above) → H_2O excretion ↓ → $[Na^+]$ in plasma ↓ → Hyponatremia

$[HCO_3^-]$ in blood ↑ → $NaHCO_3$ excretion ↑ → Compensatory → Nonresp. alkalosis

Malnutrition

Gastritis (Gastropathy)

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. 158;
- 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. 158), with the risk of massive *gastric bleeding* or *perforation* of the stomach wall (→**A1**).

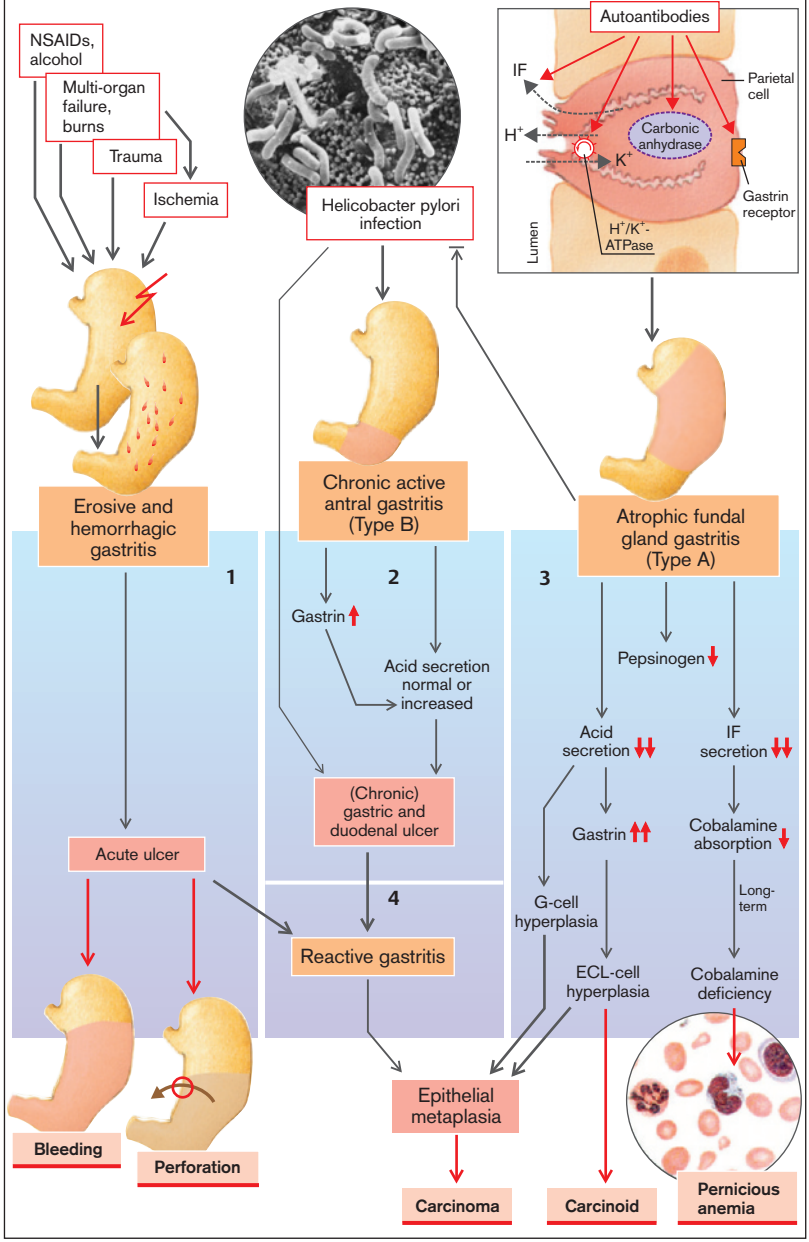
Nonerosive, chronic active gastritis (type B; →**A2**) is usually restricted to the *antrum*. It has become increasingly clear in the last decade that its determining cause is a bacterial colonization of the antrum with ***Helicobacter pylori***, which can be effectively treated with antibiotics (see also ulcer; →p. 156 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 further 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 less common 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, carboanhydrase, 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–cobalamin complexes by cells in the ileum, ultimately resulting in cobalamine deficiency with **pernicious anemia** (→blood, p. 38). 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 gastin. These cells carry gastrin receptors and are responsible for producing histamine in the gastric wall. This ECL cell hyperplasia can sometimes progress to a **carcinoid**. 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.).

A. Gastritis



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** (→ **A 1**) is achieved through neural, endocrine, paracrine, and autocrine mechanisms. **Stimulation** is provided by *acetylcholine*, the postganglionic transmitter of vagal parasympathetic fibers (muscarinic M_1 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, H_2 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 E_2 and I_2), transforming growth factor α (TGF-α) and adenosine (all paracrines and autocrines). The inhibition of gastrin secretion by a high concentration of H^+ ions in the gastric lumen is also an important regulatory mechanism (negative feedback; → **A 1**, 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 (→ **A 2**):

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 HCO_3^-** 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 HCO_3^- 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 HCO_3^- 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.

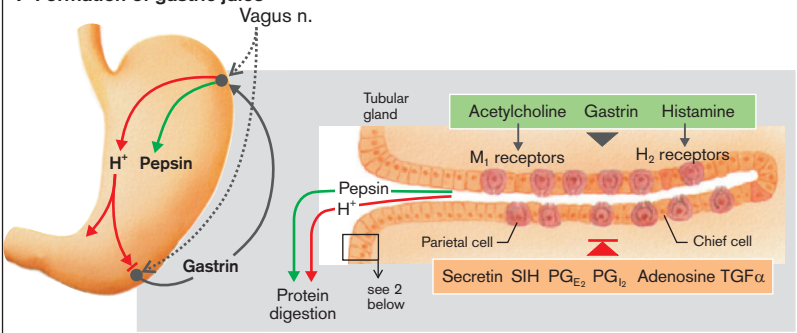
◆ If ultimately the basement membrane is also destroyed, **acute wound healing processes** are initiated: attraction of leukocytes and macrophages; phagocytosis of necrotic cell residua; revascularization (angiogenesis); regeneration of extracellular matrix as well as, after repair of the basement membrane, 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 (→ **A 3** and **B**, top). Gastric and duodenal ulcers may thus have quite different **causes**.

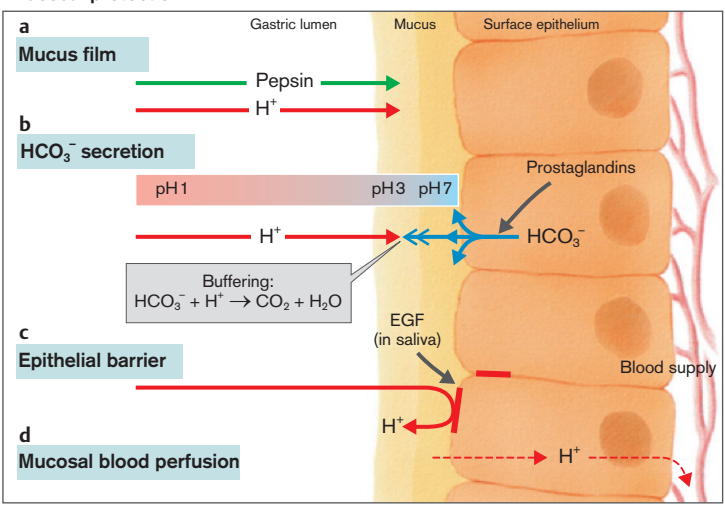
Infection with *Helicobacter pylori* (*H. pylori*) is the *most common cause* of ulcer. As a consequence, administration of antibiotics has been shown to be the most efficacious treatment in most ulcer patients not receiving nonsteroidal

A. Gastric Juice Secretion, Mucosal Protection and Risk of Ulcer

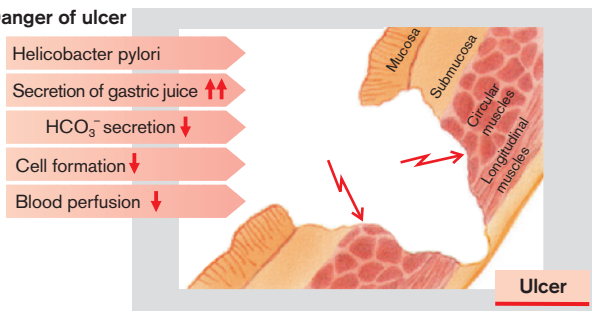
1 Formation of gastric juice



2 Mucosal protection



3 Danger of ulcer



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 CO_2 and NH_3, and HCO_3^- and NH_4^+, 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. 154). 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 (→ **A, 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 nonsteroidal anti-inflammatory drugs (NSAIDs; → p. 154), 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 HCO_3^- secretion*, on the one hand (weakened mucosal protection; → **B**, top left), and *stops inhibition of acid secretion*, on the other (→ **A 1**). In addition, these drugs damage the mucosa locally by non-ionic diffusion into the mucosal cells (pH of gastric juice ≪ pK_a' 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*.

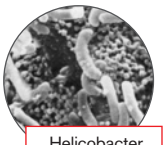
Often **psychogenic factors** favor ulcer development. Strong emotional stress without an outward "safety valve" (high cortisol levels) and/or disturbed ability to cope with "normal" stress, for example, in one's job, are the usual causes. Psychogenically raised secretion of gastric acid and pepsinogen, 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 secretion by blocking H^+/K^+ATPase (→ p. 155, right above). 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.

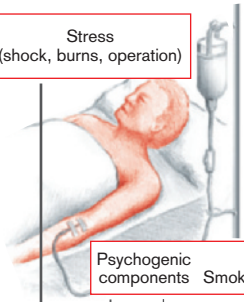
B. Ulcer Formation



Helicobacter pylori infection

Indomethacin, diclofenac, acetylsalicylic acid, etc.

Stress (shock, burns, operation)



Smoking

Psychogenic components

Smoking

Gastrinoma, etc.

Prostaglandin synthesis ↓

H^+ secretion ↑

Pepsinogen secretion ↑

Gastritis

Blood perfusion ↓

Mucosal protection ↓

Bile salts, pancreatic enzymes

O_2 radicals

Smoking

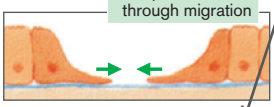
Barrier function disturbed

Chemical aggression ↑

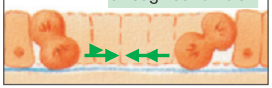
Epithelial damage

Smoking

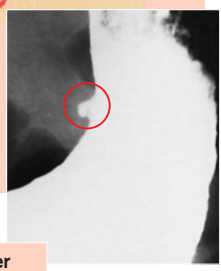
Rapid restitution through migration



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

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). Nonselective 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 reflex 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 after VT (no vagovagal reflex) and in gastric resection after Billroth II or Roux, in which chyme circumvents the duodenal chemosensors.

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 hemoglobin in food or for absorption of fat including the fat-soluble vitamin D (see below).

◆ High concentrations of carbohydrate and especially sugar (e.g., marmalade) 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**.

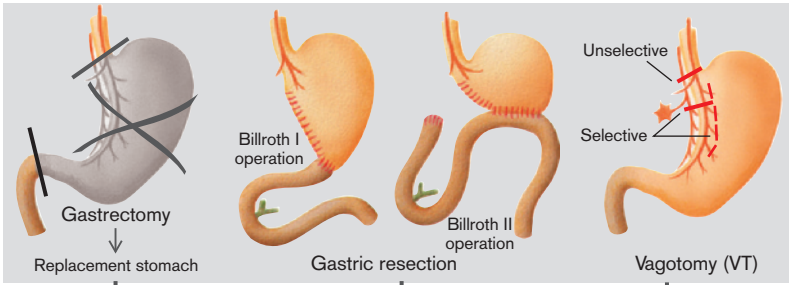
◆ Rapid gastric emptying also exceeds the digestive capacity of the upper small intestine. Moreover, after VT pancreatic secretion is decreased to half, and in Billroth II the upper duodenum does not receive the flow of chyme, so that there is no physiological stimulus for secretin and CCK secretions. As a result, the *distal small intestine* takes part in the digestion and absorption of nutrients. Its chemosensors 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* (→ pp. 38 and 164).

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 anemia** (→ p. 42).

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 its normal value, *cobalamin absorption* is affected so that (long-term) **cobalamin deficiency** can arise and the anemia is further aggravated (→ p. 38). **Osteomalacia** will ultimately result from *Ca^{2+}* and *vitamin D deficiency* (→ p. 144).

A. Disorders After Stomach Surgery



Gastric volume ↓
Accommodation reflex ↓
Emptying ↑
Preparation of chyme ↓
Pancreatic secretion ↓
Gastric secretion ↓

Sugar
Volume
Hypertonic chyme
Nutrients
Meat

Wall distension ↑
Glucose absorption ↑
Intestinal distension ↑
Water secretion
Digestion moved distally
Fe^{II} absorption
Fe^{II} salts ↓

Hypovolemia
Dilution of enzymes and bile salts
Heme-Fe availability ↓

Hyperglycemia
Vasomotor reactions
Diarrhea

Premature satiety ↑
Fat absorption ↓
IF deficiency

Reactive hypoglycemia
Fe deficiency

Food intake ↓
Vitamin D deficiency
Cobalamine deficiency
Ca^{2+} ↓

30–60 min after meal
Vomiting, pain
Flushing, tachycardia
Early dumping syndrome

90–180 min after meal: clouding of consciousness
Late dumping syndrome

Weight loss
Osteomalacia
Anemia

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 not or only slowly absorbable even normally, or in **malabsorption** (→ p. 164 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. (**H_2O 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 H_2O, 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 coloscopy).

In **malabsorption of carbohydrates** (→**B**, right and p. 164 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**, middle). 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.

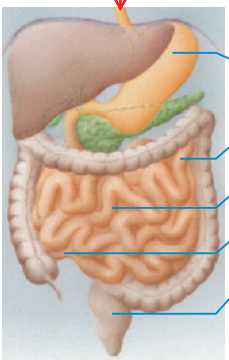
Secretory diarrhea (in the narrow sense) occurs when Cl^- secretion of the small intestinal mucosa is activated (→**C**). Within the mucosal cells Cl^- is secondarily actively enriched by a basolateral Na^+-K^+-2 Cl^- symport carrier and is secreted via *luminal Cl^- channels*. These open more frequently 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 HCO_3^- (*hypovolemic shock*, *hypokalemia*, *nonrespiratory acidosis*).

Overproduction of VIP (**v**asoactive **i**ntestinal **p**eptide) 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 H_2O* 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 H_2O



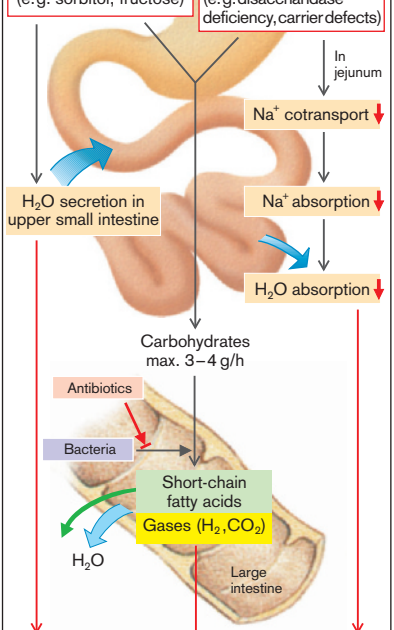
H_2O (mL)	PEG (mmol)	[PEG] (mmol/L)	$[Na^+]+[K^+]$ (mmol/L)	[Anions] (mmol/L)	Osmol. (mosm/L)	
250	150	600	~0	~0	600	Secretion of H_2O+Na^+ (+anions+K^+)
750	150	200	45	45	290	
1000	150	150	70	70	290	
750	150	200	45	45	290	Absorption of H_2O+Na^+; secretion of K^+
600	150	250	20	20	290	

(after K.D. Fine et al.)

B. Malabsorption of Carbohydrates

Poorly absorbed carbohydrates (e.g. sorbitol, fructose)

Disorder of carbohydrate digestion and absorption (e.g. disaccharidase deficiency, carrier defects)

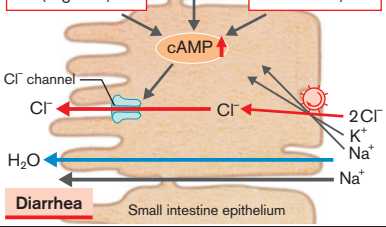


C. Raised Cl^- Secretion

Hormones and neurotransmitters (e.g. VIP)

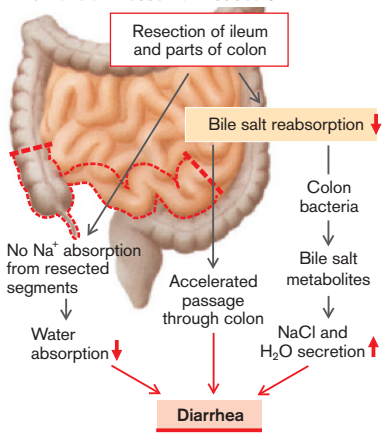
Laxatives

Toxins (cholera, clostridium difficile)



D. Partial Intestinal Resection

Resection of ileum and parts of colon



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. 160), 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 (cobalamin, 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**):

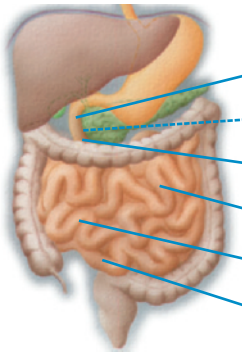
◆ **After gastric resection** and/or **vagotomy** (see also p. 160), the stimulation of enteral hormone secretion (CCK, e.g.) is reduced and the synchronization of chyme apportioning with pancreatic secretion, gallbladder emptying, and choleresis is disturbed. Furthermore, passage through the small intestine 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. 174), carcinoma of the pancreas, cystic fibrosis (→ p. 176), 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 HCO_3^- which is necessary for buffering acidic chyme.

◆ **Atrophic gastritis** with **achlorhydria** (→ p. 154) 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. 160). The bacteria deconjugate bile salts (→ **D**) and split the binding between cobalamine and intrinsic factor. The resulting cobalamine malabsorption leads to **cobalamin deficiency,** as does a reduced intake (strictly vegetarian diet; it is true also for breastfed infants of such mothers, because their milk also lacks cobalamine), intrinsic factor deficiency (achlorhydria; see also p. 154), lack of enzymatic liberation of cobalamin from its binding with other proteins (high gastric pH, trypsin deficiency), or resection of the terminal ileum, the site of absorption of the cobalamin–intrinsic factor complex.

◆ **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

A. Sites of Absorption of Potentially Malabsorbed Substances



Proximal duodenum: monosaccharides

Inflow of **bile** and **pancreatic juice**

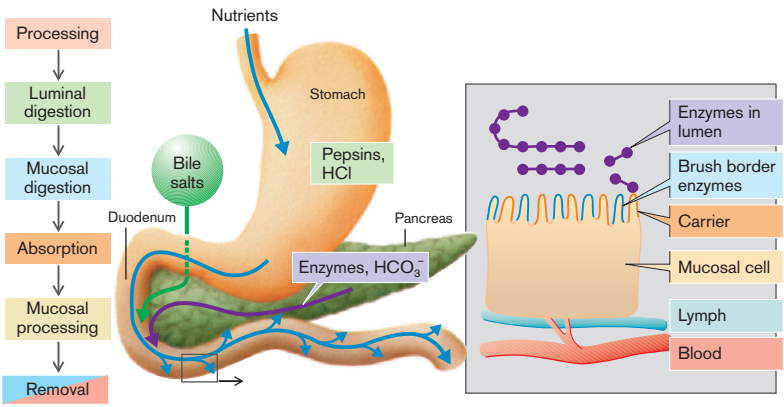
Distal duodenum: disaccharides, fat-soluble vitamins, Fe, Ca^{2+}

Jejunum: Proteins (as amino acids), starch (as glucose), water-soluble vitamins

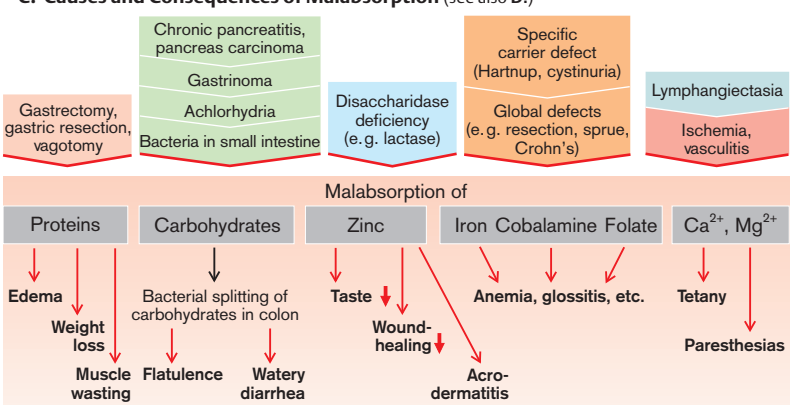
Ileum: fats

Terminal ileum: bile salts, cobalamines

B. Steps in Digestion the Failure of which Leads to Malabsorption



C. Causes and Consequences of Malabsorption (see also D.)



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 *cystinuria* for cationic (basic) amino acids and cystine (→ p. 104). (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 (→ p. 170), 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 folate 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* 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. 250).

◆ **Malabsorption of carbohydrates** in the small intestine (→ **C**) means that some of them are metabolized to *short-chain fatty acids* and to gases (CO_2, H_2) resulting in **distension** and **flatulence**. If more than 80 g/d of carbohydrates fail to be absorbed, osmosis-induced watery *diarrhea* occurs (→ p. 162).

◆ **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 (→ p. 144). In **vitamin A deficiency** *hyperkeratosis* and *night blindness* develops.

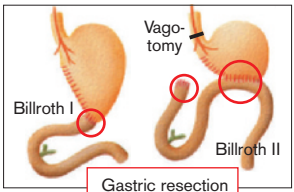
◆ **Malabsorption of the water-soluble vitamin cobalamine** (B_{12}) (for causes, see above) and **folate** (e.g., in global malabsorption or methotrexate administration) leads to macrocytic anemia (→ p. 38), termed *pernicious anemia* in case of cobalamine deficiency, to *glossitis* and *aphthous ulcers*. Cobalamin deficiency leads to neurological defects (nerve degeneration).

◆ **Iron malabsorption** (see also p. 42) leads to hypochromic anemia.

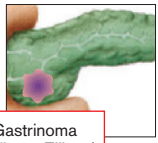
D. Malabsorption of Fat

Achlorhydria

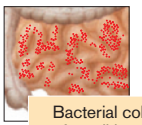
Intestinal stasis



Gastric resection

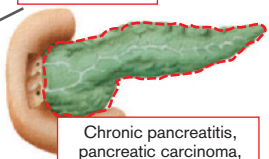


Gastrinoma (Zollinger-Ellison)



Bacterial colonization of small intestine

Desynchronization of chyme emptying and
bile secretion
pankreatic secretion



Chronic pancreatitis, pancreatic carcinoma, pancreatic resection, cystic fibrosis, etc.

Bile salt deconjugation

Liver damage

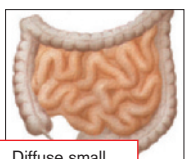
Pancreatic HCO_3^- secretion ↓

Duodenal pH ↓

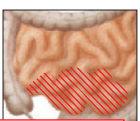
Bile salt synthesis ↓

Cholestasis, biliary tract occlusion

Lipase inactivation



Diffuse small intestinal disease



Ileum resection

Bile salt precipitation

Pancreas stimulation ↓

Bile salt resorption ↓

Abetalipoproteinemia
Obstruction of lymphatic vessels
Ischemia

Bile salt deficiency

Lipase deficiency

Abnormal micellar formation

Maldigestion of fat

Fat removal ↓

Fat malabsorption

Vitamin K deficiency

Vitamin D deficiency

Steatorrhea

Bleeding

Osteomalacia

Weight loss

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 rectoanal inhibitory reflexes, i.e. the internal anal sphincter fails to open when rectum fills. In *Chagas' disease* the causative organism (*Trypanosoma cruzi*) denervates 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 (→ p. 150), 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 fulminant 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

Rectal distension

Contraction (instead of dilation) of the pelvic floor

Surgery, trauma, peritonitis, etc.

Acute reflex

Paralytic ileus

Mechanical obstruction: luminal, mural, external (foreign body, tumor, hernia, adhesion, stricture, etc.)

Neurogenic or myogenic disorder of transport

Paralysis

Abnormal dilatation

see photo below

Food low in bulk

Intestinal volume ↓

Intestinal motility ↓

Drugs (opiates, phenothiadiazines, etc.)

Constipation

Obstruction **Pseudo-obstruction**

Far towards anus

Ascension of bacteria

Distension

Ischemia

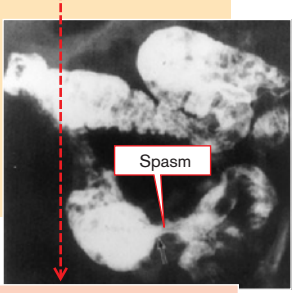
Endotoxins

Inflammation

VIP, prostaglandins

Wall edema

Absorption ↓, secretion ↑



Megacolon
(here: Hirschsprung's disease)

Vomiting **Hypovolemia** **Pain**

Photo: Sleisenger, Fortran. Gastrointestinal Disease. 5th ed. Philadelphia: WBSaunders; 1993; Vol. 1: 892

Chronic Inflammatory Bowel Disease

Crohn's disease and ulcerative colitis are inflammatory bowel diseases (**IBD**) with a remitting and relapsing clinical course. The onset of the diseases is usually prior to the age of 30. The diseases affect distinct intestinal portions (→ **A1a, A2a**). First degree relatives of patients suffering from IBD bear a 5 – 20-fold increased risk to similarly develop IBD.

The inflammation of **Crohn's disease** is *transmural* (→ **A1b**); it is mainly localized in the ileum (Ileitis) and colon (ileocolitis), but may affect further portions of the intestinal tract. Biopsy reveals noncaseating *granulomas* of the intestinal wall (→ **A1c**: granuloma with macrophages, giant cells, and epitheloid cells). *Symptoms* include diarrhea and abdominal pain, complications include abscesses (arising from crypts), fistula, and adhesions with the risk of bowel occlusion. The fistula frequently connect to other organs. There is a sharp transition between affected and nonaffected intestinal tissue. Patients are at an enhanced risk of developing intestinal carcinoma.

Ulcerous colitis is characterized by ulcers in the rectal mucosa, from which the inflammation may spread in the oral direction, eventually affecting the complete colon. The patients suffer from bloody diarrhea. In contrast to Crohn's disease, ulcerous colitis is confined to mucosal and submucosal tissue (→ **A2b, c**: purulent microabscess with invading neutrophils). Transmural progression of the ulcerations may occur and may lead to peritonitis as well as to inflammatory extension of the colon (toxic megacolon) and subsequent perforation. The risk to develop colonic carcinoma is high.

The **pathogenesis** of inflammatory bowel disease involves:

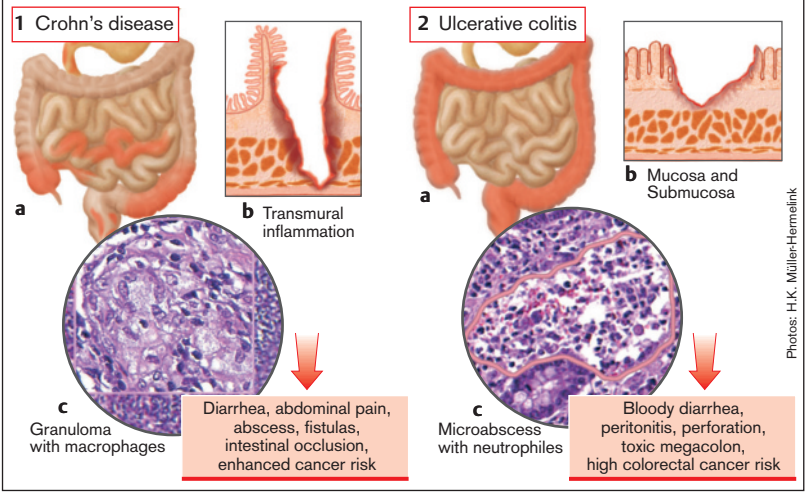
- the intestinal mucosa with its barrier function (including mucins and proteins from the crypt cells),
- Toll-like receptors (TLR), their cytosolic nucleotide binding oligomerization domain (NOD)-like receptors (NLRs), and their chemokine and Fc receptors,
- commensural bacteria particularly in the colon,
- the unspecific (innate) and specific intestinal immune system (→ p. 46 ff.), whereby the innate immune system involves the enterocytes,
- a variety of susceptibility genes predisposing to IBD,
- psychosocial factors (e.g., death of a close relative, divorce), which may aggravate the symptoms of IBD, and
- appendectomy, which is protective against ulcerous colitis but not Crohn's disease.

Normally a **homeostasis** is maintained between the *normal intestinal flora and the intestinal defense mechanisms*, leading to some immune tolerance (→ **B1**). Accordingly, bacterial peptidoglycans (PGNs) bind to TLR2 and CpG (cytosine–phosphatidyl–guanosine, a DNA-internal dinucleotide) to TLR9 of enterocytes. Activation of the TLR9 suppresses the activation of the IκB-kinase complex (IKK) and thus the activity of *NFκB* (→ p. 7). The intestinal microflora is further controlled by α-defensins (→ **B1**).

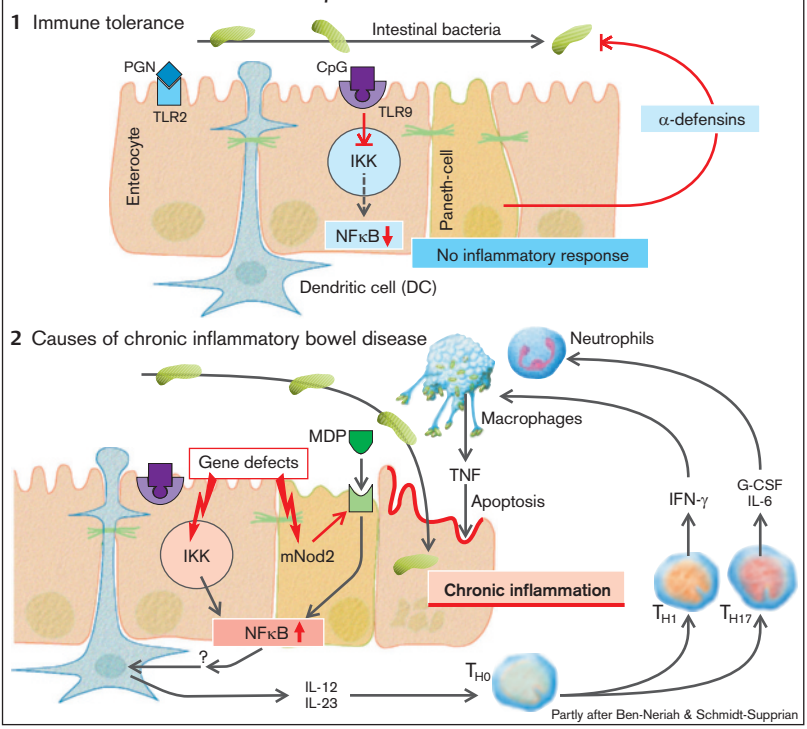
Contact of the intestinal wall with pathologic foreign **antigens** (e.g., worms; → **B2**) leads to full activation of NFκB. The subsequent attack against the antigens involves β-defensins or dendritic cells, which are activated by thymic stromal lymphopoietin protein TSLP, eosinophils, and IgE-secreting B-lymphocytes (→ **B2** and p. 52).

Certain **gene defects** result in labile homeostasis between the intestinal flora and the defense mechanisms. A gene defect of *IKK* (→ **B3**), a lack of TSLP or of β-defensin, result in the pathological activation of dendritic cells, which release IL-12 and IL-23 and thus trigger an *inflammatory reaction*, which involves Interferon γ (IFN-γ; → p. 50, **B6**), invading neutrophils (→ **A2c**) and monocytes, as well as apoptosis inducing tumor necrosis factor (TNF-α). A genetic defect of the *Paneth cells* (gain-of-function mutation of the *mNOD2* gene) leads to enhanced sensibility of the MDP (muramyl-dipeptide) receptor leading to Crohn's disease and eventually to inflammation (→ **B4**). Several of the pathophysiologic mechanisms have been unravelled recently but the pathophysiology of IBD is still incompletely understood.

A. Inflammatory Bowel Disease



B. Normal and Defective Mucosa / Bacterial Homeostasis



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. In the following, neutrophils are attracted (pancreatitis), which apparently contribute to the activation of trypsin.

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 (for instance 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 **duodenopancreatic reflux** occurs (in most cases when the duodenum is obstructed distally), the enzymes activated in the duodenum pass back into the pancreas (→ **A3**).

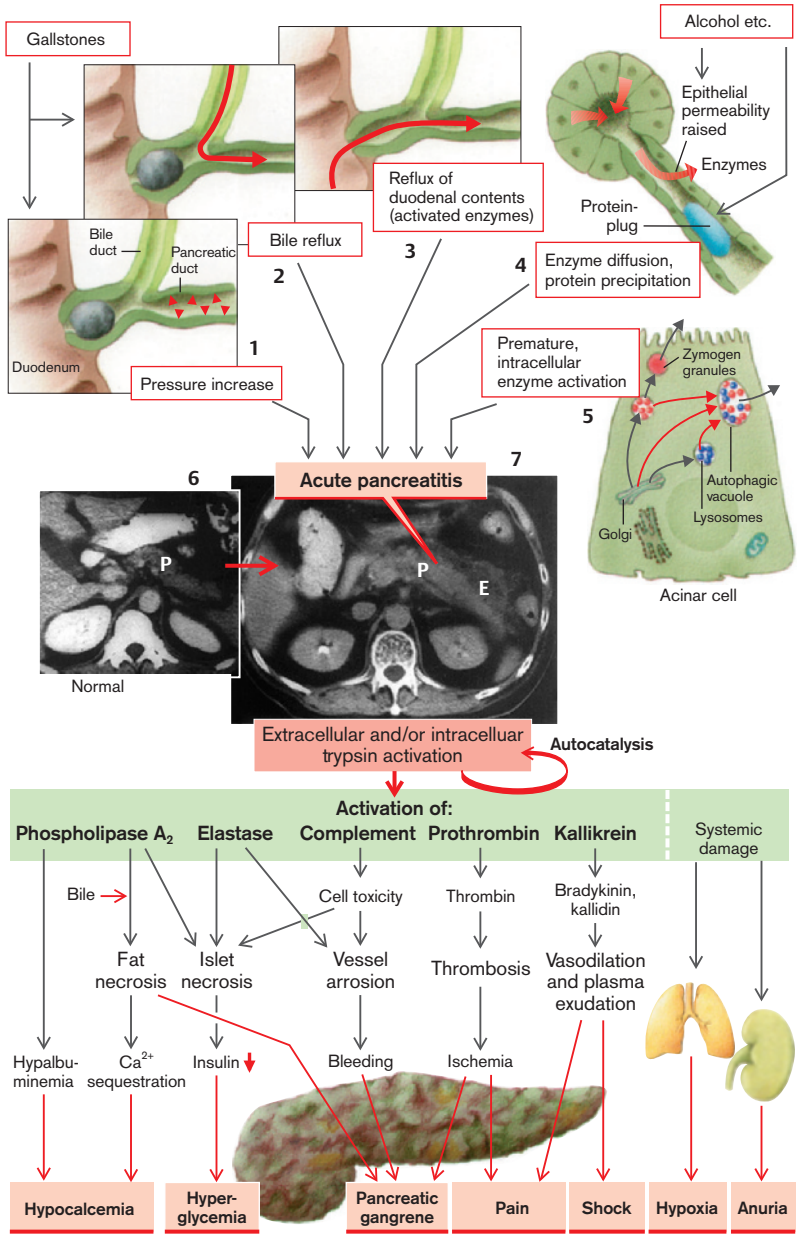
◆ Alcohol, acetylsalicylic acid, histamine, etc. increase the **permeability of the pancreatic duct epithelium**, so that larger molecules can pass through it. Enzymes secreted by the acinar cells thus diffuse into periductal interstitial tissue and damage it (→ **A4**). In addition, alcohol in the duct 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 A_2, 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 erosion* 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* (→ p. 308 ff.). Fat necrosis develops **around the pancreas** with accompanying soap formation, a process that uses up Ca^{2+} (Ca^{2+} sequestration) and also causes hypocalcemia (see below). Mg^{2+} ions in the plasma binding to the liberated fatty acids cause *hypomagnesemia* (→ p. 136). 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 A_2 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



CTs from: Sleisenger, Fortran. Gastrointestinal Disease. 5th ed. Philadelphia: WB Saunders; 1993; Vol. 2: 1641 (Supplied by E.T. Steward, M.D.)

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 secretion), 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. 172), 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. 172).

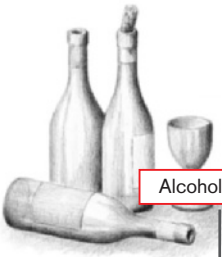
◆ The less common **chronic–obstructive pancreatitis** (→ **A**, right) is caused by *occlusion of the main excretory duct*(*s*) by tumors, scar stricture, or stenosis of the papilla, among others. There is no calcification, but the **ductal system is** markedly **dilated** upstream of the stenosis (→ **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. 172). 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.

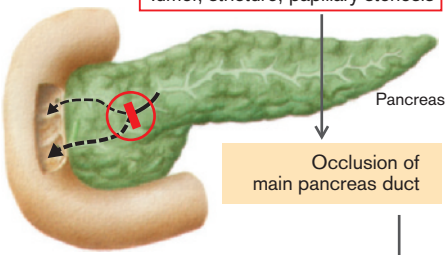
The **results** of chronic pancreatitis are tissue atrophy, ductal stenosis, and periductal fibrosis with scarring. This gradually leads to *loss of parenchyma*, which will cause exocrine and later also endocrine **pancreatic insufficiency**. Intermittent or continuous *pain*, *malabsorption* (→ p. 164 ff.), diarrhea (→ p. 162), and *weight loss* as well as *diabetes mellitus* (→ p. 308 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



Pancreas

Occlusion of main pancreas duct

Pancreatic juice:

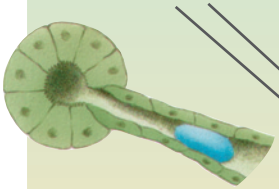
Secretion of HCO_3^- and fluid ↓

Citrate concentration ↓

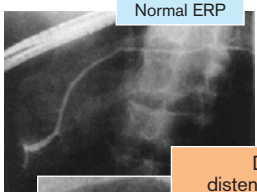
Lithostatin concentration ↓

Proenzyme concentration ↑

Calcium salt precipitation

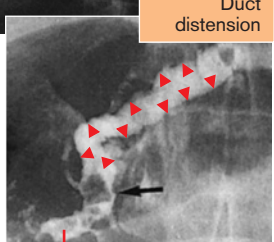


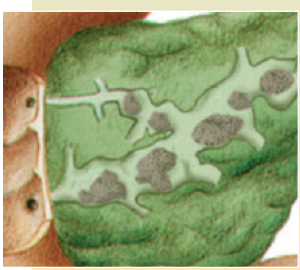
Protein plug



Normal ERP

Duct distension





Calcium deposition

Epithelial lesions

Enzyme activation

Chronic inflammation and fibrosis of exocrine and endocrine pancreas, damage to neighboring organs

Tissue atrophy	Pain	Diabetes mellitus	Obstructive jaundice
Ductal stenosis	Malabsorption	Pancreatic ascites	Diarrhea
Periductal fibrosis	Weight loss	Thrombosis of portal and splenic veins	Pseudocysts

Photo of dilated duct from: Thurn P. et al. Einführung in die radiologische Diagnostik. 10th ed. Stuttgart: Thieme; 1998

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 (→ **A 1**) and affects the epithelial transport protein **CFTR** (**c**ystic **f**ibrosis **t**ransmembrane conductance **r**egulator). CFTR in healthy people consists of 1480 amino acids that form 12 transmembrane domains, two nucleotide-binding domains (NBD_1, NBD_2), and a regulator domain. At the latter, CFTR is regulated by a cAMP-dependent protein kinase A (→ **A 2**; CFTR is shown opened up frontally). CFTR is a **chloride channel** that opens when the intracellular cAMP concentration is raised and, in addition, ATP is bound to NBD_1 (and split?). Furthermore, intact 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 NBD_1* (→ **A 3**): either the amino acid 508, phenylalanine (= F; mutation ΔF508), is missing, or glycine (= G) in position 551 is replaced by aspartate (= D) (mutation G551 D).

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 antiport carrier (→ **A 4**). The opening of CFTR—for example, by secretin, which increases intracellular cAMP concentration—allows 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; → p. 174).

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** leads to congenital aplasia of the vas deferens (CADV) and thus to *infertility*, in the female 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 CTFR 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

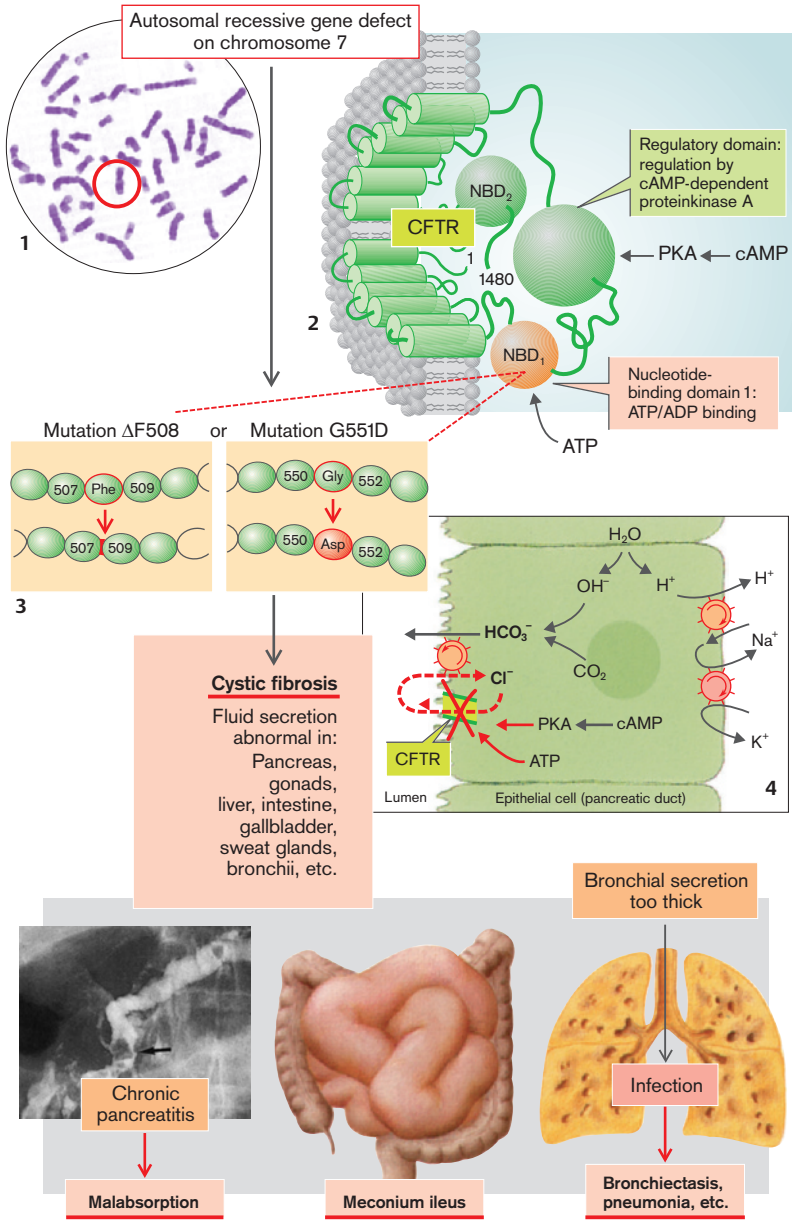


Photo from: Thurn P. et al. Einführung in die radiologische Diagnostik. 10th ed. Stuttgart: Thieme; 1998

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* (→ **A 4**, green area). If the concentration *ratio* **[Ch]/[BS + Pch]** increases, Ch will remain, within a small range, in a "supersaturated" micellar solution (→ **A 4**, 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 (→ **A 2**) 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** (→ **A 2**; → **A 4**, red area). These crystals are the precursors of gallstones.

Important **causes** of an increased [Ch]/[BS + Pch] ratio are:

◆ **Increased cholesterol secretion** (→ **A 2**). 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 acyl-CoA-cholesterol-acyl transferase [ACAT]).

◆ **Reduced bile salt secretion** (→ **A 1**). 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**; → p. 180, 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 anemia*, in which there is so much bilirubin that the glucuronidase-mediated process of conjugation in the liver does not meet demand (→ p. 183);

◆ Reduced conjugating capacity in the liver, for example, in *liver cirrhosis* (→ p. 186);

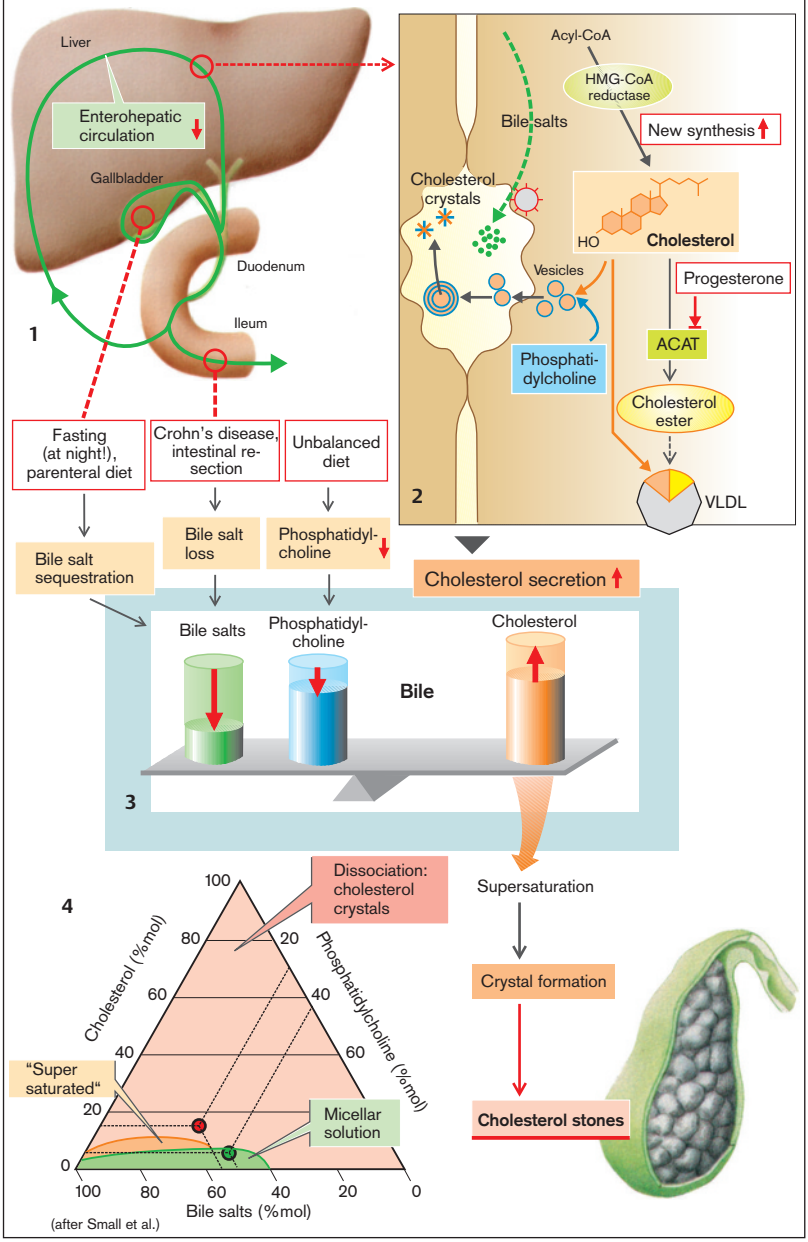
◆ *Nonenzymatic deconjugation* of (especially monoglucuronated) bilirubin in bile;

◆ Enzymatic deconjugation (β-glucosidase) by *bacteria*.

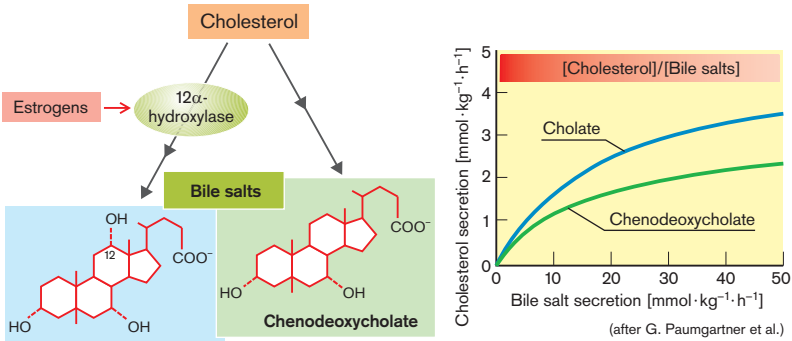
The latter is almost always the cause of *brown pigment stones*. The bacteria also enzymatically deconjugate the bile salts (decreased micellar formation with cholesterol precipitation) and additionally liberate, by means of its phospholipase A_2, palmitate and stearate (from phophatidylcholine) which 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.

The **gallbladder,** in which the specific bile components (Ch, BS, Pch) are concentrated many times over by withdrawal of water, also plays

A. Cholelithiasis: Abnormal Bile Salt to Cholesterol Ratio



B. Cholesterol/Bile Salts: Dependence on Bile Salt Type and Bile Salt Secretion Rate



▶

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* (→ p. 160) 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**):

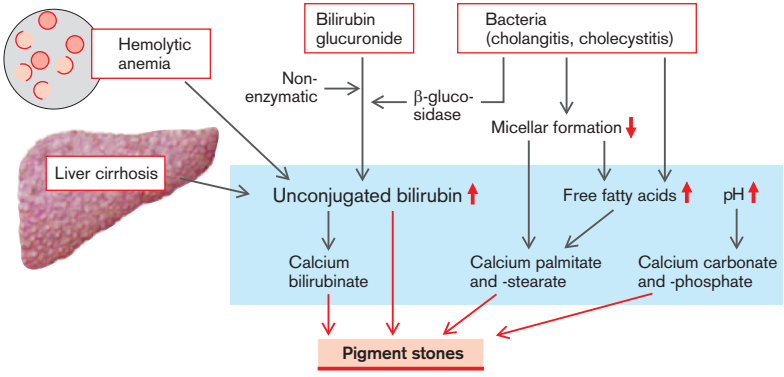
◆ **Colic**. When the cystic duct or the common bile duct is transiently blocked by a stone, pressure rises in the bile ducts and increased peristaltic contraction in the region of the blockage causes severe visceral *pain* in the epigastric area, possibly with radiation into the back, as well as *vomiting* (→ p. 152).

◆ 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 A_2. 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.

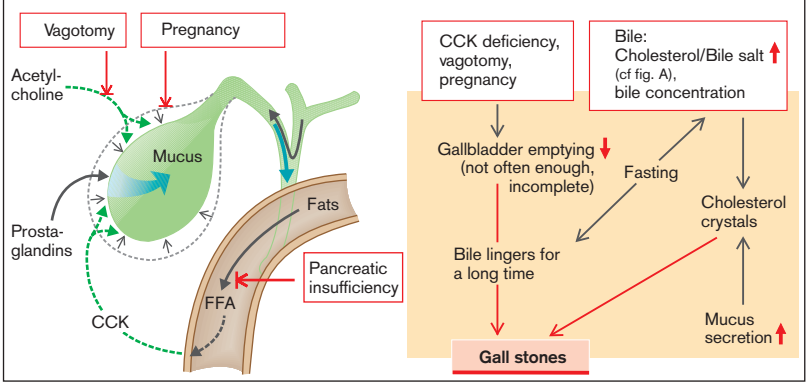
◆ Bacterial **cholangitis** usually develops when bile flow is stopped because of cholelithiasis. A rise in pressure with dilation of the bile ducts is the result, and posthepatic cholestasis and biliary pancreatitis may also develop.

◆ In relatively rare cases **gallbladder cancer** develops on the basis of gallstone disease.

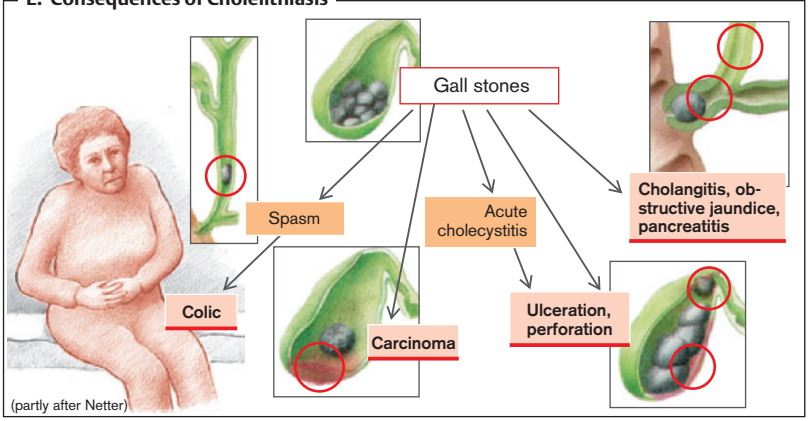
C. Causes of Pigment Stone Formation



D. Role of Gall Bladder in Cholelithiasis



E. Consequences of Cholelithiasis



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-monoglucuronide and bilirubin-diglucuronide. This **conjugated** (*direct* reacting) bilirubin is water-soluble and secreted into the bile canaliculi. Some 85% are excreted in the stool. The remaining 15% are deglucuronated 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 (→ **A**).

◆ **Prehepatic jaundice** is the result of increased bilirubin production, for example, in *hemolysis* (hemolytic anemia [→ p. 44] or toxins), inadequate erythropoiesis (e.g., megaloblastic anemia, → p. 38), 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–Meulengracht syndrome), *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** (→ p. 184), for example, in viral hepatitis, alcohol abuse, drug side effects (e.g., isoniazid, phenytoin, halothane), liver congestion (e.g., right heart failure, → p. 228), sepsis (endotoxins), or poisoning (e.g., the Amanita phalloides mushroom).

◆ In **posthepatic jaundice** the extrahepatic bile ducts are blocked, in particular by gallstones (→ p. 178 ff.), tumors (e.g., carcinoma of the head of the pancreas), or in cholangitis or pancreatitis (→ p. 172). In these conditions it is particularly conjugated bilirubin that is increased.

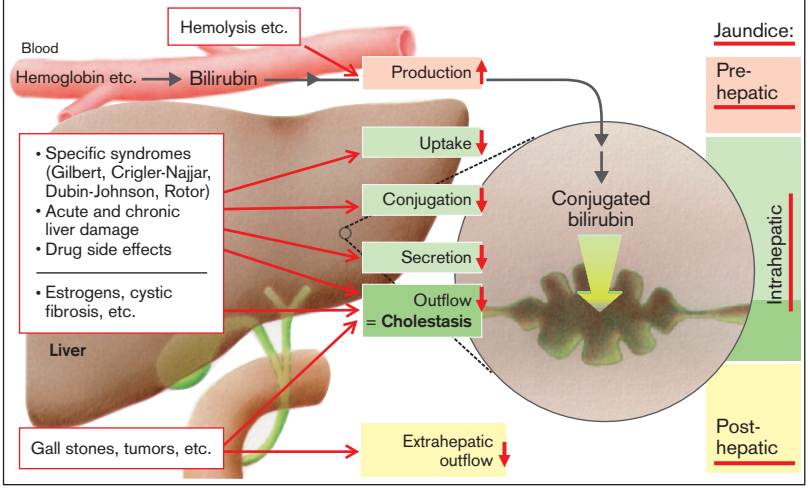
Cholestasis

Cholestasis (→ **A**, **B**), i.e., blockage of bile flow, is due to either **intrahepatic disorders**, for example, cystic fibrosis (→ p. 176), granulomatosis, drug side effects (e.g., allopurinol, sulfonamides), high estrogen concentration (pregnancy, contraceptive pill), graft versus host–reaction after transplantation, or, secondarily, **extrahepatic bile duct occlusion** (see above).

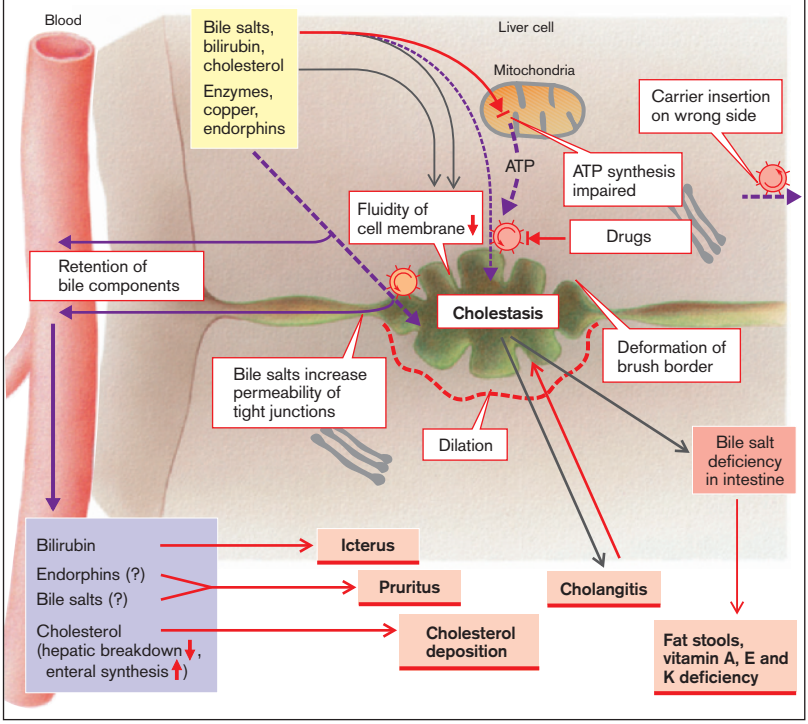
In cholestasis the bile canaliculi are enlarged, the *fluidity* of the canalicular **cell membrane** is decreased (cholesterol embedding, bile salt effect), their brush border is deformed (or totally absent) and the function of the cytoskeleton, including *canalicular motility*, is disrupted. In addition, 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, akanthocytes). The distressing *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. 164 ff.). Finally, infection of accumulated bile leads to *cholangitis*, which has its own cholestatic effect.

A. Types of Jaundice



B. Mechanisms and Consequences of Cholestasis



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. 244);
- **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. 186) 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 depositions* can have a similar obstructive effect. Finally, in acute hepatitis and acute liver necrosis the sinusoidal space can also be obstructed by *cell debris*.

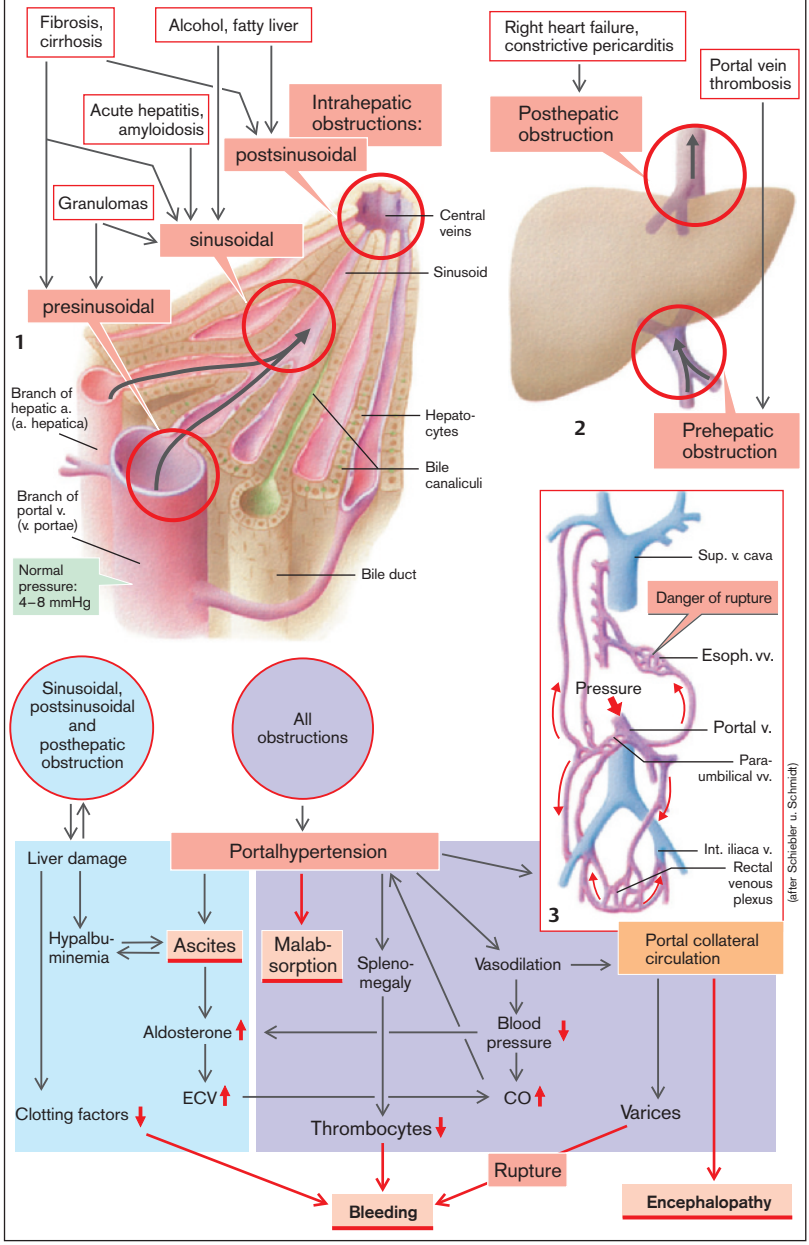
Consequences of portal hypertension. Wherever the site of obstruction, an increased portal vein pressure will lead to disorders in the preceding organs (*malabsorption, splenomegaly* with anemia and thrombocytopenia) as well as to blood flowing from abdominal organs via vascular channels that bypass the liver. These **portal bypass circuits** (→ **A3**) use collateral vessels that are normally thin-walled but are now greatly dilated (**formation of varices**; "hemorrhoids" 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. 188) that results in an increase in extracellular volume.

As blood from the intestine bypasses the liver, toxic substances (NH_3, 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 **portalsystemic** ("hepatic") **encephalopathy** develops (→ p. 188).

A. Causes and Consequences of Portal Hypertension



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 fulminant 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. 184) or after other liver damage, for example, as final stage of a *storage disease* (hemochromatosis, Wilson's disease; → p. 270 ff.) 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* ($\bullet O_2^-$, $\bullet HO_2$, H_2O_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.

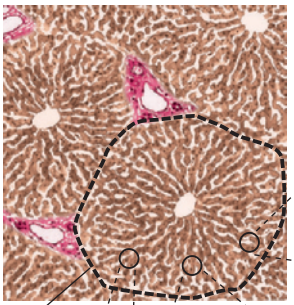
Fibrosis of the liver develops in several steps (→ **A**). When damaged hepatocytes die, lysosomal enzymes, among others, leak out and release **cytokines** from the extracellular matrix. These cytokines and the debris of the dead cells **activate the Kupffer cells** in the liver sinusoids (→ **A**, 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 immigrated 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 collagens (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. 184).

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. 182), *portal hypertension* (→ p. 184), and *metabolic liver failure* (→ p. 188).

A. Fibrosis and Cirrhosis of the Liver



Liver lobule

Noxious factors (alcohol, viral hepatitis etc.)

Necrosis

Hepatocyte

Matrix

Enzyme leak

Cell debris

Cytokines and other matrix components

Chemotaxis of inflammatory cells

Activation of Kupffer cells

Kupffer cell

Granulocytes
Lymphocytes

Monocyte

Growth factors and cytokines

MCP-1 → Chemotaxis

Ito (fat) cell

Chemotaxis

TGFβ

Myofibroblast

Macrophage

Extracellular matrix production ↑↑

Fibroblast proliferation

Collagen type I, III, IV ↑
Proteoglycans ↑
Matrix glycoproteins ↑

Fibrosis

Nodular regeneration with loss of lobular structure

Cirrhosis

Cholestasis

Portal hypertension

Metabolic failure

Liver Failure (see also p. 184 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. 186) 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. 184)
- a number of *inherited diseases* (→ chap. 8), for example, glycogen storage diseases, Wilson's disease, galactosemia, hemochromatosis, α_1-antitrypsin deficiency;
- intrahepatic or posthepatic *cholestasis* (→ p. 182) for prolonged periods, for example, in cystic fibrosis (→ p. 176), a stone in the common bile duct (→ p. 178 ff.), or tumors.

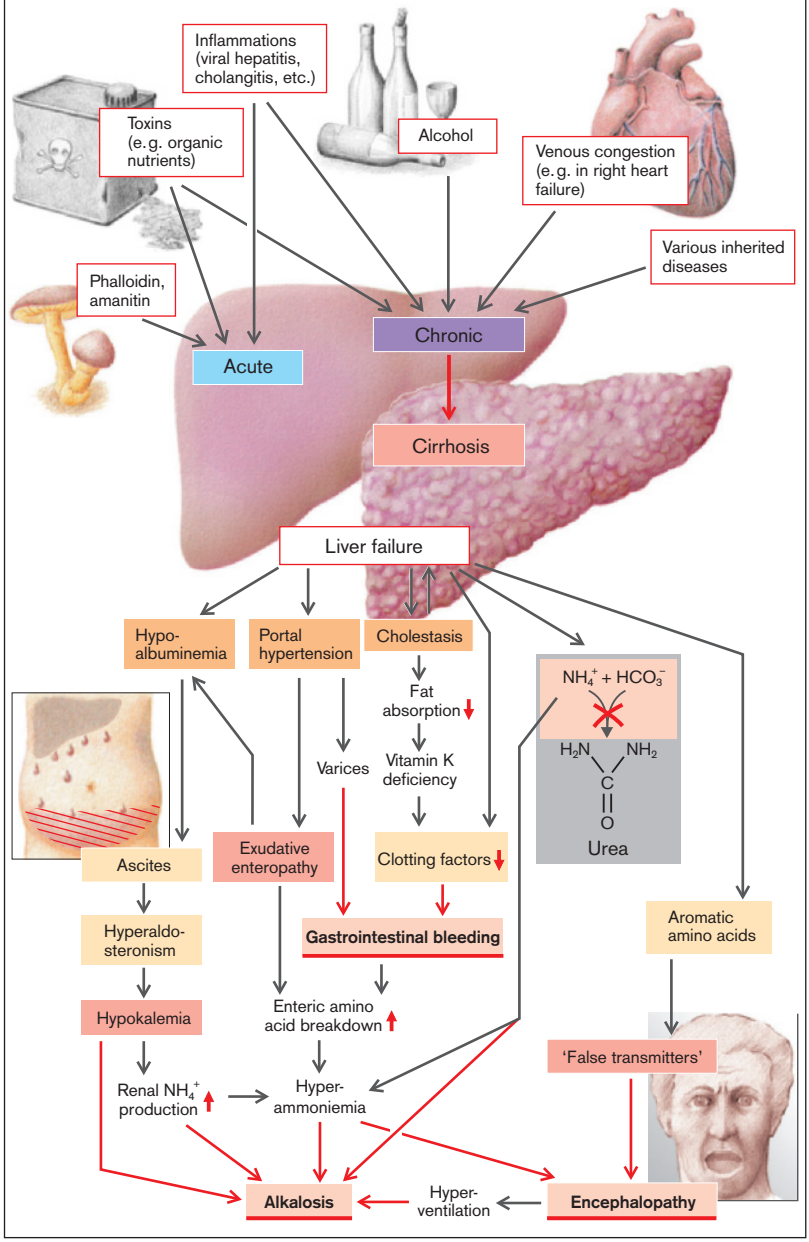
The most serious **consequences of liver failure** are:

- **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. 250). 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. 182), 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. 184) 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*, → p. 342) 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 ($NH_3 \rightleftharpoons NH_4^+$) 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. 128).

A. Causes and Consequences of Liver Failure



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. 32), of which about 80% is held in the so-called *low pressure system*, i.e., the veins, right heart, and the pulmonary circulation (→ **A**, left). 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 H_2O) is a good measure of the blood volume.

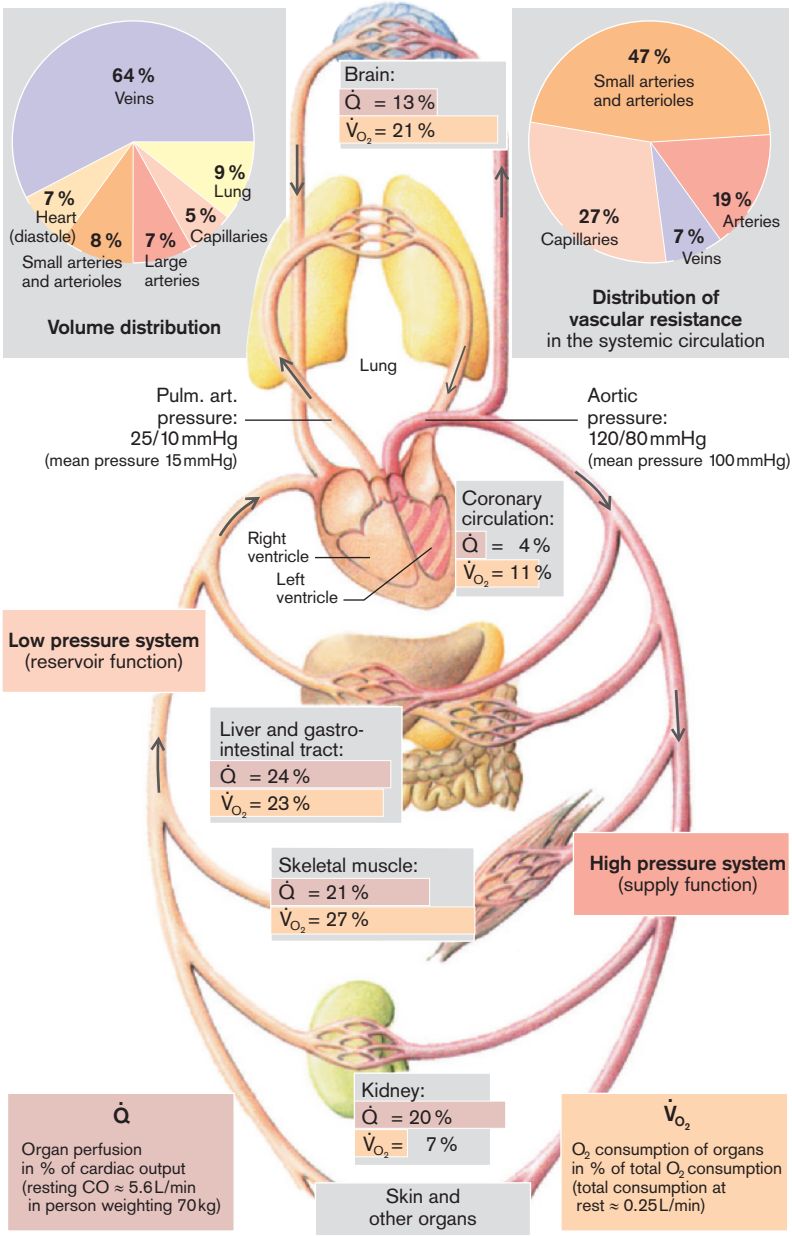
Cardiac output (**CO**) is the product of *heart rate and stroke volume* and at rest amounts to ca. 70 [min^{-1}] · 0.08 [L], i.e., ca. **5.6 L/min** (more precisely, a mean of 3.4 L/min per m^2 body surface area, a value called **cardiac index** (**CI**). CO can be increased many times over by a rise in heart rate and/or stroke volume (SV).

CO is distributed among the **organs** that are arranged in parallel within the **systemic circulation** (→ **A**, $\dot{Q}$ 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 f.). Blood flow through the coronary arteries of the *heart muscle* (at rest ca. 4% of CO; → p. 230) 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. 246), 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. ¾ 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. 24 ff.), but can, on the other hand, be reduced in favor of vital organs (pallor, e.g., in shock; → p. 246 ff).

The *entire* CO flows through the **pulmonary circulation**, since it is connected in series with the systemic circulation (→ **A**). Via the *pulmonary arteries* 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 a small fraction of *total peripheral resistance* (*TPR*), so that the mean pressure that has to be generated by the RV in the pulmonary arteries (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**, top right), which for this reason are called *resistance vessels*.

A. Cardiovascular System



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 arteries (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 systole with the **iso(volu)metric period** (period 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 (→ **A2**).

This starts the **ejection period** (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 ventricles (*endsystolic volume* [*ESV*]; → **A4**).

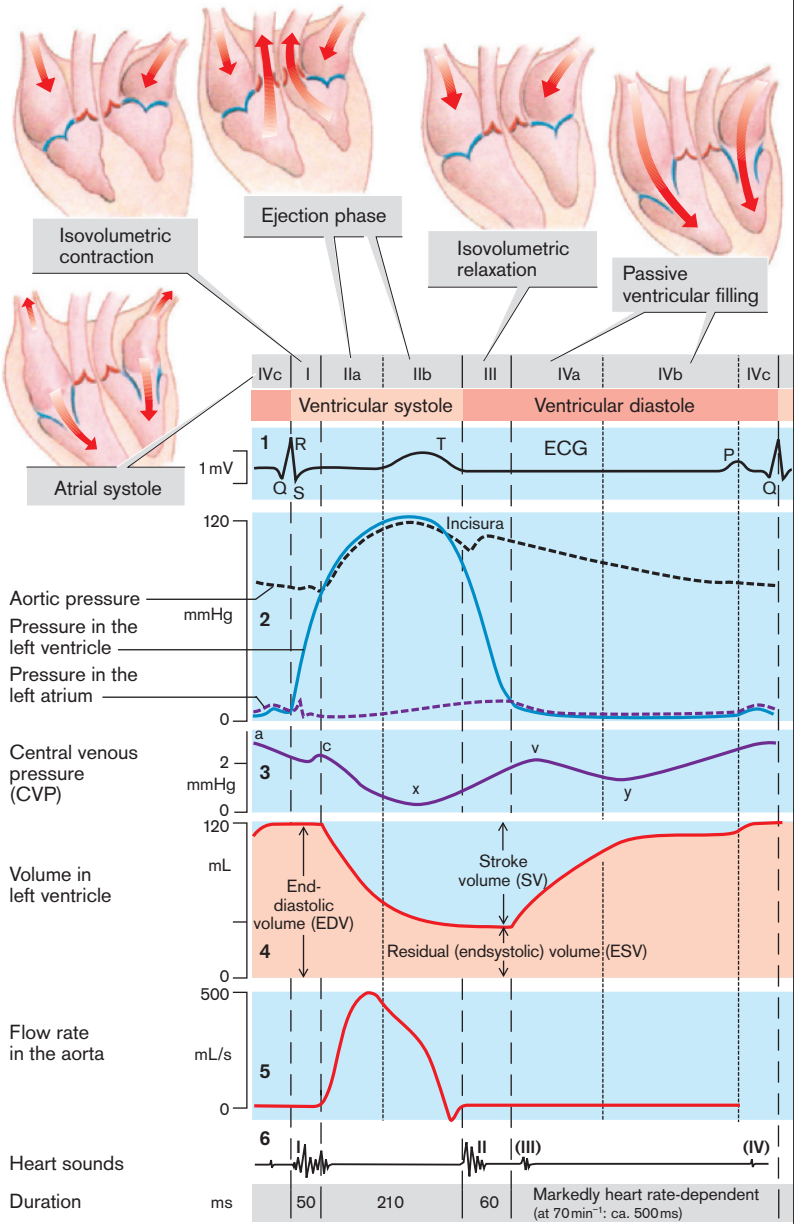
Diastole now begins with the iso(volu)metric **relaxation period** (period III). In the meantime the atria have filled again, a process to which the suction effect produced by the *lowering of the valve level* (momentarily enlarging atrial volume) during the ejection period has contributed the most (drop 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** (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. 211 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)



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). The myocytes of the atria and ventricles are branched and form bundles. They are not insulated from one another but connected through gap junctions (nexus). 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 atrioventricular 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. 198 and **C**).

The potential in the cells of the sinus node is a **pacemaker potential** (→ **B1**, top). 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**, bottom): Beginning with the MDP, nonselective conductance is increased and influx (I_f; f = funny) of cations into the cell leads to slow depolarization (prepotential = PP). Once the TP has been reached, g_{Ca} now rises relatively rapidly, the potential rising more steeply so that an increased influx of Ca^{2+} (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

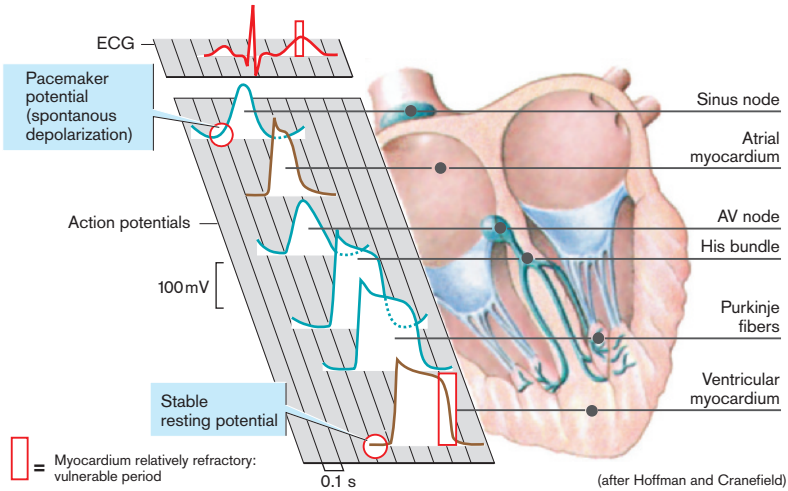
- the *rise of the slow depolarization becomes less steep* (→ **B3a**),
- the TP becomes less negative (= negative bathmotropic action, → **B3b**),
- the *MDP* becomes more negative so that spontaneous depolarization begins at a lower level (→ **B3c**), or
- *repolarization* in an AP starts later or 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. 200 ff.), 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).

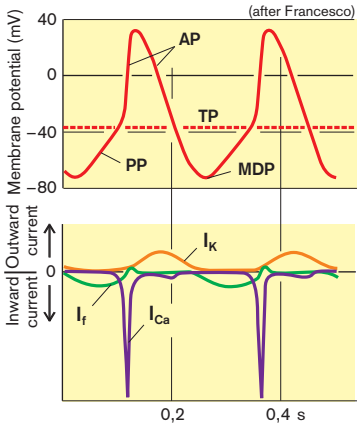
In contrast to the sinus and AV nodes with their relatively slowly rising AP, due largely to an influx of Ca^{2+} (→ **A**), there are in the **working myocardium** so-called rapid, voltage-gated *Na^+ channels* that at the beginning of the AP briefly cause a high Na^+ influx and therefore, compared 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 it the shape of a *plateau,* has an important function in that it prevents circles of myocardial excitation (*reentry*; → p. 200 ff.). This also holds true

A. Cardiac Excitation

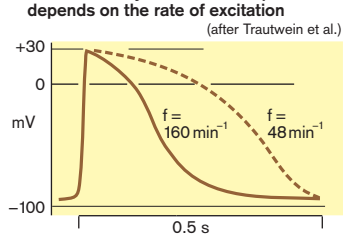


B. Pacemaker Potential and Excitation Rate in the Heart

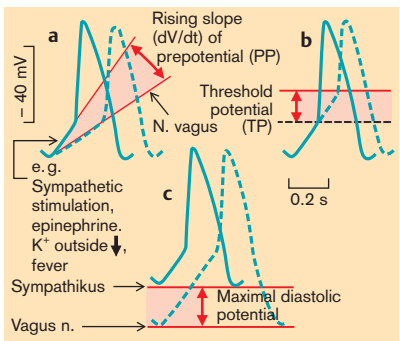
1 Ionic currents and pacemaker potential



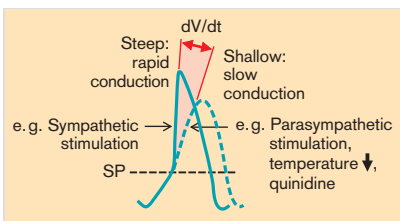
2 Duration of myocardial action potential depends on the rate of excitation



3 Heart rate changes due to changes in pacemaker potential



4 Factors influencing conduction of the action potentials (AV node)



for very high and low heart rates, because the duration of AP adapts to the heart rate (→ **B 2**).

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 SERCA = 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^+ 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);
- The velocity of relaxation by modification of the SERCA activity (lusitropism);
- *Excitability* of the heart in the sense of changing its excitability threshold (bathmotropism).

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 (→ **B 3 a** and **B 3 c**, 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 (→ **B 3 c** and **B 4**). Changes in g_K and g_{Ca} play an important role here as well.

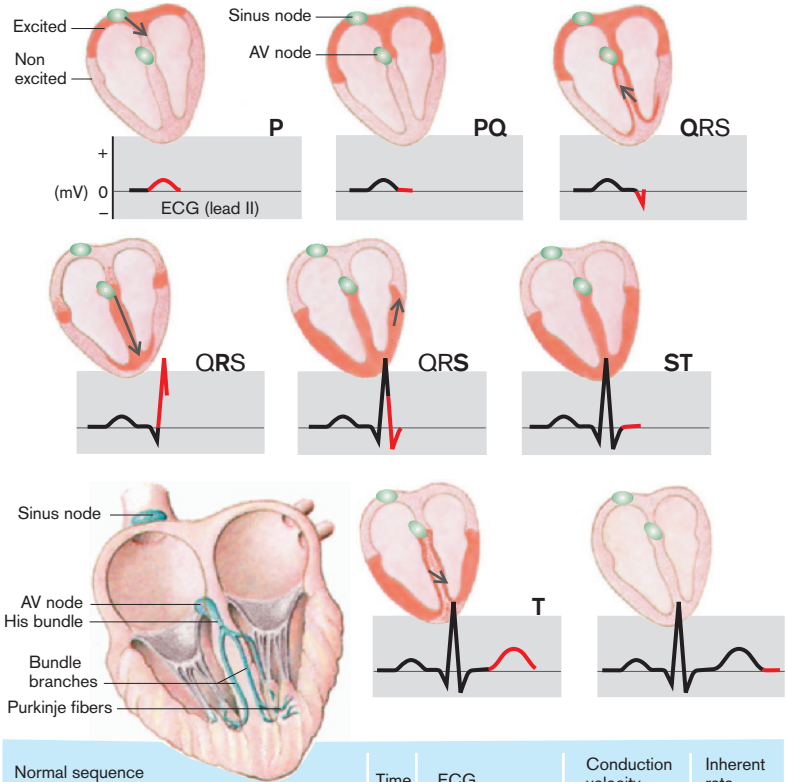
In contrast to chronotropism and dromotropism, the sympathetic nervous system, by being positively inotropic, has a direct effect on the working myocardium. The increased **contractility** is due to an *increase in Ca^{2+} influx*, mediated by β_1-adrenergic-receptors, from outside the cell that allows 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*).

The β_1-adrenergic action on the heart further leads to phosphorylation of phospholamban, which increases the SERCA activity and thus the myocardial relaxation (*positive lusitropic action*).

Contractility is also increased by prolonging the AP (and as a result lengthening 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		Time (ms)	ECG	Conduction velocity ($m \cdot s^{-1}$)	Inherent rate (min^{-1})
Sinus node					60–100
Impulse formation		0	P wave	0.05	
Impulse arrival at distant parts of atrium	right atrium	50		0.8–1.0 in atrium	
	left atrium	85			
AV node			PQ segment (excitation delayed)		40–55
Impuls arrival		50		0.05	
Impuls transmission		125			
His bundle activated		130		1.0–1.5	25–40
Distal bundle activated		145		1.0–1.5	
Purkinje fibers activated		150		3.0–3.5	
Subendocardial myocardium completely activated	right ventricle	175	QRS complex	1.0 in myocardium	None
	left ventricle	190			
Subepicardial myocardium completely activated	right ventricle	205			
	left ventricle	225			

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.

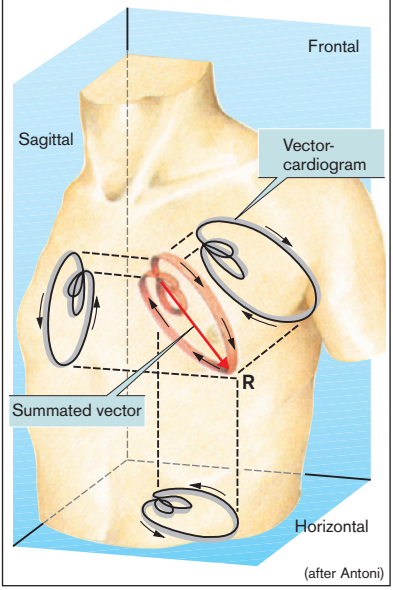
The ECG potentials originate at the border between excited and nonexcited parts of the myocardium. Nonexcited or completely excited (i.e., depolarized) myocardium does *not* produce any potentials which are visible in the ECG. During the **propagation of the excitation front** through the myocardium, 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 oscilloscopically in the *vectorcardiogram*.

The **limb and precordial leads** of the ECG record the temporal course of the summated 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 (→ **C 1**) and lie in the frontal plane. For the *unipolar Goldberger* (*limb*) *leads*, aVL, aVR, and aVF (a = augmented) (→ **C 3**), 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* V_1–V_6 (*Wilson leads*; → **C 4**) 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 V_1–V_3, positive in V_5–V_6.

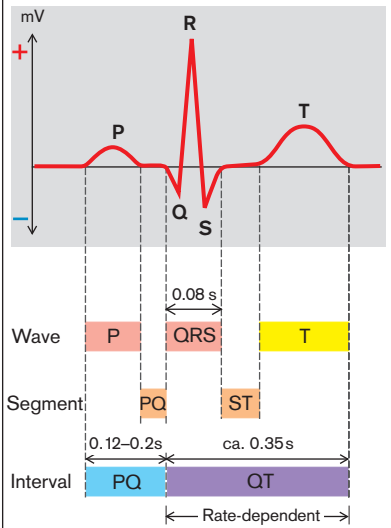
An **ECG tracing** (→ **B** and p. 197 C) has *waves, intervals, and segments* (deflection upward +, downward –). The *P wave* (normally < 0.25 mV, < 0.1 s) records depolarization of the two atria. Their repolarization is not visible, because it is submerged in the following deflections. The *Q wave* (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 (→ **C 3**). 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 (→ **C 2**, 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 → **C 3**). 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.

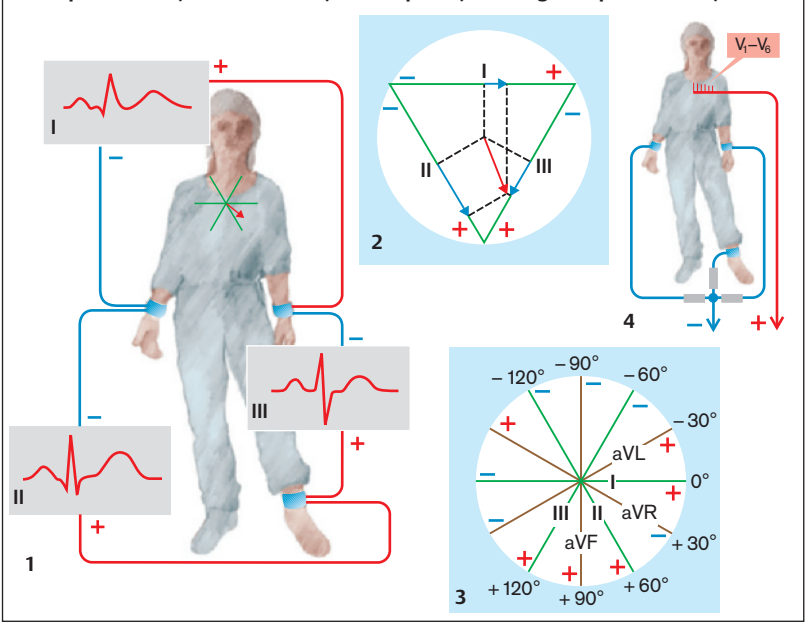
A. Vector Loops in Cardiac Excitation



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.

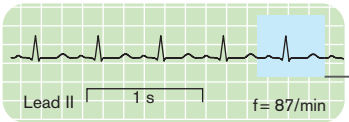
Action potential formation in the sinus node occurs at a rate of 60 – 100 per minute (usually 70 – 80 per minute at rest; → **A 1**). During sleep and in trained athletes at rest (vagotonia) and also in hypothyroidism, the rate can drop below 60 per minute (*sinus bradycardia*), while during physical exercise, excitement, fever (→ p. 24), or hyperthyroidism it may rise to well above 100 per minute (*sinus tachycardia*; → **A 2**). 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 (→ **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 (→ **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 ([ES] see below; → **B 3**, second ES). Ventricular filling and ejection are reduced and *ventricular fibrillation* occur (high-frequency and uncoordinated twitchings of the myocardium; → **B 4**). If no countermeasures are taken, this condition is just as fatal as cardiac arrest, because of the lack of blood flow.

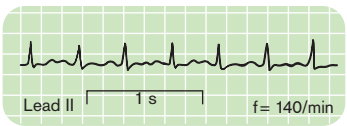
Extrasystoles (**ES**). When an action potential from a supraventricular ectopic focus is transmitted to the ventricles (atrial or nodal extrasystole), it can disturb their regular (sinus) rhythm (**supraventricular arrhythmia**). An atrial ES can be identified in the ECG by a distorted (and premature) 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 (→ **B 1**, 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_{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_{ES}–R > R–R and (R–R_{ES} + R_{ES}–R) < 2 R–R (→ **B 1**). An ectopic stimulus may also occur in a ventricle (**ventricular extrasystole**; → **B 2, 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*; → **B 2**). 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–R_{ES} + R_{ES}–R = 2 R–R. (For causes of ES, see below).

Conduction disorders in the AV node (*AV block*) or the Tawara branches of the His bundle can also cause arrhythmias. First degree (1°) AV block is characterized by an abnormally prolonged AV transmission (PQ interval > 0.2 s); second degree (2°) AV block by intermittent AV transmission (every second or third P wave); and third degree (3°) AV block by completely blocked AV transmission (→ **B 5**). In the latter case the heart will temporarily stop ▶

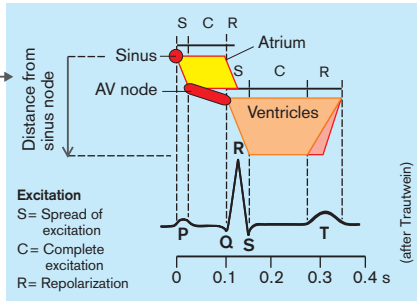
A. Normal Stimulus Formation with Normal Transmission



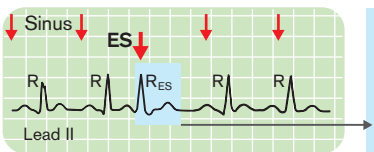
1 Normal sinus rhythm



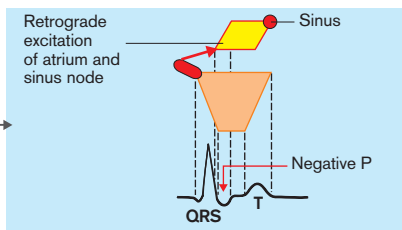
2 Sinus tachycardia

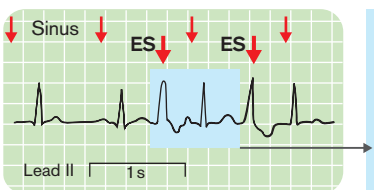


B. Ectopic Origin of Stimulus (1–5) and Abnormal Conduction (5)

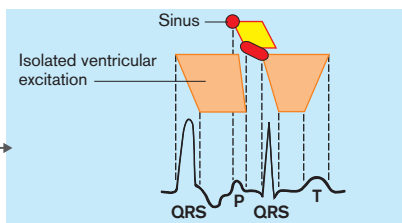


1 Nodal (AV) extrasystole with postextrasystolic pause

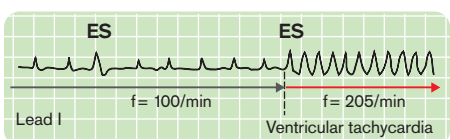




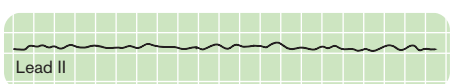
2 Interposed ventricular extrasystole



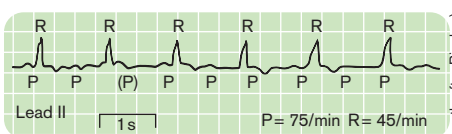
3 Ventricular tachycardia after extrasystole



4 Ventricular fibrillation



5 Complete AV block with idioventricular rhythm



(*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 (→ **B5**), 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. 194) 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 deplorization is dependent on the slow Ca^{2+} influx (L type Ca^{2+} channels; blockable by verapamil, diltiazem or nifedipine). The Ca^{2+} 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 Ca^{2+} 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.

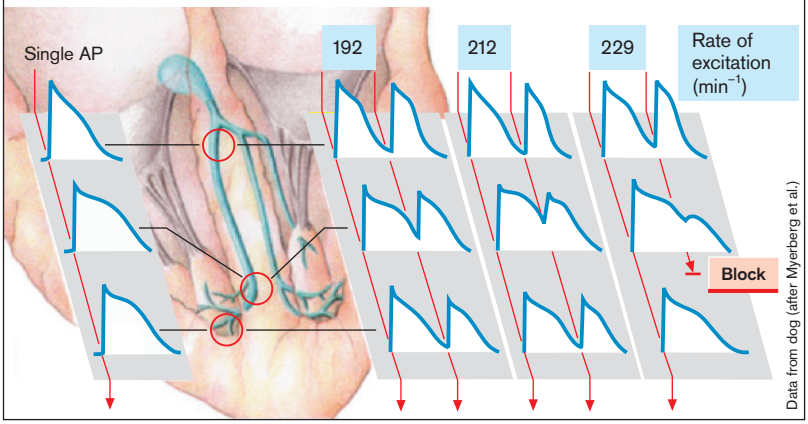
Causes of ESs (→ **H4**) include:

- 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 Ca^{2+} channel blockers verapamil and diltiazem. Certain genetic defects in the Na^+ channels or in one of the K^+ channels (HERG, KV_{LQT1} 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 (*torsades de pointes*).

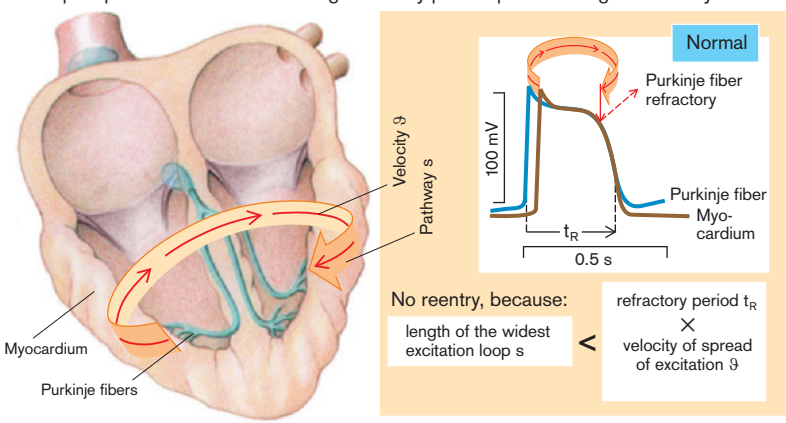
The *late DAPs* are usually preceded by post-hyperpolarization that changes into postdepolarization. If the amplitude of the latter reaches the threshold potential, a new AP is triggered. (→ **H3**). Such large late DAPs occur mainly at high heart rate, digitalis intoxication, and increased extracellular Ca^{2+} concentration. Oscillations of the cytosolic Ca^{2+} concentration seem to play a causative role in this.

C. Conduction Block at High Rate of Excitation

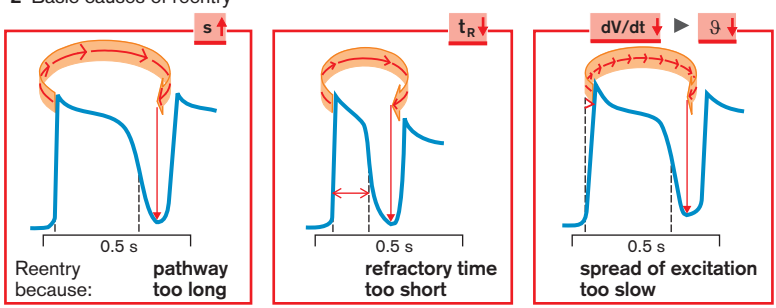


D. Reentry

1 Rapid spread of excitation and long refractory period: protection against reentry



2 Basic causes of reentry



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 upstroke 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* ($\vartheta\downarrow$), and a shortening of the AP means a *shorter refractory period* (t_R). 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 $\vartheta \cdot t_R$ is normally always greater than the length *s* of the largest excitation loop (→ **D1**). However, reentry can occur as a result if

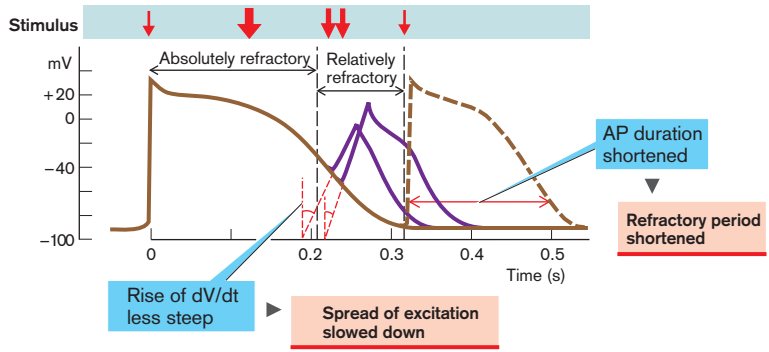
- the maximal length of the loop *s* has increased, for example, in ventricular hypertrophy,
- the refractory time t_R has shortened, and/or
- the velocity of the spread of excitation ϑ is diminished (→ **D2**).

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. 197), 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).

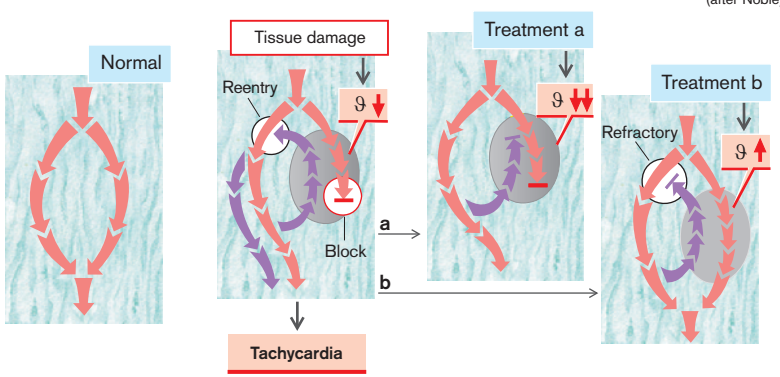
In **Wolff–Parkinson–White (WPW) syndrome** (→ **G**) the circle of excitation has an anatomic basis, namely the existence of an accessory, rapidly conducting pathway (in addition to the normal, slower conducting pathway of AV node and His bundle) between right atrium and right ventricle. In *normal 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)

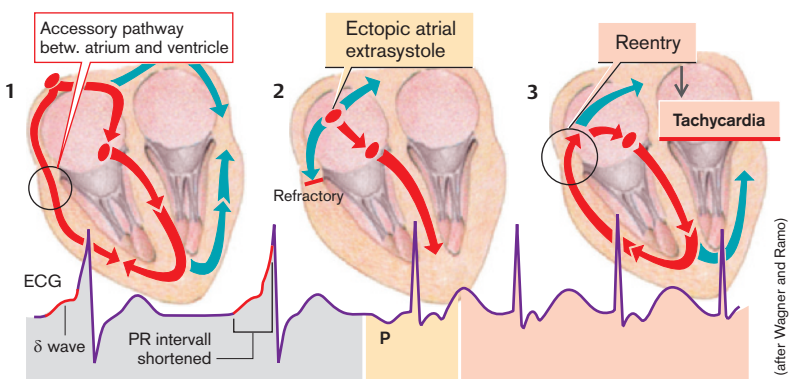


F. Block in AV Node: Reentry With Tachycardia and Drug Treatment

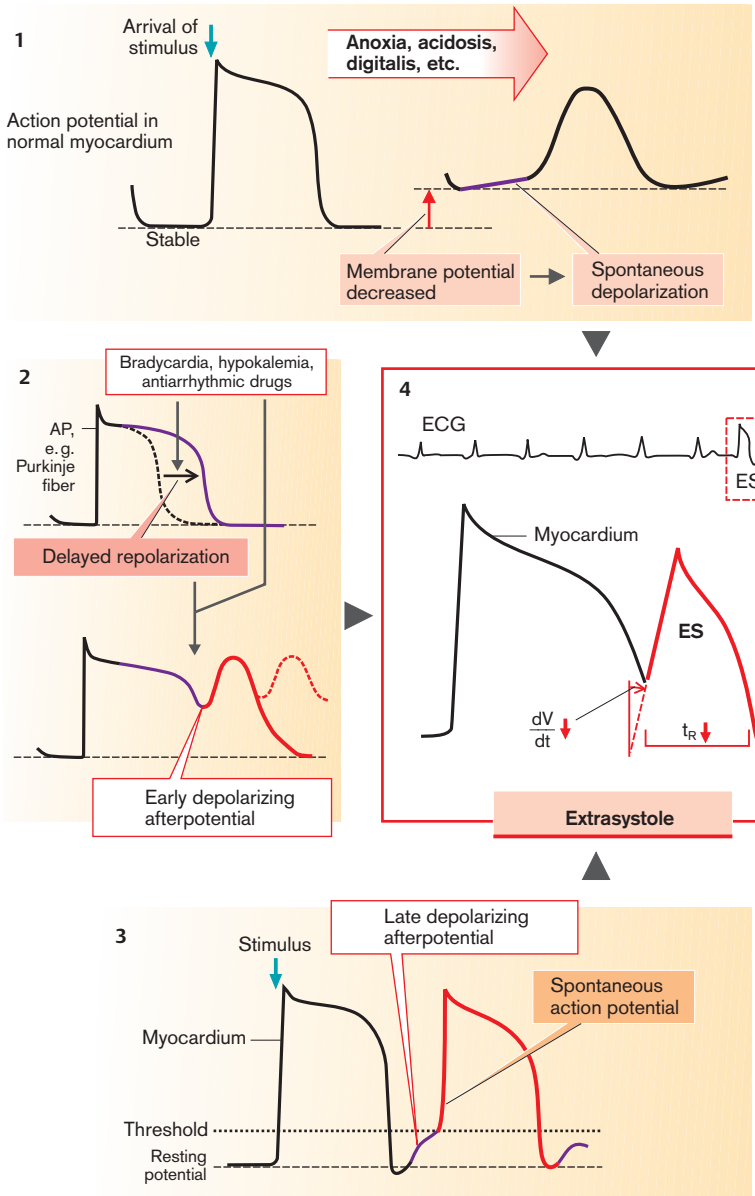
(after Noble)

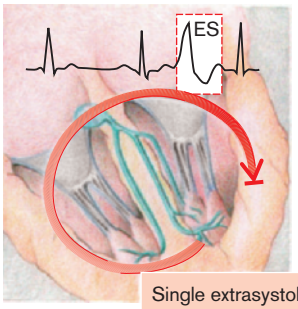


G. Reentry in Wolff-Parkinson-White Syndrome



H. Causes and Consequences of Extrasystoles





Single extrasystole

6

Synchronized myocardial excitation

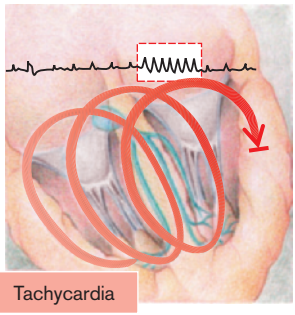
with normal potential of Purkinje fibers

Reentry

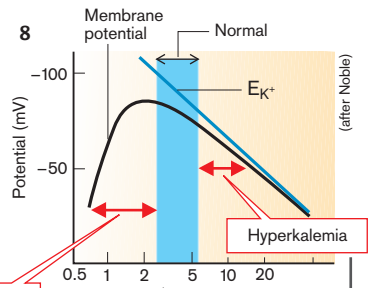
5

in

depolarized Purkinje fibers

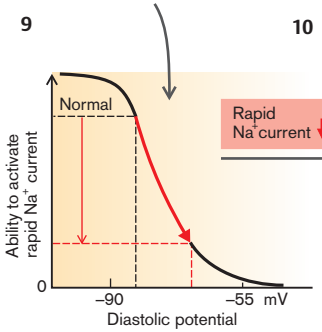


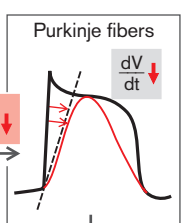
7 Tachycardia



Digitalis

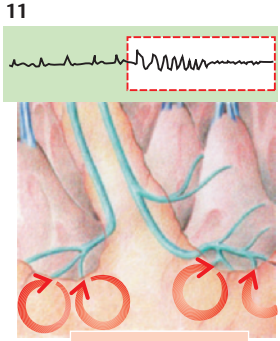
Anoxia etc.





ϑ

Desynchronized myocardial excitation



Ventricular fibrillation

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. 218; *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 cm^2. 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 cm^2, symptoms develop on strenuous physical activity (*dyspnea, fatigue, hemoptysis, etc.*). These arise during ordinary daily activities at an OA of < 1.5 cm^2, and at rest when the OA < 1 cm^2. An OA of < 0.3 cm^2 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 (AVD_{O_2}) 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* (P_{LA}) and therefore of the pressure gradient between atrium and ventricle ($P_{LA} - P_{LV}$; → **A2,** pink area). The diastolic flow rate ($\dot{Q}_d$) is therefore raised again, despite the stenosis (symptom: mid-diastolic murmur [MDM]; → **A2**).

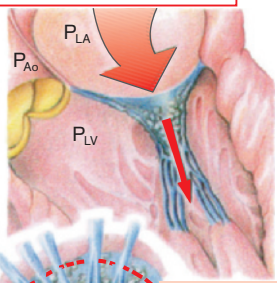
However, the further course of the disease is determined by the negative **effects** of the high P_{LA}: the *left atrium hypertropies* and *dilates* (*P mitrale* in the ECG; → **A2**). It may ultimately be so damaged that *atrial fibrillation* occurs, with disappearance of the *presystolic crescendo murmur* (PSM; → **A2**), which had been caused by the rapid inflow (poststenotic turbulence) during systole of the regularly beating atria. 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. 258). The heart (i.e., ventricular) rate is also increased in atrial fibrillation (*tachyarrhythmia*; → p. 200), 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). P_{LA} 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 (P_{LA} ↑↑).

The pressure is also raised further upstream. Such an increase in the pulmonary veins produces *dyspnea* and leads to varicosis of bronchial veins (causing *hemoptysis* from ruptured veins). It may further lead to *pulmonary edema* (→ p. 84), and finally *pulmonary hypertension* may result in *increased stress on the right heart* and *right heart failure* (→ p. 228).

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.

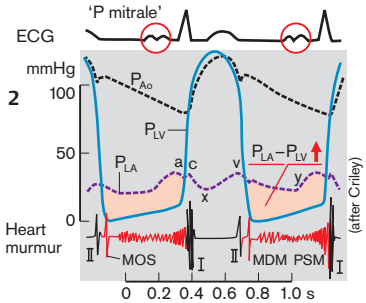


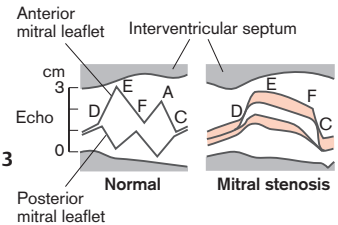
Mitral stenosis

Symptoms:
>2.5 cm^2 : none
1–2.5 cm^2 : during exercise
<1 cm^2 : at rest

Diastolic flow rate ($\dot{Q}_d$) ↓

CO ↓





Compensation

Heart rate ↓ → Stroke volume ↑↑

AVD_{O_2} ↑ → LA hypertrophy

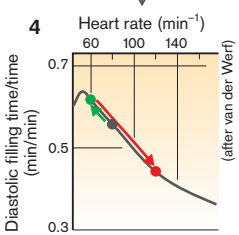
Left atrial pressure (P_{LA}) ↑

Physical exertion, fever, pregnancy

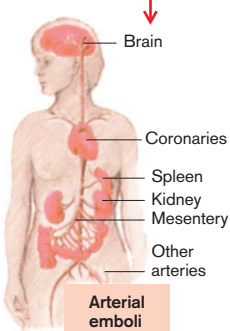
Left atrial damage → Atrial fibrillation → Heart rate ↑

Atrial fibrillation → Atrial thrombi

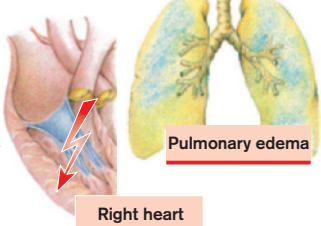
Pulmonary capillary pressure ↑ → Pulmonary hypertension → Right heart pressure load



Diastolic filling time/time ↓ → **Cardiac output** ↓



Arterial emboli



Pulmonary edema

Right heart failure

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. 232 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 midsystolic 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. 232 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

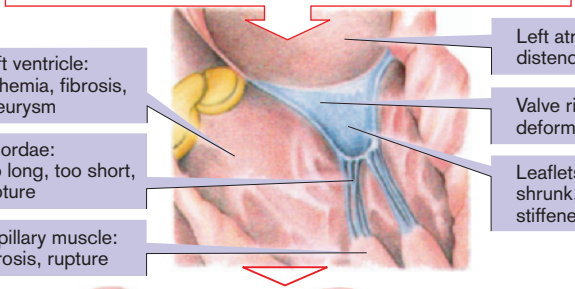
- the mitral opening area in systole,
- the pressure gradient from LV to LA during ventricular systole, and
- the duration of systole.

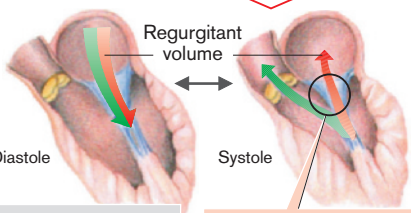
Left atrial pressure (P_{LA}) is raised if there is additional aortic stenosis or hypertension, and the proportion of ventricular systole in the cardiac cycle (systolic duration/time) is increased in tachycardia (e.g., on physical activity or tachyarrhythmia due to left atrial damage), such factors accentuating 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 end diastolic 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. 238). 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. 228) much less commonly than mitral stenosis (→ p. 208) 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.

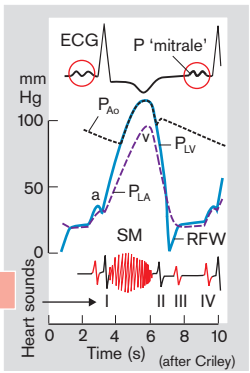
If there is **acute MR** (e.g., rupture of papillary muscle), the left atrium cannot be stretched much (low compliance). P_{LA} will therefore rise almost to ventricular levels during systole (→ **A**, right; very high *v* wave) so that the pressure gradient between LV and left atrium is diminished and 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. 246 ff.), places the patient in great danger.

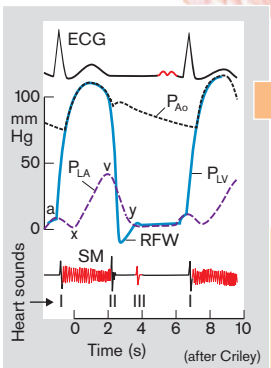
A. Causes and Consequences of Mitral Regurgitation





Mitral regurgitation





Chronic | **Acute**

high — Atrial compliance — low

Volume load

Atrial dilation

Mitral regurgitation ↑

Atrial damage

Tachyarrhythmia

Regurgitant volume ↑↑

Ventricular dilation

Left heart failure

Atrial pressure (P_{LA}) ↑

Dyspnea, hemoptysis

Pulmonary edema

Pulmonary hypertension

Right heart failure

'Forward' CO ↓

Systolic pressure ↓

Tachycardia

Regurgitant volume ↑↑

Mitral regurgitation ↑↑

Aortic Stenosis

The normal opening area of the aortic valve is 2.5 – 3.0 cm^2. 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 ($P_{LV} - P_{Ao}$; →**A1**, blue area). In aortic stenosis ([AS] 20% of all chronic valvar defects) the emptying of the left ventricle is impaired. The **causes** of AS (→**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 (→p. 208), 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 $P_{LV} - P_{Ao}$ (→**A1, 2**), is increased to such an extent that a normal cardiac output can be maintained over many years (P_{LV} up to 300 mmHg). Only if the area of the stenosed valve is less than ca. 1 cm^2 do symptoms of AS develop, especially during physical exertion (cardiac output ↑→P_{LV}↑↑).

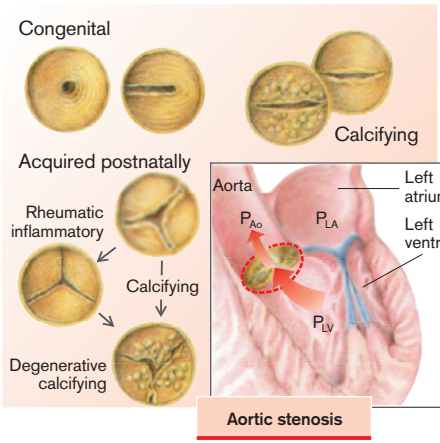
The **consequences** of AS include *concentric hypertrophy of the left ventricle* as a result of the increased prestenotic pressure load (→p. 238). This makes the ventricle less distensible, so that the pressures in the ventricle and atrium are raised even during diastole (→**A2,** P_{LV}, P_{LA}). The strong left atrium contraction that generates the high end-diastolic pressure for ventricular filling causes a fourth heart sound (→**A2**) and a large *a* wave in the left atrium pressure (→**A2**). 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; →p. 248). In addition, the ejection period is lengthened causing a small and slowly rising pulse (*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 (→**A2,** SM) and, if the valve is not calcified, an aortic opening click (→**A2**). The transmural pressure of the *coronary arteries* is diminished in AS for two reasons:

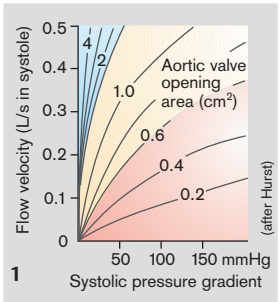
- The left ventricular pressure is increased not only in systole but also during diastole, which is so important for coronary perfusion (→p. 230).
- The pressure in the coronary arteries is also affected by the poststenotically decreased (aortic) pressure.

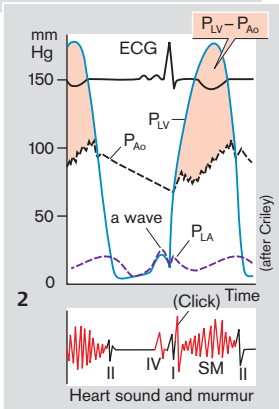
Coronary blood flow (→p. 230 ff.) is thus reduced or, at least during physical exertion, can hardly be increased. As the hypertrophied myocardium uses up abnormally large amounts of oxygen, myocardial hypoxia (*angina pectoris*) and myocardial damage are consequences of AS (→p. 232 ff.).

Additionally, on physical exertion a critical fall in blood pressure can lead to dizziness, transient loss of consciousness (*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; →**A1**). Furthermore, probably in response to stimulation of left ventricular baroreceptors, additional "paradoxical" 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 (→**A**). *Heart failure* (→p. 238 ff.), *myocardial infarction* (→p. 234), or *arrhythmia* (→p. 200 ff.), which impairs ventricular filling, contribute to this vicious circle.

A. Causes and Consequences of Aortic Stenosis







Aortic stenosis

CO ↓

Systemic hypotension

Ventricular hypertension ↑

Stimulation of ventricular baroreceptors (?)

"Paradoxical" vasodilation

Transmural coronary artery pressure ↓

Coronary artery flow ↓

Physical exercise

Left heart hypertrophy

Cardiac O_2 consumption ↑

Myocardial hypoxia (angina pectoris)

Vasodilation during exercise

Arrhythmia

Ventricular filling ↓

Blood pressure ↓↓

Syncope

Left heart failure

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. 193), 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.

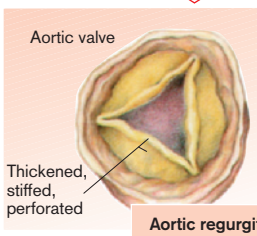
The **consequences** of AR depend on the regurgitant volume (usually 20–80 mL, maximally 200 mL per beat), which is determined by the *opening area* and the *pressure difference* during diastole ($P_{Ao} - P_{LV}$) as well as the *duration of diastole*. To achieve an adequate *effective* stroke volume (= forward flow volume) the total stroke volume (→ **A 2**, SV) must be *increased* by the amount of the regurgitant volume, which is possible only by raising the end diastolic volume (→ **A 2**, 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 (→ **A 2,** ESV) is also greatly increased. According to Laplace's law (→ p. 239), ventricular dilation demands greater myocardial force as otherwise P_{LV} would decrease. The dilation is therefore accompanied by **left ventricular hypertrophy** (→ p. 238 f.). 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 (→ **A 1**). 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 (→ **A 1**, SM).

The above-mentioned mechanisms allow the heart to **compensate** for chronic AR for several decades. In contrast to AS (→ p. 212), 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.

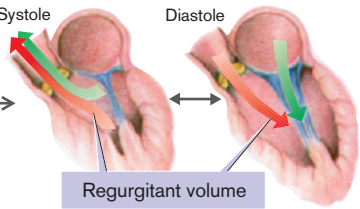
The compensatory mechanisms, however, come at a price. Oxygen demand rises as a consequence of *increased cardiac work* (= pressure times volume; → **A 2**, orange area). In addition, the diastolic pressure, which is so important for *coronary perfusion* (→ p. 230), is reduced and simultaneously the 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. 238) and *angina pectoris* or *myocardial infarction* (→ p. 234) 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 (→ **A 2**, 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. 228), 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 regurgitation



Regurgitant volume

Diastolic blood pressure ↓

Effective stroke volume ↓

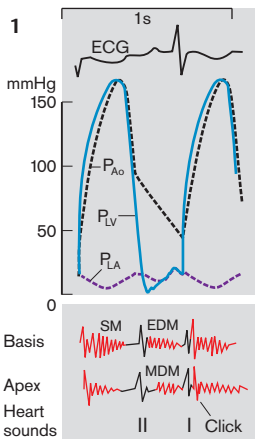
Compensation

Ventricular dilation
Laplace's law
Wall tension ↑
LV hypertrophy
O_2 consumption ↑

End-diastolic volume ↑
Total stroke volume ↑
Effective stroke volume normalized

Years to decades

1



(after Criley)

Myocardial hypoxia (angina pectoris)

Decompensation

Left heart failure

Effective stroke volume ↓

Ventricular dilation ↑↑

Functional mitral regurgitation

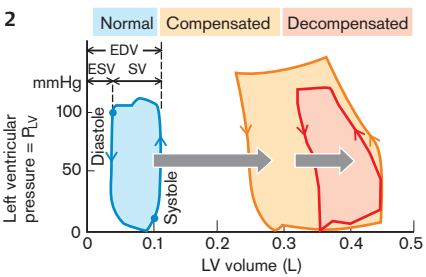
Ventricular compliance ↓

Left atrial pressure ↑

Pulmonary edema

Left heart failure

2



(after Rackley et al.)

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. 208 – 215). 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. 218), 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 cm^2, reduced to < 1.5 – 2.0 cm^2). 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. 193), 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. 228). **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. 228). 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.

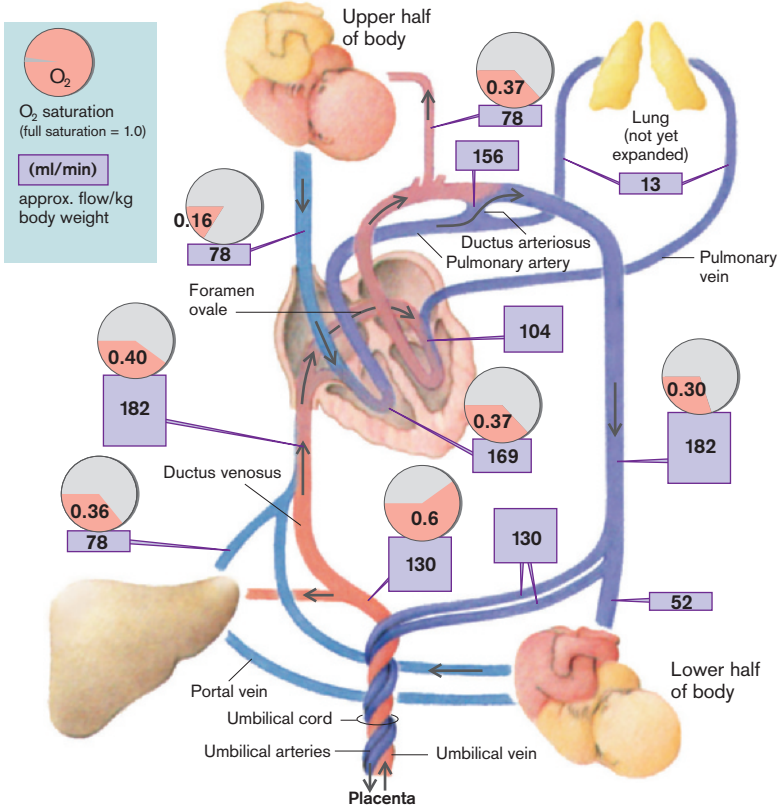
In the **fetal circulation** (→ **A**) there is

- low resistance in the systemic circulation (placenta!),
- 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).

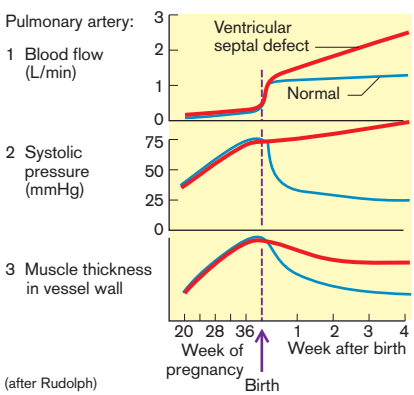
At birth the following important changes occur:

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_{O_2} 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**).

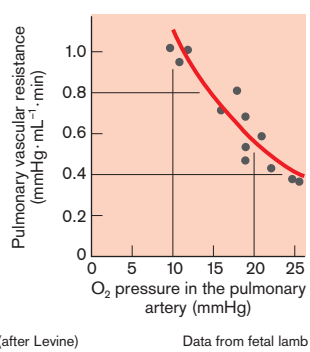
A. Fetal Circulation



B. Pulmonary Circulation



C. Fetal Hypoxic Vasoconstriction



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*.

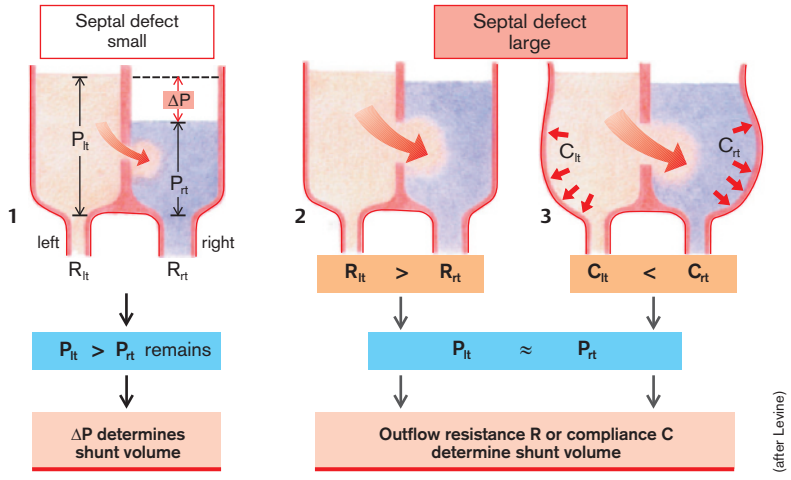
Abnormal shunts can be caused by *patency* of the duct (patent or persisting DA [PDA]; →**E**) or of the FO (PFO), by defects in the *atrial* or *ventricular septum* (ASD or VSD), or by *arteriovenous fistulae*, etc. **Size** and **direction of the shunt** in principle depend on: 1) the *cross-sectional 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 (→**D 1**). 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 (→**D 2**; e.g., PDA), as well as 4) their *compliance* (*= volume distensibility;* e.g., of the ventricular walls in VSD; →**D 3**).

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 ("*machinery 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 (→**D 1**, ΔP), 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.

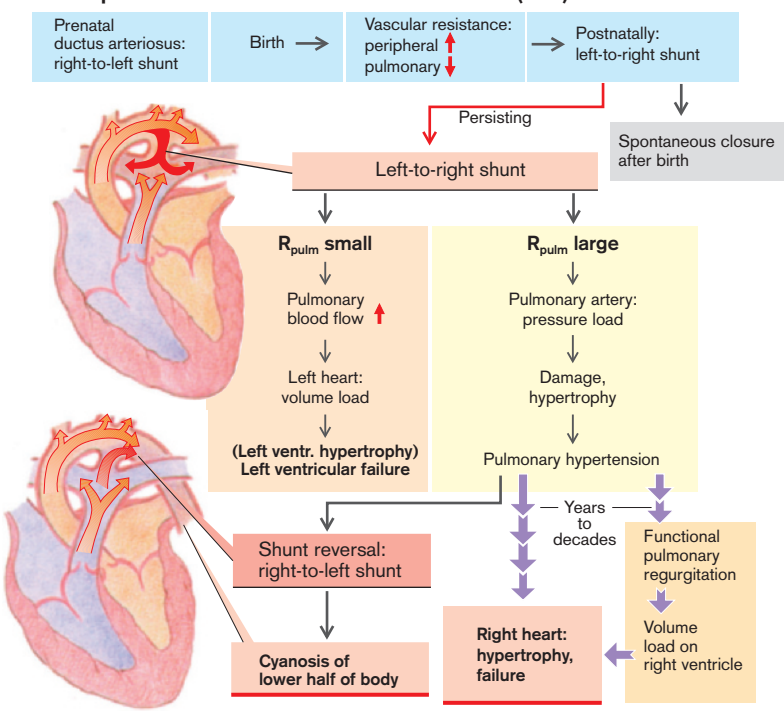
If, on the other hand, the pulmonary vascular resistance (R_{pulm}) remains relatively high postnatally (→**E**, right), and therefore the shunt volume through the ductus is relatively small despite a large cross-sectional area, a moderately increased left ventricular load can be compensated for a long 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. 228). 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



E. Consequences of Postnatal Patent Ductus Arteriosus (PDA)



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**). The optimal resting (sitting or recumbent) P_D ranges from 60 – 80 mmHg (8 – 10.7 kPa); the optimal P_S ranges from 100 – 130 mmHg (13 – 17.4 kPa) (→ p. 222). The difference between P_D and P_S is the **blood pressure amplitude** or **pulse pressure** (→ **A**).

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.

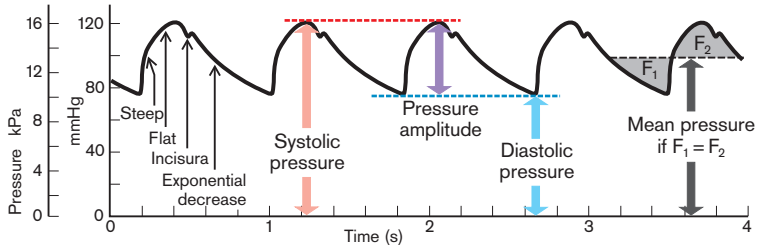
In the vascular system the flow fluctuations in the great arteries are dampened through the "windkessel" (compression chamber) effect to an extent that precapillary blood no longer flows in spurts but continuously. Such a system consisting of highly compliant conduits and high-resistance terminals, is called a *hydraulic filter*. The arteries become more rigid with age, so that the P_S rise per volume increase ($\Delta P/\Delta V$ = elasticity) 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.

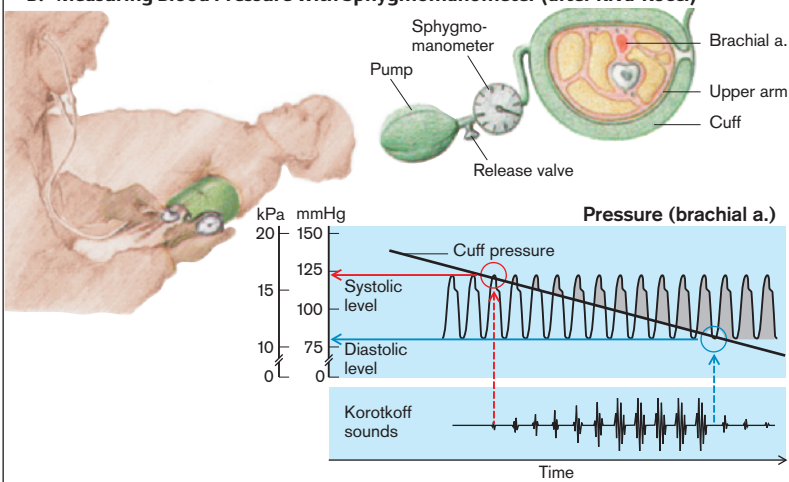
Sources of error when measuring blood pressure. Complete disappearance of the sound sometimes occurs at a very low pressure. The difference between phases 4 and 5 (normally about 10 mmHg) is increased by conditions and diseases that favor flow turbulence (physical activity, fever, anemia, thyrotoxicosis, 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. 222) 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.

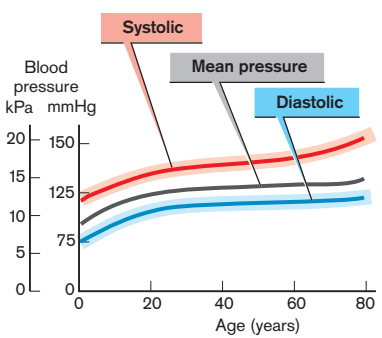
A. Aortic Pressure Curve (Invasive Measurement)



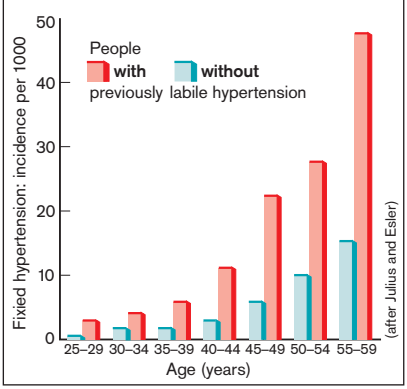
B. Measuring Blood Pressure with Sphygmomanometer (after Riva-Rocci)



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. 228). 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 following values are applicable to all age groups (mmHg/7.5 = kPa):

	Optimal	Prehypertensive	Threshold hypertension	Hypertension
Diastolic pressure (P_D [mmHg])	60–80	80–89	90–95	> 95
Systolic pressure (P_S [mmHg])	100–130	130–139	140–160	> 160

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. 221 D). Assessment of blood pressure should be based on the mean values of at least 3 readings on two days (see also p. 220).

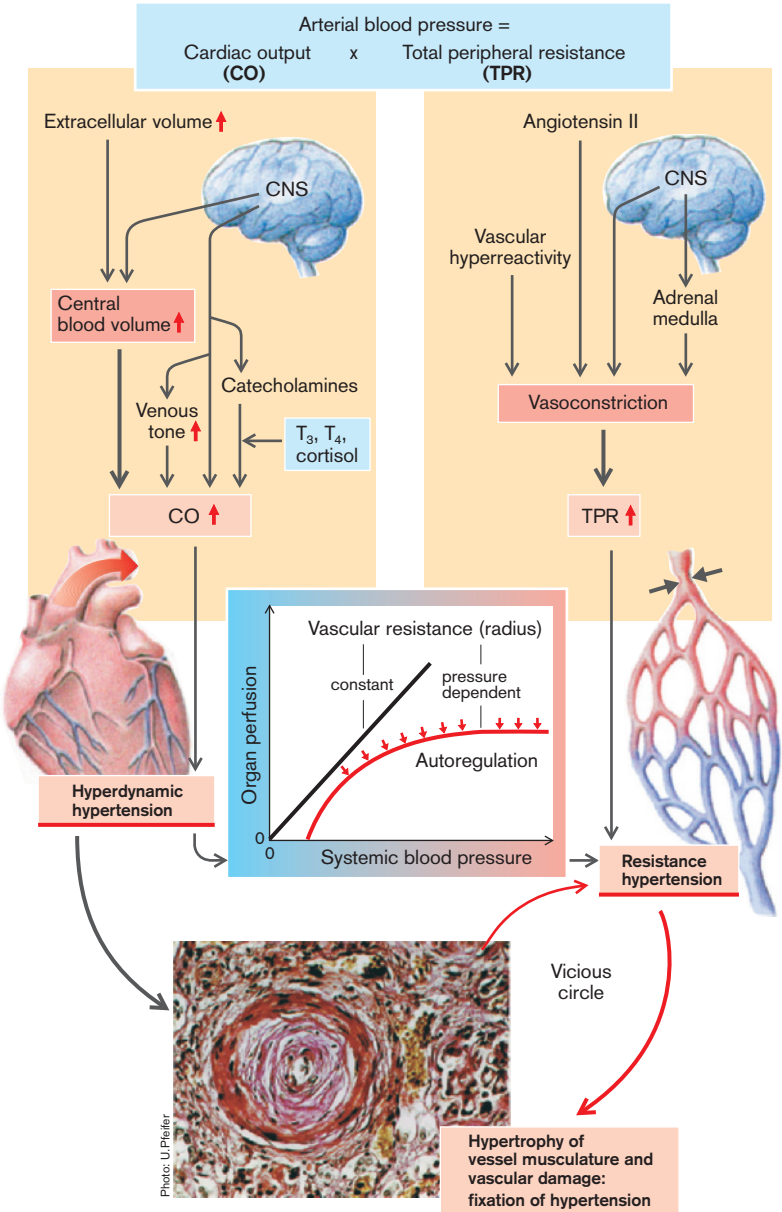
The product of *cardiac output* (= stroke volume [SV] · heart rate) and *total peripheral resistance* (TPR) determines blood pressure (Ohm's law). H. thus develops after an increase in cardiac output or TPR, or both (→ **A**). In the former case one speaks of *hyperdynamic H.* or *cardiac output H.*, with the increase in P_S being much greater than that in P_D. In the second case one speaks of *resistance H.*, in that type of hypertension 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*. *Autoregulatory 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; → **B 2, 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** (→ **B 1**). 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. ⅓ 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) e.g., through an increase in aldosterone, those with an increased salt sensitivity are apparently relatively unprotected against a high NaCl intake. In these patients, aldosterone release is so strongly inhibited even at "normal" Na^+ intake (> 5.8 g/d) that it cannot be lowered any further. A diet with low NaCl intake would in this

A. Principles of the Development of Hypertension



case bring NaCl balance into the aldosterone regulatory range.

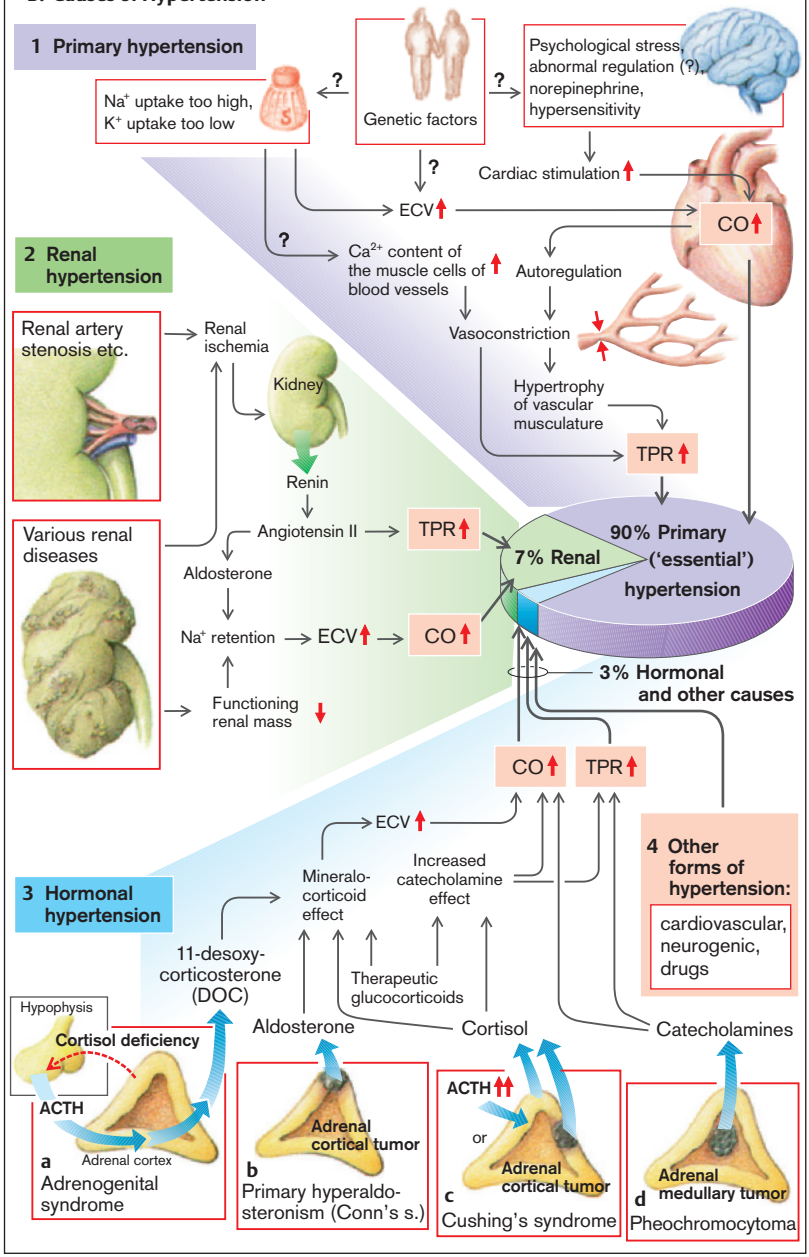
The actual **connection between NaCl sensitivity and primary H.** has not been fully elucidated, but the possibility is being considered that responsiveness to catecholamines is raised in people sensitive to NaCl. This results, for example, on psychological stress, in a greater than normal rise in blood 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 (→ **B 2, 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 (→ **B 2**, see also p. 124): 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, polycystic kidney disease, see also p. 110), 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 (→ **B 2**). 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 hypervolemic form of renal H. Renal H. can also be caused by a *renin-producing tumor*. The kidney is also central to other forms of hypertension that do not primarily originate from it (primary H., hyperaldosteronism, adrenogenital syndrome, Cushing's syndrome). Furthermore, in every case of chronic H. secondary changes in the kidney 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 (→ **B 3**):

◆ In the *adrenogenital syndrome* (→ **B 3 a**) 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,

B. Causes of Hypertension



11-deoxycorticosterone (DOC), are produced and released (→ p. 286 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; →**B 3 b**). 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* (→**B 3 c**). 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. 286 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 cortisone but rather has its full effect on the renal mineralocorticoid receptor.

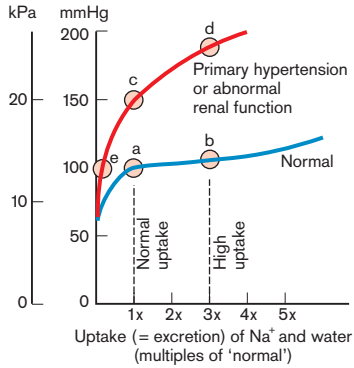
◆ *Pheochromocytoma* (→**B 3 d**) is an adrenomedullary tumor that produces catecholamines, resulting in uncontrolled high epinephrine and norepinephrine levels and thus both cardiac output hypertension and resistance hypertension.

◆ *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.

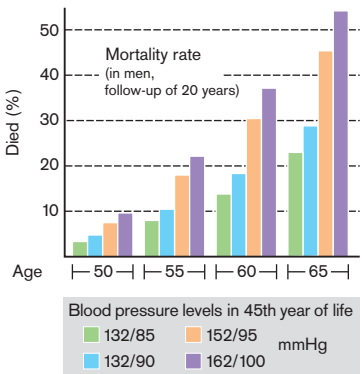
The **consequences of hypertension** (→**E**) most importantly result from *atherosclerotic damage* in arterial vessels (→ p. 252 ff.), which can be observed well by means of funduscopy. Because of the resulting increase in flow resistance, every form of hypertension ultimately creates a vicious circle. 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. 254). *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 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



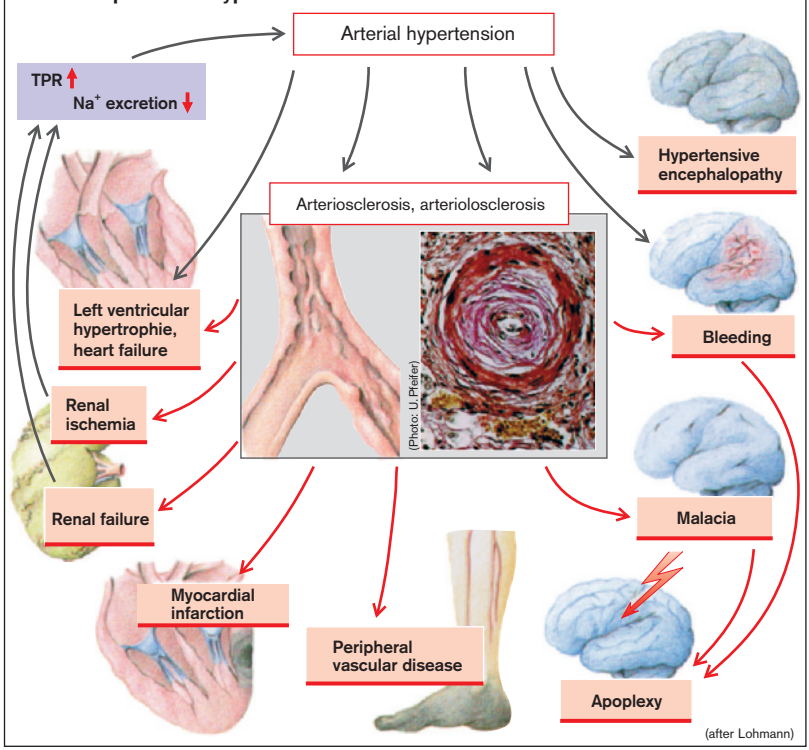
(after Guyton et al.)

D. Mortality and Hypertension



(after Society of Actuaries: Build and Blood Pressure Study, 1959)

E. Consequences of Hypertension



(after Lohmann)

Pulmonary Hypertension

The mean pulmonary artery pressure ($\bar{P}_{PA} \approx 15$ mmHg = 2 kPa) is determined by three variables, namely pulmonary vascular resistance (PVR), cardiac output (CO), and left atrial pressure (P_{LA} = ca. 5 mmHg = 0.7 kPa).

According to Ohm's law $\Delta P = PVR \cdot CO$.

As $\Delta P = \bar{P}_{PA} - P_{LA}$,

$$\bar{P}_{PA} = PVR \cdot CO + P_{LA}.$$

Pulmonary hypertension (PHT) develops when one (or several) of the above variables is raised so much that at rest $\bar{P}_{PA}$ is *over 20 mmHg*; on exercise it is above 32 mmHg (see pulmonary edema, p. 84). 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. 208).

◆ **Cardiac output increase**, except in left-to-right shunt (→ p. 218). 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.

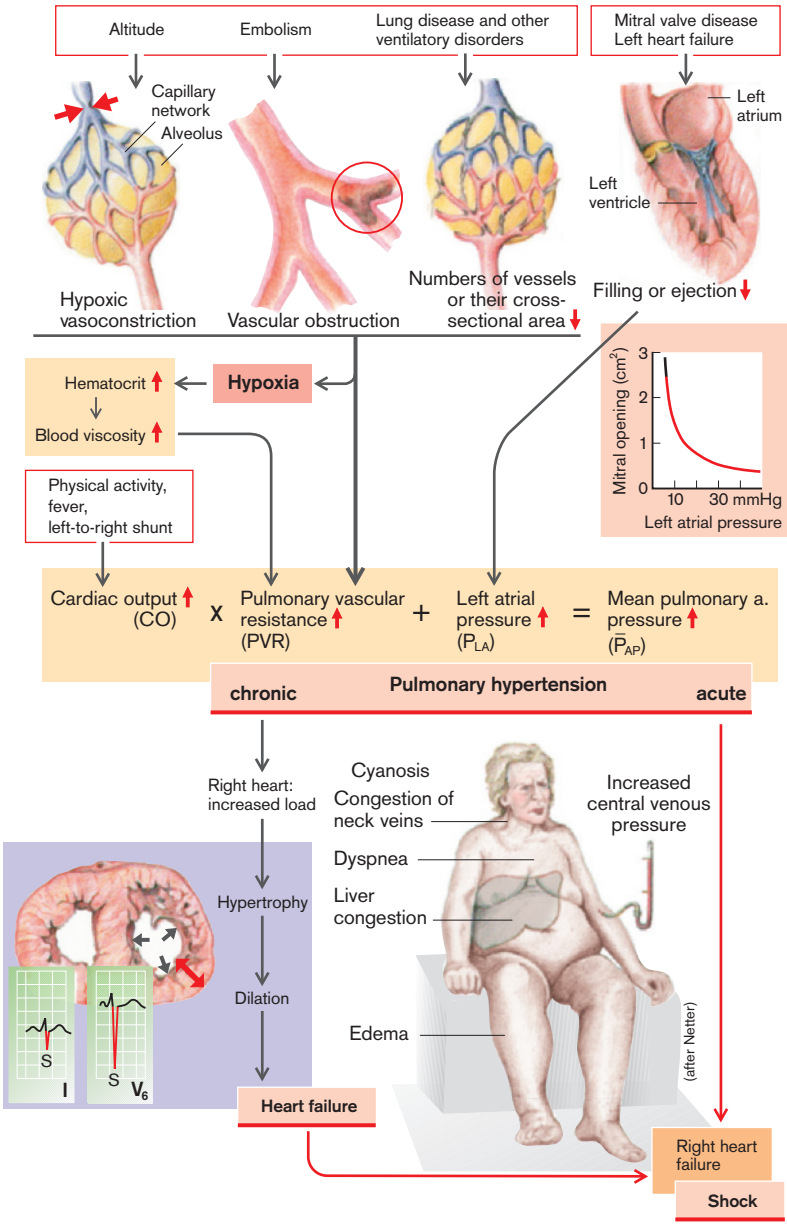
Acute PHT almost always results from a reduction in the cross-sectional area of the vascular bed (of at least 50%, because of the high vascular distensibility), as by *pulmonary embolism*, i.e., migration of *thrombi* or (rarely) other emboli from their site of origin into the pulmonary arteries (→ **A**, top and p. 258). 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. 246).

Among the **causes of chronic PHT** are:

a *Lung disease* (asthma, emphysema, chronic obstructive bronchitis [smoking!] 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:* ECG!; → **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. 208 ff.) or *left heart failure* (→ p. 238 ff.) develop PHT.

A. Causes and Consequences of Pulmonary Hypertension



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, $\dot{Q}_{cor}$, has a few special features:

1. Phasic flow. $\dot{Q}_{cor}$ 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 atrium 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, $\dot{Q}$, multiplied by the arteriovenous O_2 concentration difference $(C_a - C_v)_{O_2}$. If O_2 demand of the myocardium rises, for example, through physical activity or hypertension (→ **C**, right and p. 232), both variables may in principle be increased, but $(C_a - C_v)_{O_2}$ and thus oxygen extraction $(= 100 \cdot [(C_a - C_v)/C_a]_{O_2}) \approx 60\%$ 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 $\dot{Q}_{cor}$ (= aortic pressure P_{Ao}/coronary resistance R_{cor}). If P_{Ao} remains unchanged, R_{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 $\dot{Q}_{cor}$ 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. 233 A, normal).

3. $\dot{Q}_{cor}$ 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 $\dot{Q}_{cor}$. Several factors are involved in this autoregulation:

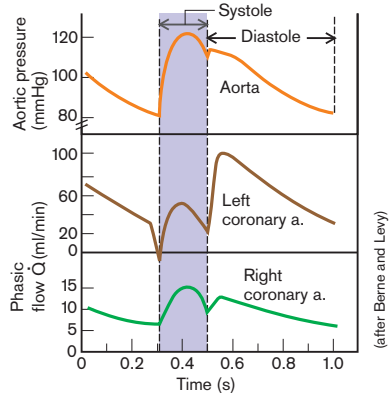
◆ *Metabolic factors*. First of all, O_2 acts as a vasoconstrictor, i.e., *O_2 deficiency* dilates the coronary arteries. AMP, a metabolic breakdown product of ATP, cannot be sufficiently regenerated to ATP during hypoxia, and thus the concentration of AMP and its breakdown product *adenosine* rises 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. 233 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 guanylylcyclase activity, and thus intracellularly raises the concentration of cyclic guanosine monophosphate (cGMP). Finally, cGMP activates protein kinase G, which relaxes the vascular musculature.

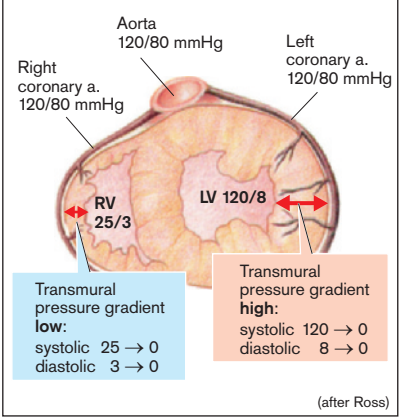
◆ *Neurohumoral factors*. Epinephrine and norepinephrine, circulating and released from the sympathetic nerve fiber endings, respectively, act as vasoconstrictors on the α_1-adrenoreceptors that prevail in *epicardial vessels*, and as vasodilators at β-adrenoceptors that predominate in *subendocardial 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 insufficiency** (hypoxia) results (→ **C, D** and p. 232 ff.).

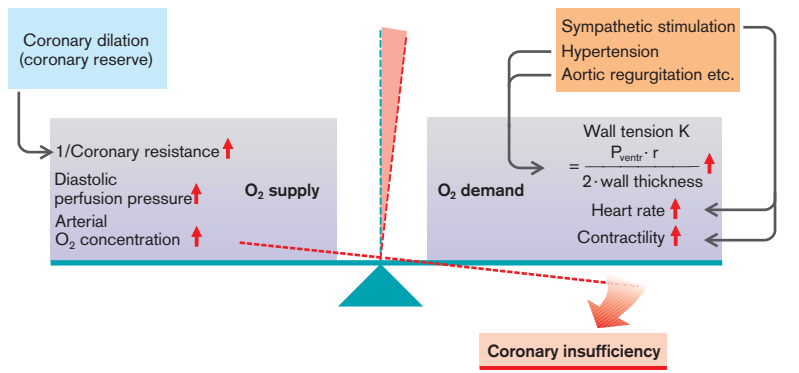
A. Coronary Blood Flow



B. Pressure Gradients in Myocardium



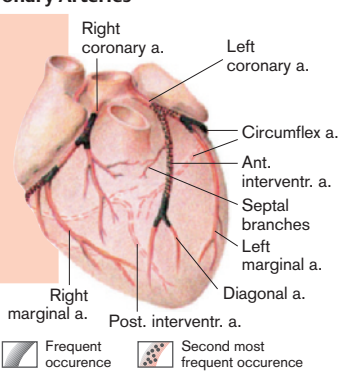
C. Components of O_2 Balance in Myocardium

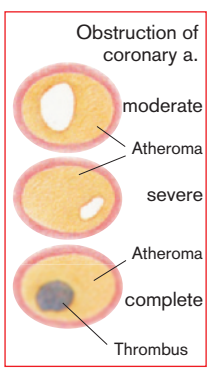


D. Atherosclerosis of Coronary Arteries

Risk factors of atherosclerosis

Smoking
Overweight
Lack of exercise
Food (fat, cholesterol)
Psychological stress
Lipid metabolism
Diabetes mellitus
Hypertension
Age etc.





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 O_2 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 O_2 supply no longer being able to meet any increased O_2 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)

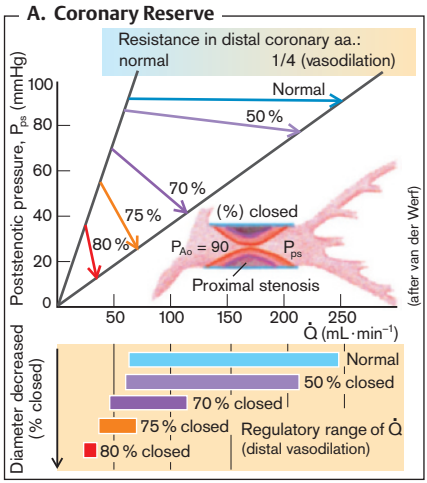
The **main cause** of CHD is narrowing of the proximal large coronary arteries by **atherosclerosis** (→ pp. 231 D and 252 ff.). The poststenotic blood pressure (P_{ps}) is therefore significantly lower than mean diastolic aortic pressure (P_{Ao}; → **A**). To compensate for this raised resistance or 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 O_2 supply is reduced, for example, by a lowered diastolic blood pressure (hypotension, aortic regurgitation), arterial hypoxemia (staying at high altitude), or decreased O_2 capacity (anemia), O_2 balance is disturbed, even when there is only mild coronary artery stenosis (→ p. 231 C).

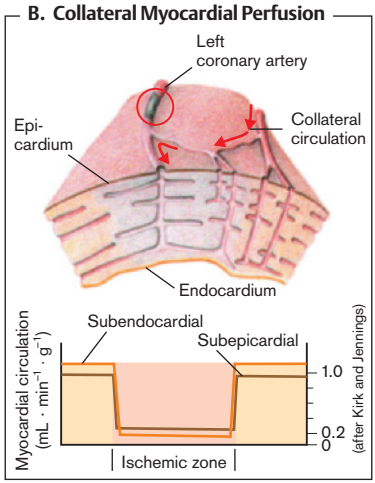
If the pain ceases when the physical or psychological stress is over, the condition is called **stable angina pectoris**. When a patient with chronic stable angina pectoris suddenly has stronger and more frequent anginal pain (**unstable angina pectoris**), it is often a premonitory sign of acute myocardial infarction, i.e., complete occlusion of the relevant coronary artery (see below).

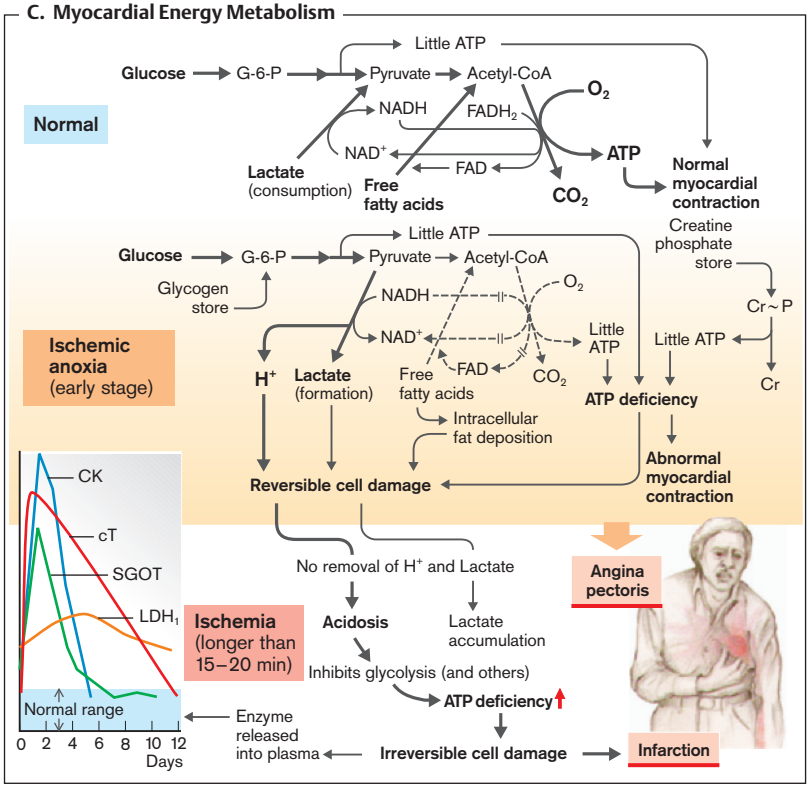
However, complete coronary occlusion does not necessarily lead to infarction (see below), because in certain circumstances a *collateral blood supply* may develop as long-term adaptation so that, at least at rest, the O_2 demand can be met (→ **B**). The affected region will, however, be particularly in danger in cases of hypoxemia, a drop in blood pressure, or an increased O_2 demand.

Pain resulting from a lack of O_2 can also occur at rest due to a **spasm** (α_1-adrenoreceptors; → p. 230) 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 1.2-fold, 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 O_2 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 ($N \cdot m^{-2}$) 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. 231 C). Thus if, without change in wall thickness, the ventricular pressure (P_{ventr}) rises (aortic valve stenosis, hypertension; → pp. 212 and 222) and/or the ventricular radius increases (greater filling in mitral or aortic regurgitation; → pp. 210 and 214), the wall tension necessary for maintaining normal cardiac output and thus myocardial O_2 demand are raised. Should ▶







this continue over a long period, the ventricular myocardium will hypertrophy (→ p. 238 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* (→ p. 238 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 (→ **C**, normal). When blood supply is interrupted (ischemia), this aerobic energy gain stagnates, so that ATP can only be formed anaerobically. Lactatic acid is now produced, dissociating into H^+ ions and lactate. In these circumstances not only is lactate not used up, it is actually produced (→ **C**, early "ischemic anoxia"). The ATP yield is thus quite meager and, furthermore, the H^+ ions accumulate because of the interrupted blood flow, both events being responsible for abnormal ventricular contraction (reversible cell damage; → **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 and of cardiac troponin (cT) into the blood (→ **C**, left).

ATP deficiency leads to:

- Impairment of the *systolic pumping action* of the ventricle (systolic dysfunction; → p. 238 ff.) as well as
- *Decreased compliance* of the myocardium during diastole (diastolic dysfunction; → p. 238 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
- *Acute mitral regurgitation* (→ p. 210).
- Finally, disorder of myocardial excitation caused by the ischemia (→ **E**) may precipitate dangerous *arrhythmias* (ECG; → p. 200 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 (→ p. 231 C) in patients with angina are:

- Lowering myocardial O_2 consumption (β-adrenergic blockers; organic nitrates that reduce the preload by generalized vasodilation; 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 atherosclerotically 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.

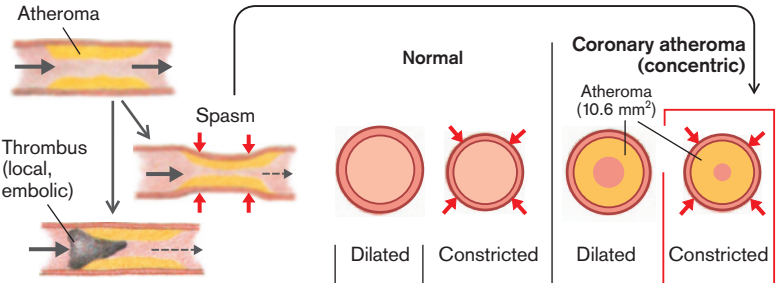
This development is promoted by

- *turbulence*, and
- *atheroma rupture* with collagen exposure.

Both events

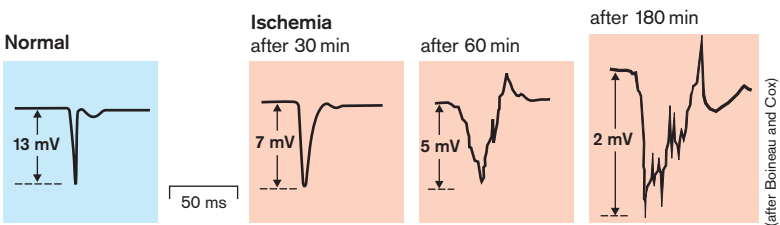
- activate *thrombocytes* (aggregation, adhesion, and vasoconstriction by release of thromboxan). Thrombosis is also encouraged through
- *abnormal functions of the endothelium*, thus its vasodilators (NO, prostacyclin) and antithrombotic substances are not present (tissue plasminogen activator [t-PA], anti-

D. Acute Ischemia in Coronary Atherosclerosis



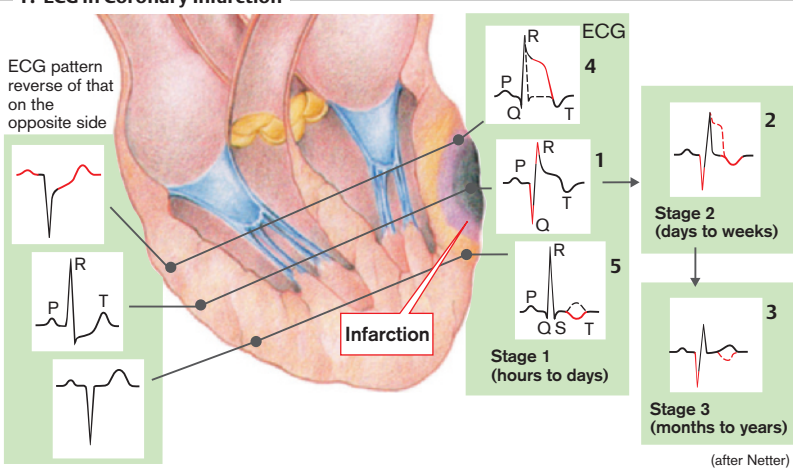
	Normal		Coronary atheroma (concentric)	
	Dilated	Constricted	Dilated	Constricted
Circumference of muscle ring	100 %	95 %	100 %	95 %
Internal radius (mm)	2	1.9	0.78	0.47
Lumen area (mm^2)	12.5	11.3	1.9	0.7
Lumen area reduced by	0 %	10 %	85 %	94 %
Resistance (~ $1/r^4$) (muscle wall thickness ignored)	(1)	x 1.2	x 43	x 328 !

E. Excitation of Myocardial Cell in Ischemia



Bipolar intramural electrogram

F. ECG in Coronary Infarction



thrombin 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 O_2 demand at rest (e.g., in aortic stenosis).

ECG (→ **F**). A prominent characteristic of *transmural infarction* (tmI) 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 anymore an 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 V_5, V_6, 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**)

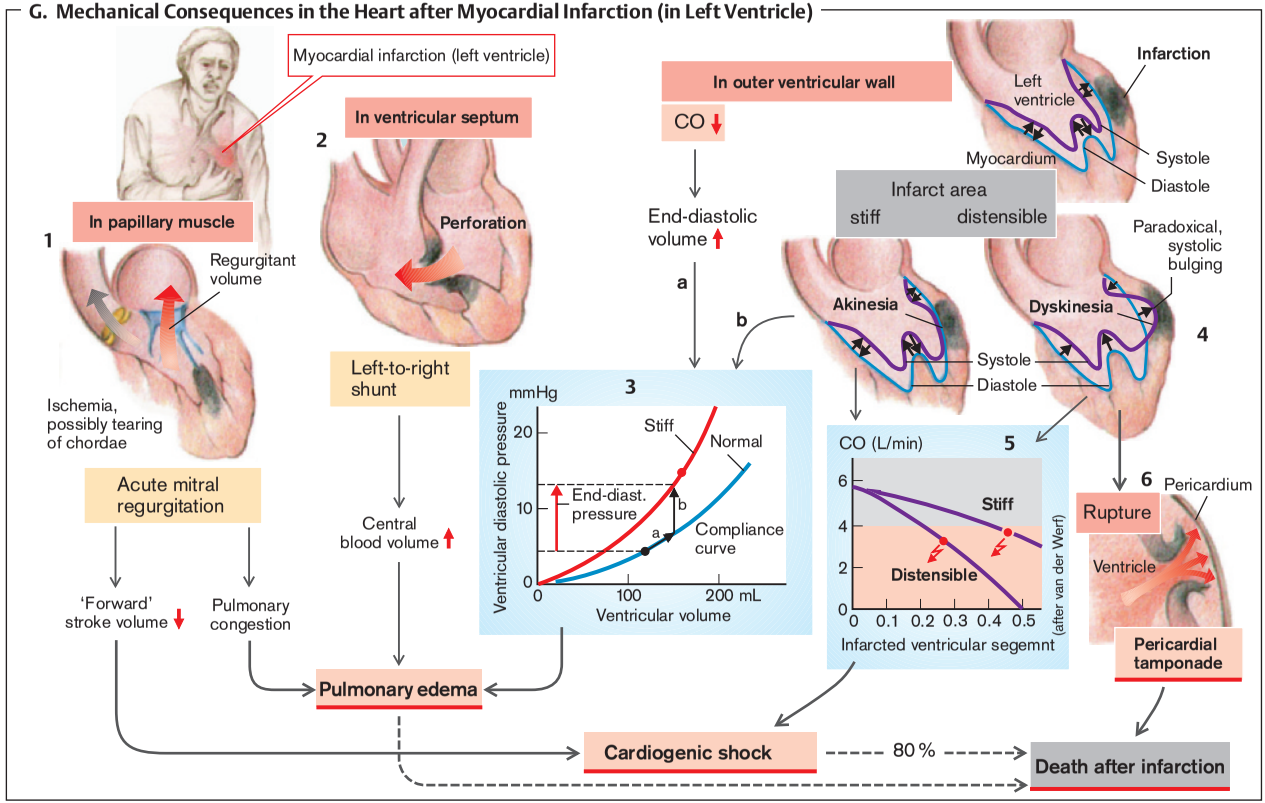
The ST segment returns to normal one to two days after an MI, but for the next few weeks the **T wave** will be inverted (→ **F5**, **F2**).

If sizeable portions of the myocardium die, **enzymes** and other intracellular components of cardiomyocytes are released into the bloodstream. It is not so much the level of the 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 (LDH_1) on days three to five (→ **C**, bottom). However, as plasma concentrations of those enzymes may increase without cardiac infarction, at present the plasma concentration of cardiac troponin (cT) is taken as a diagnostic parameter: cT increases within approximately 3 hours, reaches its maximum within 20 hours, and gradually decays to reach normal levels within 10 – 14 days after cardiac infarction (→ **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. 200 ff.), 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. 210);
- Perforation of the interventricular septum with left-to-right shunting (→ **G2** and p. 218);
- 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. 238). 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. 244).

G. Mechanical Consequences in the Heart after Myocardial Infarction (in Left Ventricle)



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. 232 ff.) and hypertension (→ p. 222 ff.), which account for some three-quarters of all cases. However, nearly all other forms of cardiac disease (valvar defects, cardiomyopathies; → **A**) as well as certain extracardiac diseases can result in HF. In particular, *right ventricular failure* may result from pulmonary hypertension (→ p. 228) in addition to right heart defects and shunts (→ p. 216 ff.). The right ventricle (RV) may also be affected secondarily by decreased function of the left ventricle (mitral stenosis, left HF). Usually HF only becomes manifest initially on *severe physical work* (when maximal O_2 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).

In principle, a distinction is made between HF with *systolic dysfunction* and HF with *diastolic dysfunction.* At a **systolic dysfunction** ventricular contractility is decreased (→ **A, C1:** U → U'), the ventricles are not sufficiently emptied during contraction, the end diastolic volume (EDV) increases and the stroke volume (SV) decreases (→ **C1**). As a result the *ejection fraction* (EF = SV/EDV → p. 192) decreases. The most frequent **cause** of a systolic dysfunction is *cardiac infarction*. Depending on its localization it is the LV or the RV that is affected, whereby a HF of the LV frequently results in a secondary RV failure. Systolic failure involves disorders of energy supply and utilization, cardiac excitation, contractile apparatus, and regulation of cytosolic Ca^{2+}.

The **ventricular filling** is a function of the magnitude and speed of ventricular **relaxation**, which is an ATP-dependent process. The time course of relaxation depends, in part, on the decline of cytosolic Ca^{2+}, i.e., the rapidity of the **Ca^{2+}** reuptake into the sarcoplasmatic reticulum ($SERCA_{2A}$) and the interstitium (sarcolemmal Ca^{2+}-ATPases). Beyond that, the passive stiffness of the myocardium is modulated by phosphorylation of the titin "tension springs" by protein kinase G (PKG). Moreover, the relaxation is accelerated by phosphorylation of phospholamban during β-adrenergic myocardial stimulation (positive lusitropy).

At **diastolic dysfunction** the ventricular filling is decreased, which frequently (♀ > ♂) results from *insufficient relaxation*, for instance due to decreased Ca^{2+}-pump rate as a result of ATP deficiency during ischemia. Further causes of a diastolic dysfunction include enhanced stiffness of the ventricular wall and an impairment of ventricular distension by:

- *cardiac hypertrophy* due to a hypertrophic cardiomyopathy or due to a) pulmonary or systemic hypertension and b) enhanced ventricular pressure at stenosis of the pulmonary or aortic valve (impairment of ejection, → pp. 212, 216);
- interstitial myocardial deposition of *collagen* during aging, of *amyloid* in amyloidosis (→ p. 274), or of Fe in hemochromatosis (→ p. 270);
- *restrictive cardiomyopathy*
- *constrictive percarditis* or pericard tamponade (→ p. 244).

A **consequence** of diastolic dysfunction is a decrease of both stroke volume and endodiastolic volume (EDV) (→ **C3**), while the ejection fraction (EF) rather remains constant or even increases, in order to maintain the cardiac output despite insufficient ventricular filling. Nevertheless, a substantial decrease of LV filling may lead to a decline of cardiac output with the respective clinical consequences (see below). An *increase of the pressure in the respective atrium* enhances the ventricular filling but may, by the same token, lead to edema in the respective upstream capillary bed (see below).

HF caused by myocardial disease: In *coronary heart disease* (ischemia; → p. 232) and after *myocardial infarction* (→ p. 234) the load on the noninfarcted myocardium increases and causes a *systolic dysfunction* (see above) with reduced cardiac contractility and decreased stroke volume (→ **A**). Hypertrophy of the remaining myocardium, a stiff myocardial scar as well as the diminished Ca^{2+} pump rate in the ischemic myocardium further lead to *diastolic dysfunction*. Finally, a compliant infarct scar may bulge outward during systole (dyski-

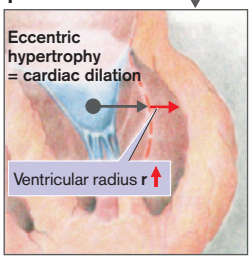
A. Causes and Mechanical Consequences of Systolic Ventricular Dysfunction

Aortic regurgitation
Myocardial infarction
Myocardial ischemia
Hypertension, aortic/ pulmonary stenosis

Regurgitant volume → **Volume load**
Mass of intact myocardium ↓ → Load on remaining myocardium ↑
Pressure load → $P_{ventr.}$ ↑ → $T_{ventr.}$ ↑

Laplace:
Wall tension T = $P_{ventr.}$ · radius r / 2 · wall thickness d

1



Contractility ↓ (flatter U curve)

see C.1, C.2

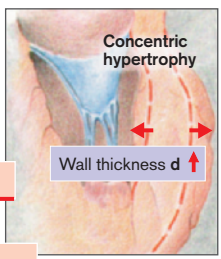
EDV ↓ → Ejection fraction ↓

Dilatative cardiomyopathy → r ↑ → $T_{ventr.}$ ↑

Decompensation → EDV ↑↑ SV ↓↓ (see C.5)

Temporary improvement

2



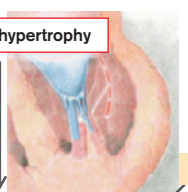
Ventricular hypertrophy

Diastolic dysfunction

see B.

B. Causes and Mechanical Consequences of Diastolic Ventricular Dysfunction

Hypertrophic cardiomyopathy → **Ventricular hypertrophy**



Myocardial hypoxia
ATP deficiency
Diastolic: cytosolic [Ca^{2+}] ↑
Relaxation slowed

Restrictive cardiomyopathy
Myocardial deposition in fibrosis, amyloidosis, hemochromatosis, sarcoidosis etc.
Pericardial tamponade
Constrictive pericarditis

→ Ventricular compliance curve rises steeply

see C.3

EDV ↓, SV ↓ (see C.3, C.4)

Temporary improvement

Atrial pressure ↑ → **Edema** ↑

nesia, → p. 237, **G4**), resulting in additional volume load (regurgitant volume). *Cardio-myopathies* can also lead to HF, whereby in the hypertrophic and restrictive forms the diastolic dysfunction prevails.

HF caused by volume load: Aortic and pulmonary regurgitation, for example, are characterized by the *regurgitant volume* (→ p. 214 ff.) that is added to the effective stroke volume. The endodiastolic volume (EDV), and therefore the radius (**r**) of the left ventricle, is 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, should rise to achieve a normal, effective stroke volume. As this succeeds only inadequately, stroke volume, and thus cardiac output (= heart rate · stroke volume), decreases and the blood pressure falls. If chronic volume load develops, the dilated ventricle reacts with **hypertrophy** to compensate with an increased wall thickness (**d**). However, **r** remains elevated (*eccentric hypertrophy*; →**A1**, left) 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 worsens relatively rapidly because of the resulting *myocardial remodeling* (see below). 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 endodiastolic volume (→**C5**). Similar considerations apply to the *dilatative cardiomyopathy*.

HF due to pressure load: The wall tension (**T**) of the left ventricle also rises in systemic or pulmonary hypertension as well as in aortic or pulmonary stenosis, because an increased pressure in the respective ventricle (P_{Ventr}) is required (Laplace's law; →**A**, right). A systolic dysfunction develops with compensatory *hypertrophy*. The hypertrophy is *"concentric"* (→**A2**), because in this case the ventricular volume is not enlarged and may in some circumstances actually be decreased. The hypertrophy improves the systolic dysfunction, but by the same token causes a diastolic dysfunction. End diastolic volume and stroke volume are decreased (→**B** and **C3, 4**). At high pressure load, myocardial remodeling (see below) and unfavorable capillary blood supply (relative coronary ischemia) may lead to a "critical heart weight" of ca. 500 g, at which the myocardial structure gives way, causing *decompensation* (→**A** below right and **C5**).

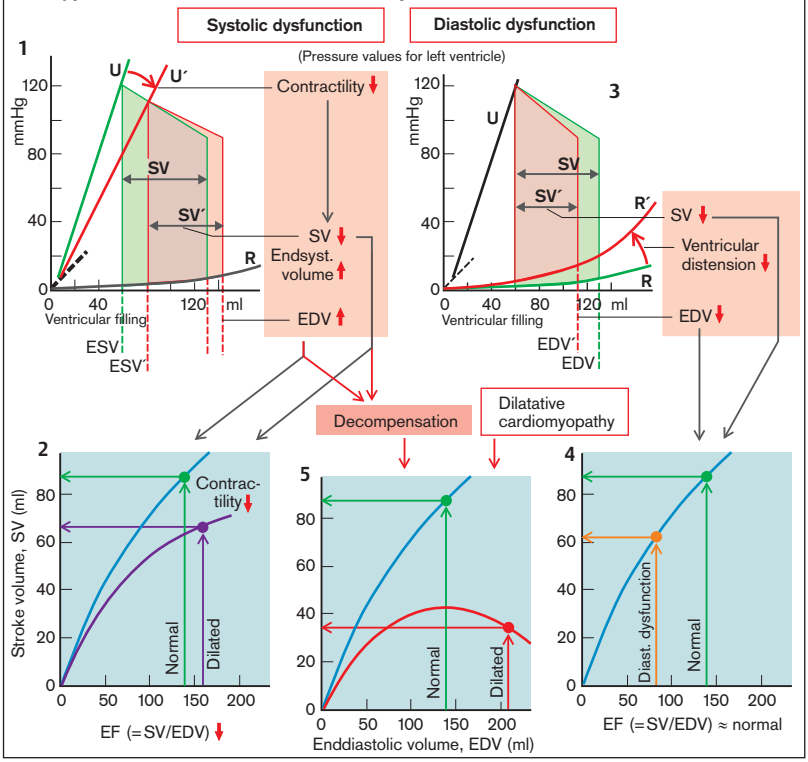
Major symptoms of **left ventricular failure (lvHF)** include fatigue, as the *cardiac output decreases* and dyspnea, as the *pulmonary venous pressure increases* (→**D**). If the pulmonary capillary pressure exceeds the oncotic pressure of plasma, fluid exits from the capillaries and enters the interstitial space or eventually the alveolar lumen, resulting in interstitial and alveolar *lung edema* (→**D** right and pp. 84, 250). The edema enhances the dyspnea and decreases the compliance of the lung (which becomes stiffer), the respiratory work increases, the ventilation–perfusion ratio (→ p. 76) decreases, and the arterial O_2 partial pressure is reduced. Continuing severe lvHF is followed by pleural effusions and the ventilation increases, which may eventually lead to respiratory alkalosis.

At **right ventricular failure (rvHF)** the systemic-venous pressure increases leading to *peripheral edema* (especially in the lower legs during the day; at night there is excretion of water with *nocturnal diuresis*) and in the abdominal organs (particularly liver and gastrointestinal tract) with fluid entering the peritoneal cavity (*ascites*). *Hepatic function* is compromised (increase of bilirubin, liver enzymes and prothrombin time in blood). The venous congestion could further lead to malabsorption, protein losing enteropathy, and cachexia (→**D** left).

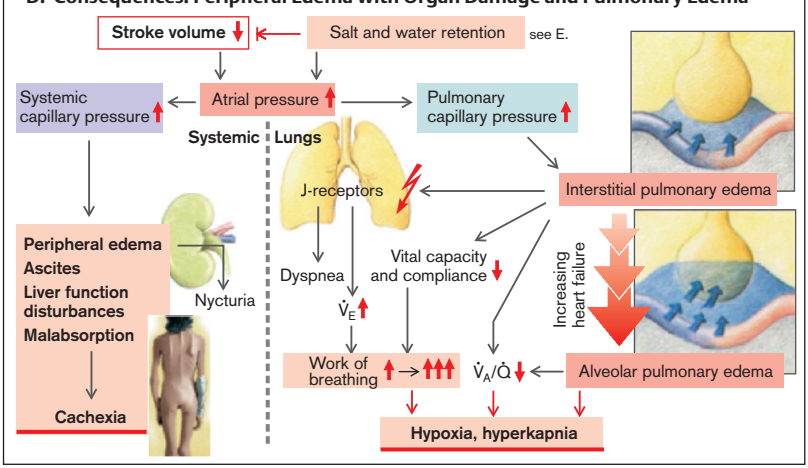
Neurohumoral consequences of HF. Next to mechanical cardiac effects (→**A–D**), HF induces a number of compensatory mechanisms that are primarily directed at restoring cardiac output and blood pressure (→**E**, "Temporary improvement"). The compensatory mechanisms involve pressoreceptors in the LV, the carotis sinus, and the aortal arch, the afferents of which lead to enhanced *ADH release* and stimulated *sympathetic tone* with increased release of norepinephrine. Those mechanisms result in:

- water retention by ADH (increases cardiac filling) and peripheral vasoconstriction;
- noradrenergic increase of *heart rate* (symptomatic tachycardia) and recovery of cardiac

C. Types of Heart Failure and their Consequences



D. Consequences: Peripheral Edema with Organ Damage and Pulmonary Edema



contractility (*positive inotropy*) and thus cardiac output;

- accelerated relaxation (positive lusitropy);
- α_1-adrenergic vasoconstriction and thus decreased perfusion of skeletal muscle (symptomatic fatigue), skin (symptomatic pallor), and kidney aiming at a redistibution of the reduced cardiac output to the perfusion of the coronaries and the brain (centralization);
- activation of the renin–angiotensin–aldosterone system (due to enhanced renal sympathetic nerve activity and decreased perfusion of the kidneys), leading to Na+ retention with subsequent increase of extracellular fluid volume (ECV) and diastolic filling of the heart (preload) in an attempt to increase cardiac output.

These **compensatory mechanisms** may prevent clinical symptoms of chronic HF for several years (NYH grade I), but in the long run have **negative consequences**: The vasoconstriction due to sympathetic innervation, angiotensin II and ADH (→ **E**), increases both pre- and afterload of the ventricles, leading to myocardial apoptosis and fibrosis (see below). Moreover, the renal fluid retention and Na^+ retention impose a chronic volume load to the ventricles.

The increased atrial pressure stimulates the atrial natriuretic peptides (**ANP**), and the enhanced ventricular wall tension triggers the release of brain natriuretic peptide (BNP) (→ **E**). However, the effect of the natriuretic peptides cannot fully reverse the excessive Na^+ retention. The plasma concentrations of **BNP** or NT-BNP, a peptide produced in parallel to BNP at the cleavage of pro-BNP, are valuable diagnostic indicators to follow the course of HF.

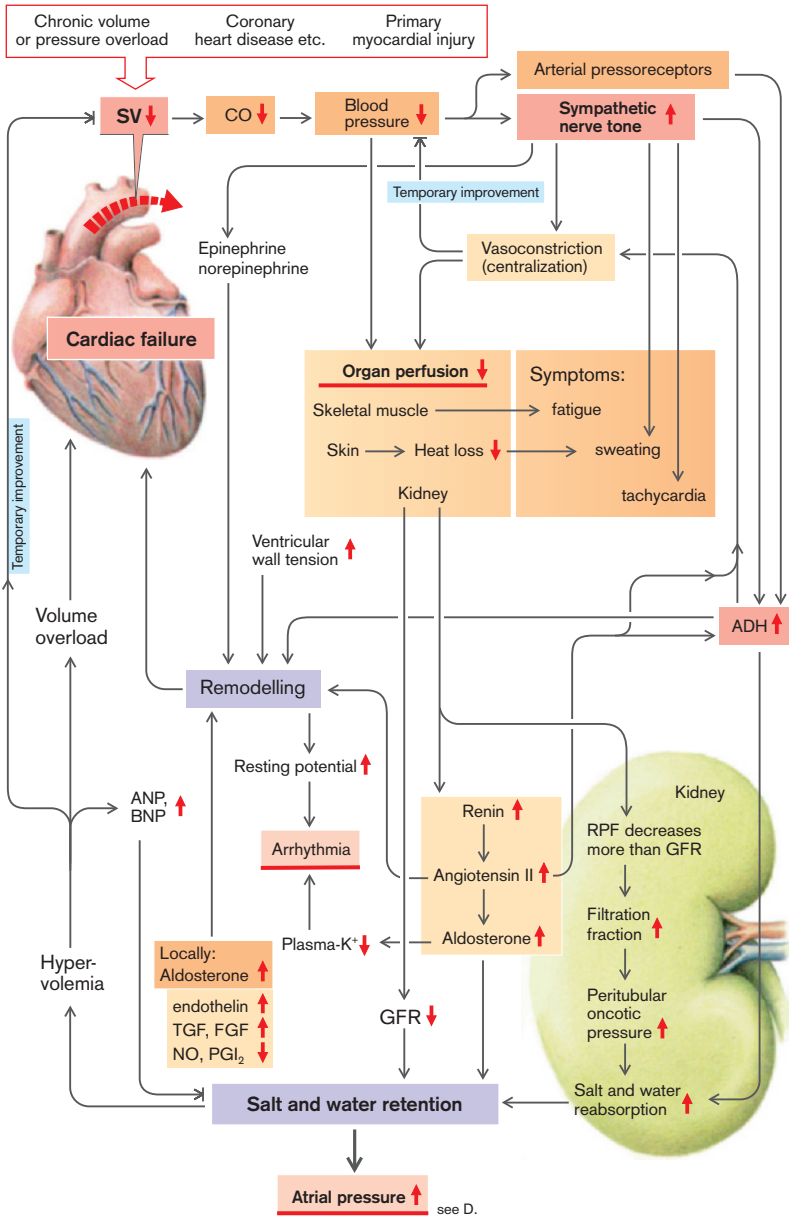
Myocardial remodeling. Remodeling of the myocardium occurs at the very beginning of HF (NYHA stage I) through mechanical and neurohormonal stimuli. This will decisively influence the progression of HF. **Causes** of the remodeling are:

1) *Increased wall tension* (→ **A**) that, among other effects, raises cytosolic Ca^{2+} concentration.
2) *Systemic growth signals* (norepinephrine, ADH, angiotensin II; insulin in type II diabetes).
3) *Local growth signals* (endothelin, CTGF [connective tissue growth factor], TGF [transforming growth factor], PDGF [platelet-derived GF], FGF [fibroblast GF], decrease in growth inhibitors [NO and PGI_2]).
4) *Inflammatory signals* (TNF-α, interleukin 6, generation of oxygen radicals by cardiac aldosterone; see below). The myocardial cells become enlarged (*hypertrophy*), but *refractoriness to catecholamines* develops (downregulation of β_1-adrenoceptors, a rise in the antagonistic G_i 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 situation can result in *arrhythmias* (reentry, afterpotentials, ectopic pacemakers; → p. 200 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 sensitive Ca^{2+} channels; → p. 196) as well as *reduced relaxation capacity* of the myocardium. The fibroblast activation (FGF and others) results in an increased deposition of collagen in the ventricular wall and *fibrosis* of myocardium.

The **therapy of the HF** aims to reverse the cardiac action of norepinephrine (*β-adrenergic receptor blockers*), the formation and action of angiotensin-II (*angiotensin converting enzyme [ACE] inhibitors* and *angiotensin [type I] receptor antagonists*) as well as the effects of aldosterone that, besides its Na^+-retaining (hypervolemia) and K^+-eliminating (risk of arrhythmias!) actions, generate oxygen radicals in heart and vessels and thus contribute to the inflammatory response with fibrosis and remodeling. The aldosterone release is only partially inhibited by ACE inhibitors, as its (partially cardiac) production during HF is only partly dependent on angiotensin II. Thus, specific *aldosterone antagonists* (e.g., eplerenon) favorably influence the survival of patients suffering from HF.

E. Cardiac Failure: Neurohumoral Consequences



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_{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 *noninfectious* (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_{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_{per}.

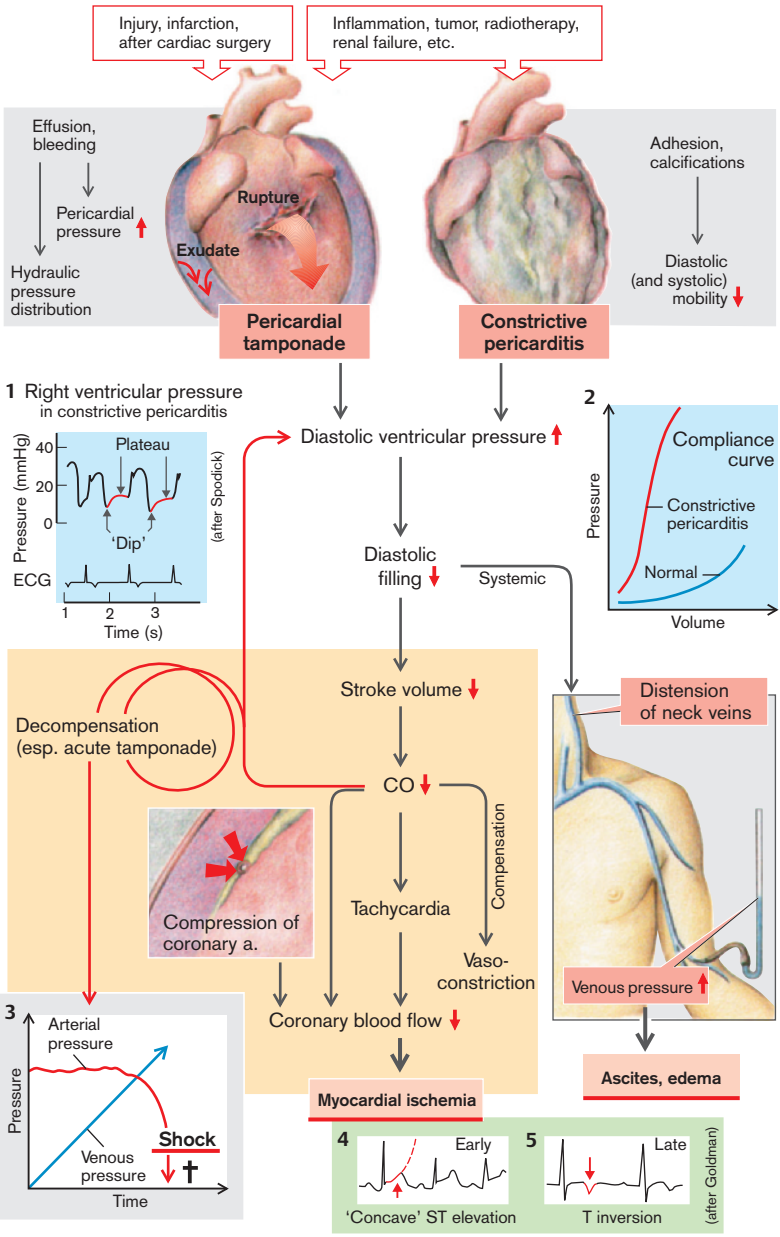
Serious **complications** of acute P. and of pericardial effusion are *pericardial tamponade* and *constrictive pericarditis*, both of which impair cardiac filling (→ **A**). *Causes* of **pericardial tamponade** (**PT**) include tumor infiltration and viral or uremic P. as well as ventricular rupture after myocardial infarction or chest trauma. A *consequence of pericardial tamponade* is a rise in ventricular pressure throughout systole to the level of P_{per}. The normal "y descent (or dip)" in the central venous pressure (CVP; → p. 193 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 curve rising much more steeply (→ **A 2**), so that the diastolic pressure in the ventricle rises again steeply after a brief fall (→ **A 1**, dip with short and rapid early diastolic filling) to a plateau (→ **A 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*". On the other hand, the Kussmaul sign, an inspiratory rise in central venous pressure, rather than the normal fall, is characteristic of constrictive pericarditis.

In both constrictive pericarditis and pericardial tamponade, diastolic **ventricular filling is decreased,** causing, among other things, a **rise in venous pressure**. In the *pulmonary veins* this gives rise to dyspnea and rales (pulmonary edema). The *increased systemic venous pressure* (congested neck veins; → **A**) leads to hepatomegaly, ascites, and peripheral edema.

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. 246 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 4, 5**; → p. 235 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 3**). constrictive pericarditis is treated by means of surgical resection of the pericardium (pericardiectomy).

A. Pericardial Tamponade and Constriction



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 O_2 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. 292), diabetic coma (→ p. 310 ff.), hypoglycemic shock (insulin overdosage, insulinoma; → p. 314), hypothyroid or hyperthyroid coma (→ p. 304), and coma in hypoparathyroidism or hyperparathyroidism (→ p. 138).

◆ **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 distension* (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 from, 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.

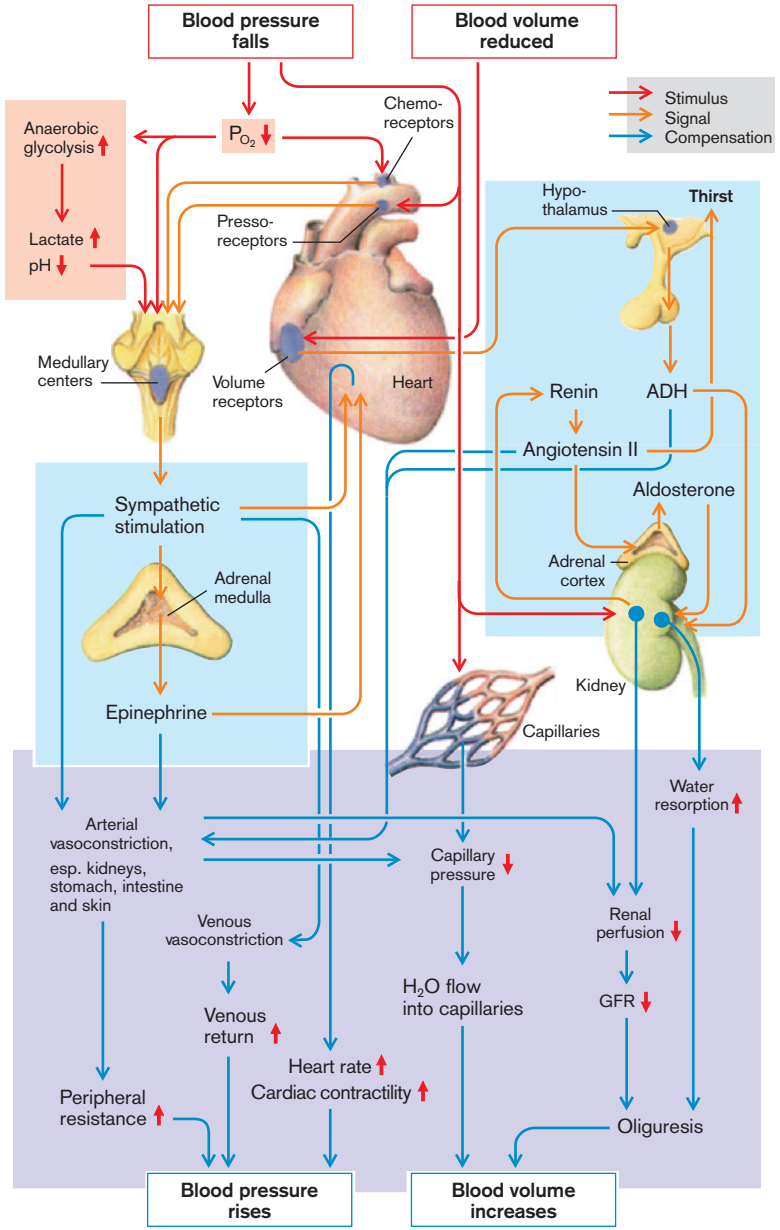
Symptoms (→ **B**, left). Hypovolemic and hemorrhagic shock is often associated with a *reduced blood pressure* (narrow pulse amplitude), *increased heart rate*, *pallor* with cold sweat (not in shock that is due to vascular distension), diminished urine output (*oliguria*), and marked *thirst*. The 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 *increased sympathetic tone. Arterial vasocon-*

A. Compensatory Mechanisms When There Is a Risk of Hypovolemic Shock



striction (not in shock caused by vascular distension) directs the reduced cardiac output away from the skin (pallor), the abdominal organs, and the kidneys to vital organs (coronary arteries, the brain), bringing about **centralization of the circulation**. *Vasoconstriction 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 these nerval system mechanisms.

◆ **Volume compensation** (→ **A**, right). The fall in blood pressure and arteriolar constriction with incipient shock *diminishes the effective capillary filtration pressure* (→ p. 250), and thus interstitial 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* (Henry–Gauer reflex). ADH acts as a vasoconstrictor (V_1 receptors) and to retain water (V_2 receptors). The reduction in renal blood pressure increases the release of *renin*, more *angiotensin II* is formed, the latter stimulating 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. 132 ff.). If the risk of shock can be averted, the lost erythrocytes will be replaced later (raised renal *erythropoietin formation*; → p. 34 ff.) and the plasma proteins will be replenished in the liver by increased synthesis.

If the organism is not able, *without outside help* (infusions etc.), to prevent the shock with the above-mentioned homeostatic compensatory mechanisms, **manifest** (or **decompensated**) **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 replacement [*protracted shock*]), the **consequences** of hypoxia will lead to *organ damage* that may culminate in extremely critical **multiorgan failure**. Frequent organ damage includes *acute respiratory failure* (= shock lung = acute respiratory distress syndrome [ARDS], → p. 88) with hypoxemia, *acute renal failure* (glomerular filtration rate [GFR] < 15 mL/min, despite normalization of blood pressure and volume), *liver failure* (plasma bilirubin is elevated, prothrombin decreased), *brain damage* (loss of consciousness, increasing degree of coma), *disseminated intravascular coagulation*, acute *ulcers* in the gastrointestinal tract with bleeding.

Several *mechanisms* may be involved in shock, some of them *self-reinforcing*. They aggravate the shock until it can no longer be favorably influenced, whatever the therapeutic measures (**irreversible** or **refractory shock**). The following vicious circles develop, among others:

1. Vasoconstriction ⇒ flow velocity ↓ ⇒ blood viscosity ↑ ⇒ flow resistance ↑ ⇒ flow velocity ↓↓ etc. until complete flow arrest (stasis with sludge phenomenon) (→ **C1**).

2 a. Volume ↓ ⇒ blood pressure ↓ ⇒ peripheral vasoconstriction → hypoxia → arteriolar opening → fluid loss into interstitial spaces → volume ↓↓ ⇒ blood pressure ↓↓ ⇒ hypoxia ↑ (→ **C2a**).

2 b. Volume ↓ ⇒ hypoxia ⇒ capillary damage ⇒ clot formation ⇒ disseminated intravascular coagulation ⇒ bleeding into tissues ⇒ volume ↓↓ (→ **C2b**).

2 c. Hypoxia ⇒ capillary damage ⇒ thrombus formation ⇒ hypoxia ↑ (→ **C2c**).

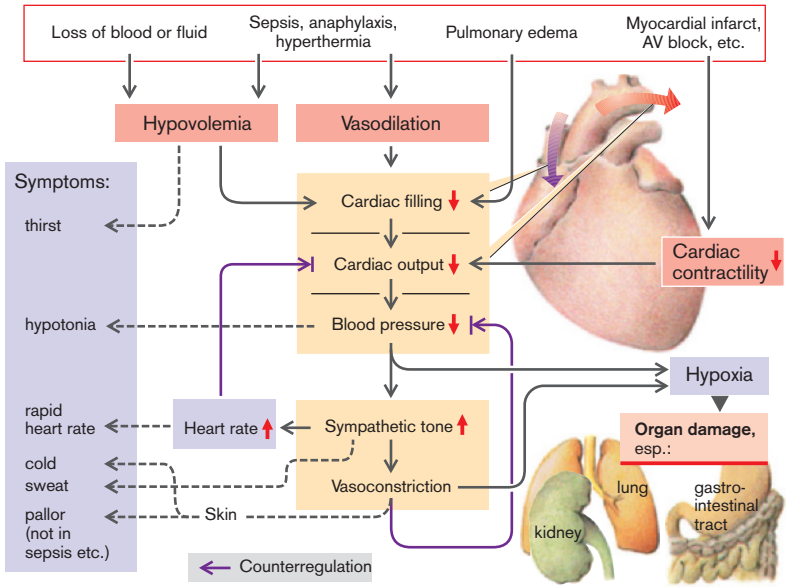
3. Cardiac output ↓ ⇒ blood pressure ↓ ⇒ coronary perfusion ↓ ⇒ myocardial hypoxia ⇒ myocardial acidosis and ATP deficiency ⇒ cardiac contractility ↓ ⇒ cardiac output ↓↓ (→ **C3,4**).

4 a. Cardiac contractility ↓ ⇒ blood flow ↓ ⇒ thrombosis ⇒ pulmonary embolism ⇒ hypoxia ⇒ cardiac contractility ↓↓ (→ **C4a**).

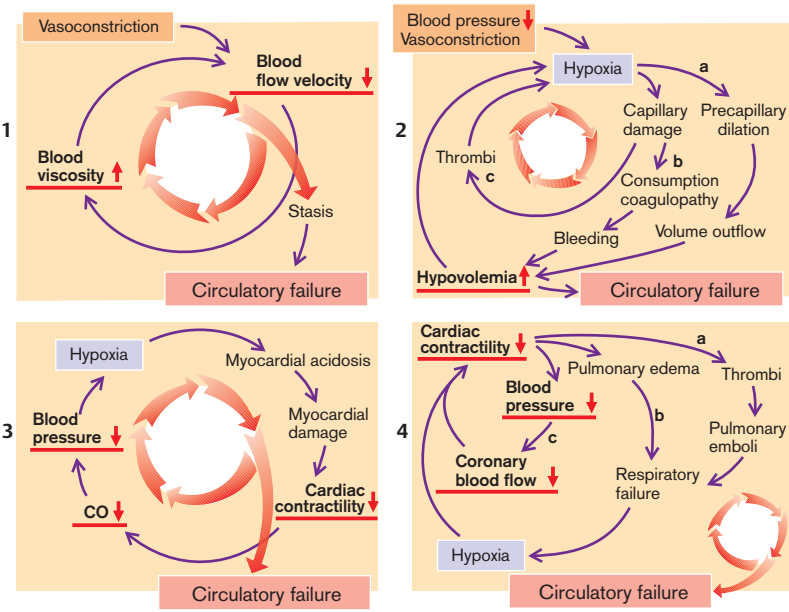
4 b. Hypoxia ⇒ cardiac contractility ↓ ⇒ pulmonary edema ⇒ hypoxia ↑↑ (→ **C4b**).

4 c. Cardiac contractility ↓ ⇒ blood pressure ↓ ⇒ coronary perfusion ↓ ⇒ cardiac contractility ↓↓ (**C4c**).

B. Causes, Symptoms, and Consequences of Shock



C. Vicious Circles (1–4) Which Lead to Irreversible Shock



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_f is determined by the **filtration coefficient K_f** (= water permeability · exchange area) of the capillary wall, as well as by the **effective filtration pressure P_{eff}** ($Q_f = P_{eff} \cdot K_f$). P_{eff} is the difference between the *hydrostatic pressure difference* **ΔP** and the *oncotic* (*colloidal osmotic*) *pressure difference* **Δπ** across the capillary wall (*Starling's law*), where **ΔP** = blood pressure in the capillaries (P_{cap}) – interstitial pressure (P_{int}, normally ≈ 0 mmHg). Δπ arises due to the protein concentration being higher in plasma than in the interstitial space by ΔC_{prot} (≈ 1 mmol/L), and it is the greater, the closer the reflexion coefficient for plasma proteins (σ_{prot}) is to 1.0, i.e., the smaller the endothelial permeability for plasma proteins ($\Delta\pi = \sigma_{prot} \cdot R \cdot T \cdot \Delta C_{prot}$). At heart level, ΔP at the arterial end of the capillaries is ca. 30 mmHg; at the venous end it falls to ca. 22 mmHg. Δπ (ca. 24 mmHg; → **A**, right) counteracts these pressures so that the initially high filtration (P_{eff} = + 6 mmHg) is turned into reabsorption for a short period of time. Usually, this results in an increase of the oncotic pressure in the pericapillary interstitium. Thus, Δπ now decreases parallel to ΔP ($P_{eff} \approx 0$; → **A**).

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 Δπ is increased along the capillaries. It is also part of self-regulation that P_{int} rises when filtration is increased (limited compliance of the interstitial space), and as a result ΔP decreases.

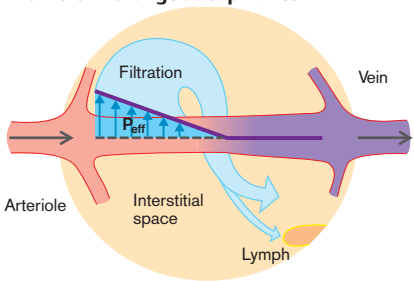
If the amount of filtrate exceeds the sum of reabsorbed volume plus lymphatic outflow, **edemas** develop, *ascites* develop in the region of portal vein supply, as do pulmonary edemas in the lungs (→ p. 84). Possible **causes** of edema are (→ **B**):

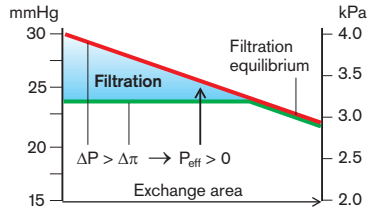
- Blood pressure rise at the arterial end due to precapillary vasodilation (P_{cap} ↑), especially during a simultaneous increase in permeability to proteins (σ_{prot} ↓ and thus Δπ ↓), for example, in inflammation or anaphylaxis (histamine, bradykinin, etc.).
- Rise in venous pressure (P_{cap} ↑ at the capillary end), which may be caused locally by venous thrombosis or systemically (*cardiac edema*), for example, by right ventricular failure (→ p. 238 ff.). Portal vein congestion leads to *ascites* (→ p. 184).
- Reduced plasma concentration of proteins (especially albumin) causes Δπ to fall excessively. This may be the result of renal loss of proteins (proteinuria; → p. 114) or of too little hepatic synthesis of plasma proteins (e.g., in liver cirrhosis; → p. 186 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 *Na^+ retention* raises the extracellular fluid volume which, while increasing the blood volume, actually makes the edema worse. Na^+ retention in renal failure also results in edema being formed.

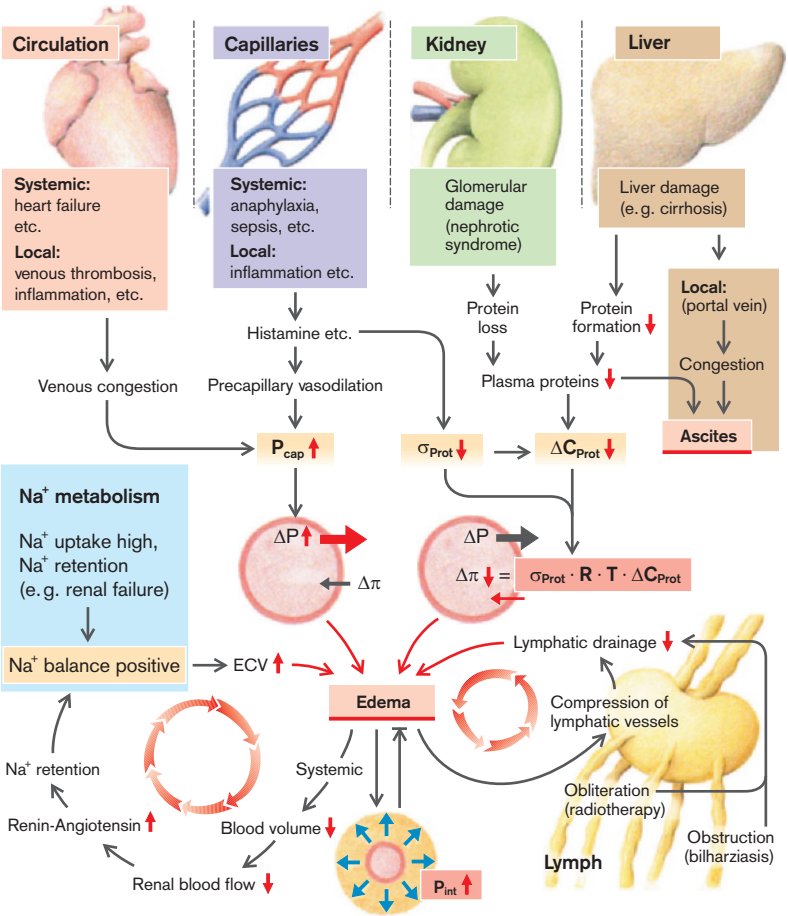
A. Fluid Exchange at Capillaries





$$P_{eff} = (P_{kap} - P_{int}) - \sigma \cdot R \cdot T \cdot \Delta C_{Prot}$$
$$= \Delta P - \Delta\pi \text{ (kPa, mmHg)}$$

B. Edema Formation



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 (→ **A 1**) is 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;* → **A 2**). Later, **fibrous plaques** or **atheroma** form (→ **A 3**), 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. (→ **C 1**), 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. 264 ff.). Further factors are overweight and a sedentary or stressful lifestyle (see as well metabolic syndrome, → p. 256 ff.).

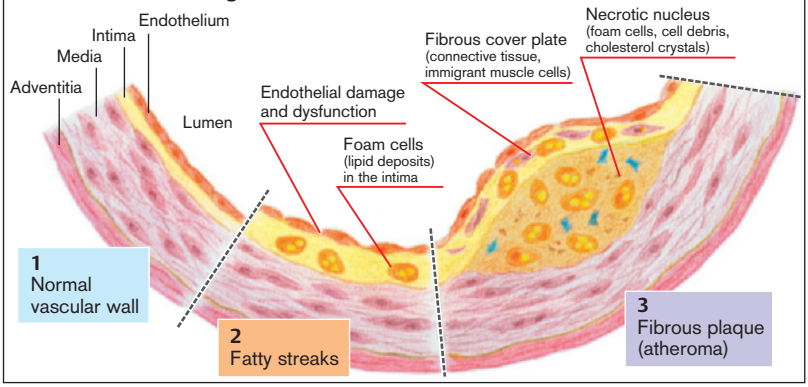
◆ **Hyperlipidemia**. *Serum cholesterol levels* higher than 265 mg/dL (6.85 mmol/L) in those aged 35 – 40 years increase the risk of coronary heart disease fivefold compared to values of < 220 mg/dL (5.7 mmol/L). 70% of this cholesterol is transported in low-density lipoproteins (LDLs) and the development of Ath. correlates closely with increased LDL levels. A defect in LDL receptors leads to very early Ath. (→ p. 264 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. 264 ff.).

◆ **Smoking** increases the risk of dying from the effects of coronary heart disease 1.4 to 2.4-fold (even light smoking), and in heavy smokers up to 3.5-fold. 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 O_2 in the Hb molecule by carbon monoxide, increased platelet adhesiveness, and raised endothelial permeability, induced by constituents in smoke.

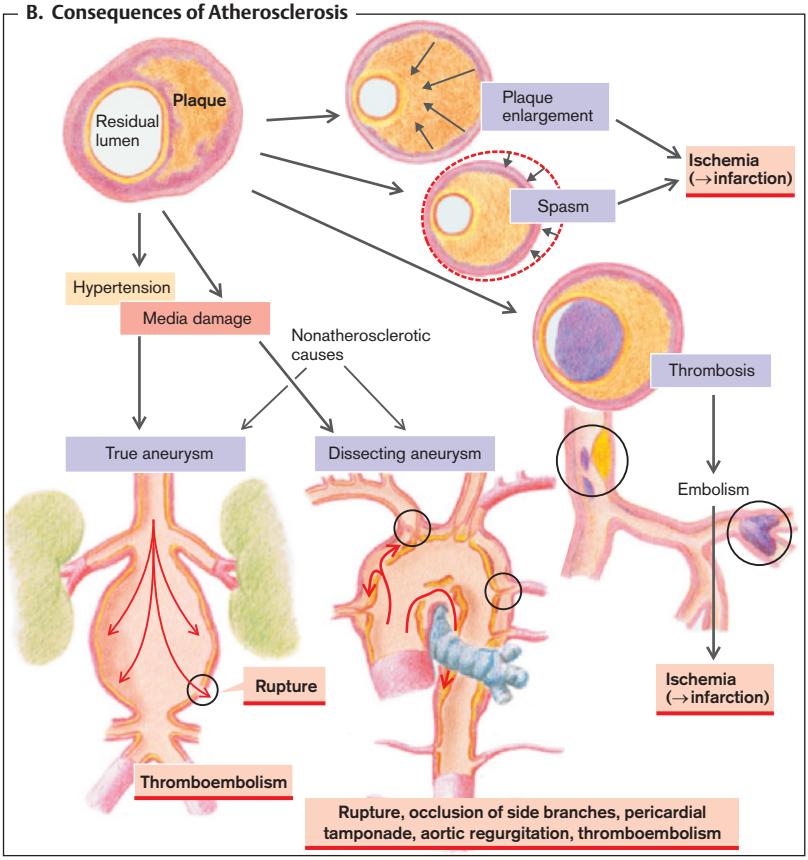
◆ **Hyperhomocysteinemia** (> 14 µg/L plasma, e.g., due to a lack of methylenetetrahydrofolate reductase [MTFR]), increases the risk of Ath., a rise of 5 µmol/L corresponding to the risk of a 20 mg/dL increase in cholesterol concentration. Homocysteine (HoCys) favors plaque formation, probably in several ways (see below). In the commonly occurring thermolabile gene polymorphism of MTFR, *folate deficiency* develops (→ p. 38). 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 are an increased *lipid uptake* in the vessel wall as well as *adhesion of monocytes and thrombocytes* (→ **C 2, 3**), helped by HoCys. The monocytes penetrate into the intima and are transformed into *macrophages* (→ **C 4**). These liberate reactive O_2 radicals, especially the superoxide anion $\cdot O_2^-$ (also helped by HoCys), which have a general damaging effect on endothelial cells and inactivate endothelium-formed **NO** on its way to the endothelium and the vascular musculature: $\cdot NO + \cdot O_2^- \leftrightarrow \cdot ONOO^-$ (→ **C 5**). 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 **C 7**). Even in the early stages of Ath., O_2 radicals *modify by oxida-*

A. Vascular Wall Changes on Atherosclerosis



B. Consequences of Atherosclerosis



tion of those *LDLs* that have entered the endothelium (→ **C 8**). 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. 264 ff.), but rather by so-called *scavenger receptors* that are contained in large amounts within the macrophages. Consequently, these now phagocytoze large amounts of LDLs and are transformed into sedentary foam cells (→ **C 9**). Lipoprotein(a) can be oxidized and phagocytozed in a similar fashion. Simultaneously, chemotactic factors of monocytes and thrombocytes trigger the *migration of smooth muscle cells* from the media *into the intima* (→ **C 6**). 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 (→ **C 10**). They form an extracellular matrix (collagen, elastin, proteoglycans) that also contributes to atheroma formation.

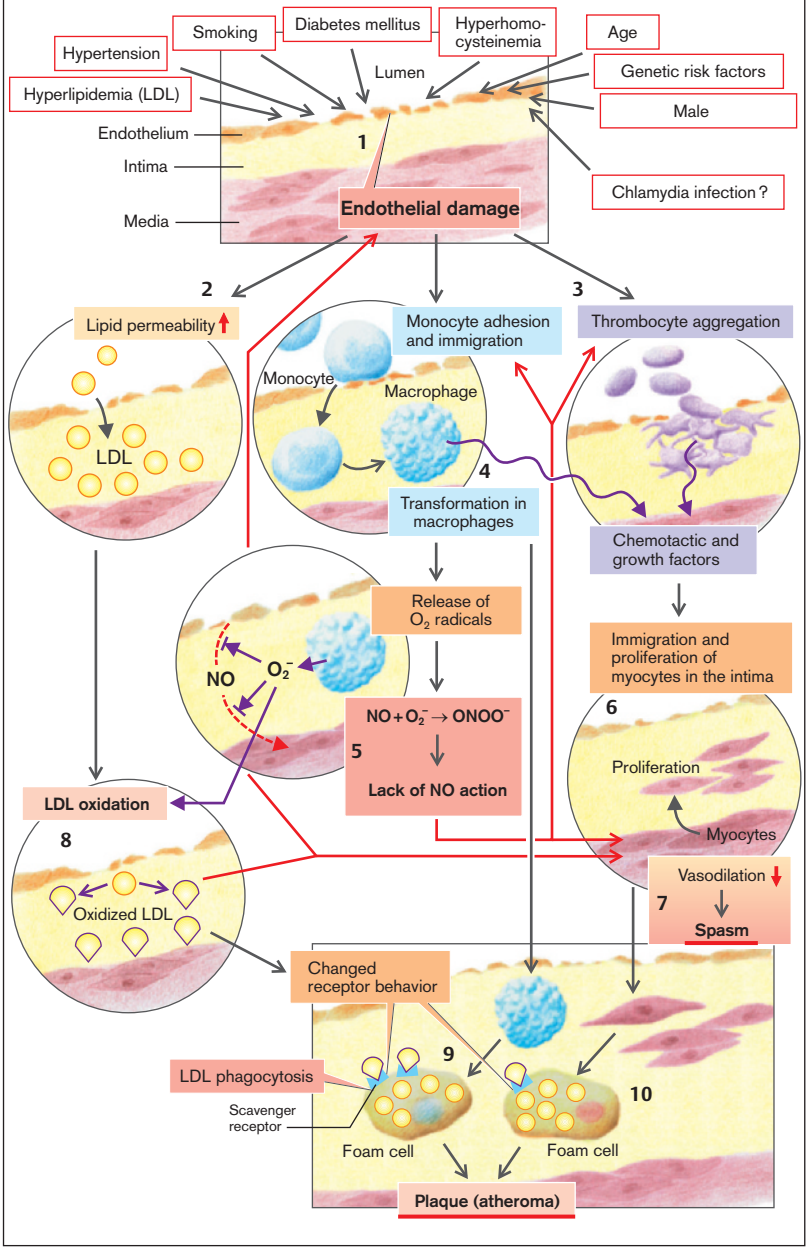
The **consequences** of plaque deposition (→ **B**) are *narrowing of the lumen* that can lead to ischemia. Coronary heart disease (→ p. 232 ff.) as well as chronic occlusive arterial disease of the limbs with painful ischemia on exercise (*intermittent claudication*) are examples of this. Other consequences 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 hematoma) 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. 354).

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 media necrosis (Marfan's, Ehlers–Danlos, or Gsell–Erdheim syndrome), or infection (syphilis, mycosis in immune-deficient patients).
- *False aneurysm* (*pseudoaneurysm*), 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. 246 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 aneurysm near the heart (especially a dissecting aneurysm) can cause acute pericardial tamponade (→ p. 244) and, if the aortic root is involved, aortic regurgitation (→ p. 214). Other complications are *thrombosis* in the aneurysm, 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



Metabolic Syndrome

White fat tissue does not only serve as an efficient energy storage but is (in normal abundance) required for the maintenance of the systemic glucose and lipid homeostasis. Lack of fat tissue thus leads to metabolic disorders (lipatrophy with diabetes mellitus and hypertriglyceridemia), as does excessive fat tissue. A common disorder resulting from **excessive fat tissue** (**obesity**), especially from excessive abdominal and visceral fat leads to the **metabolic syndrome** (**MeS;** → **A**).

Additional **metabolic risk factors,** such as disorders of lipid metabolism irrespective of body weight, genetic defects affecting insulin release or action, individual and ethnic metabolic differences, mitochondrial dysfunction, and advanced age increase the risk to develop metabolic syndrome (→ **A1**).

Metabolic syndrome is characterized by a combination of several risk factors from the following list:

- *Overweight*: increased body circumference (→ **A2**) and increased body mass index **BMI** (BMI = body weight [kg]/(body size [m])^2 → **A3**) (> 25: slight overweight; > 30: obesity).
- *Atherogenic dyslipidemia*: Hypertriglyceridemia, increased apolipoprotein B, increased non-HDL- and decreased HDL-cholesterol level in plasma (→ p. 264 ff.).
- *Hypertension:* Blood pressure ≥ 130/85 mmHg (→ p. 222 ff.).
- *Hyperglycemia* (fasting blood glucose ≥ 100 mg/dL) associated by *insulin resistance.*
- *Prothrombotic* condition (fibrinogen and plasminogen activator inhibitor 1 [PAI-1] increased).
- *Proinflammatory* condition (e.g., enhanced C-reactive protein [CRP]).

The link between obesity and these risk factors has become intelligible with the discovery of several products and signaling molecules (**adipokins**), which are released from adipocytes (→ **A4**). In obesity the *secretion* of those mediators is either *decreased*, as in the case of adiponectin, or *increased*, as in the case of free fatty acids (FFS, → p. 278 ff.), inflammatory cytokines (such as MCP-1), PAI-1 (→ p. 67), leptin (→ p. 30) and many more.

Adiponectin (30 kDa) is exclusively released from adipocytes. There is a strong negative correlation between the adiponectin plasma concentration and the BMI, i.e. the more obese an individual, the lower the adiponectin plasma concentration. Nutrition rich in fat decreases, and weight reduction of obese patients increases the adiponectin plasma concentration. Decreased plasma concentrations of adiponectin are associated with and actually precedes *insulin resistance,* indicating that adiponectin is indeed causative for the decreased insulin sensitivity. Adiponectin is mainly effective in skeletal muscle (AdipoR[eceptor]-1) and liver (AdipoR-2), where it decreases the triacylglyceride content; Moreover, the hormone decreases the hepatic gluconeogenesis, thus lowering the plasma glucose concentration. It increases the muscular FFS oxidation, thus lowering the plasma FFS concentration. Adiponectin is required for the *insulin-sensitizing* effects of PPARγ (peroxisome proliferator-activated receptor gamma)-agonists (such as glitazone), substances currently utilized for the oral therapy of type 2 diabetes mellitus.

PAI-1 (plasminogen activator inhibitor-1) is a serine protease produced in adipose tissue. PAI-1 inactivates plasminogen activators (urokinase, tPA; → p. 67) and thus inhibits fibrinolysis. Obesity increases plasma levels of PAI-1, thus increasing the risk of atherothrombotic events.

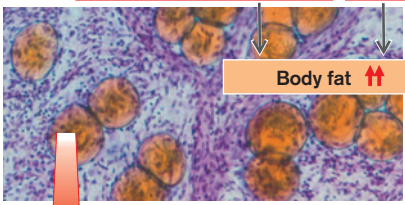
MCP-1 (= monocyte chemoattractant protein-1) is similarly produced by adipocytes. Following increased release of MCP-1 in obese fat tissue, monocytes migrate into the fat tissue and stimulate the release of proinflammatory cytokines such as TNF-α and IL-6. The subsequent inflammatory response presumably contributes to the insulin resistance in obesity.

Taken together, metabolic syndrome is–similar to hypertension and smoking–an important and in many parts of the world increasing *risk factor for atherogenic cardiovascular disease* (→ **A5** and pp. 232 ff. and 252 ff.).

A. Metabolic Syndrome as Risk Factor for Cardiovascular Diseases

High caloric diet

Lack of physical exercise



Body fat ↑↑

Release

Adiponectin ↓

Free fatty acids ↑

Cytokines (MCP1) ↑

PAI-1 ↑

4

Hyper-coagulability ↑

Invasion of macrophages ↑ into fat tissue

Inflammatory mediators ↑

Fat deposition in liver ↑ and skeletal muscle

Insulin resistance

1

Metabolic susceptibility

Disorders of lipid metabolism

- triacylglycerides ↑
- non-HDL-cholesterol ↑
- HDL-cholesterol ↓

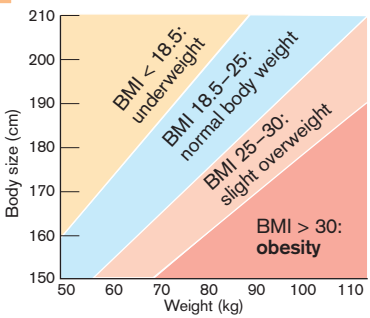
insulin resistance

polygenetic susceptibility (individual and ethnic differences)

mitochondrial dysfunction

increasing age

3



2

Obesity
waist circumference
> 102/88 cm

Foto: MEV

Diverse metabolic risk factors
= metabolic syndrome

Diabetes mellitus

Hypertension

Hypercoagulability

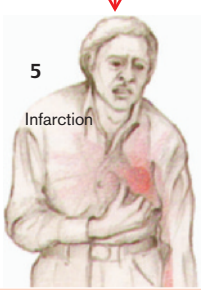
Smoking

Hypertriglyceridemia

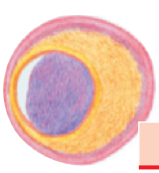
Hypercholesterinemia

Inflammatory mediators

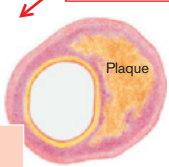
5



Infarction



Thrombosis



Plaque

Atherogenic cardiovascular diseases

Nonatherosclerotic Vascular Diseases

As in atherosclerosis (→ p. 252 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. 208), the left ventricle (dilated cardiomyopathy, myocardial infarct), or from the cardiac valves (endocarditis, mitral stenosis, valvar prosthesis). Intracardiac shunts (→ p. 216) allow venous thrombi (see below) to pass into the arterial system (*paradoxical 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). *Thromboangitis 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 erythematodes, rheumatoid arthritis). The phenomenon may occur in younger women as a primary disease, in the absence of any other condition (*Raynaud's disease*).

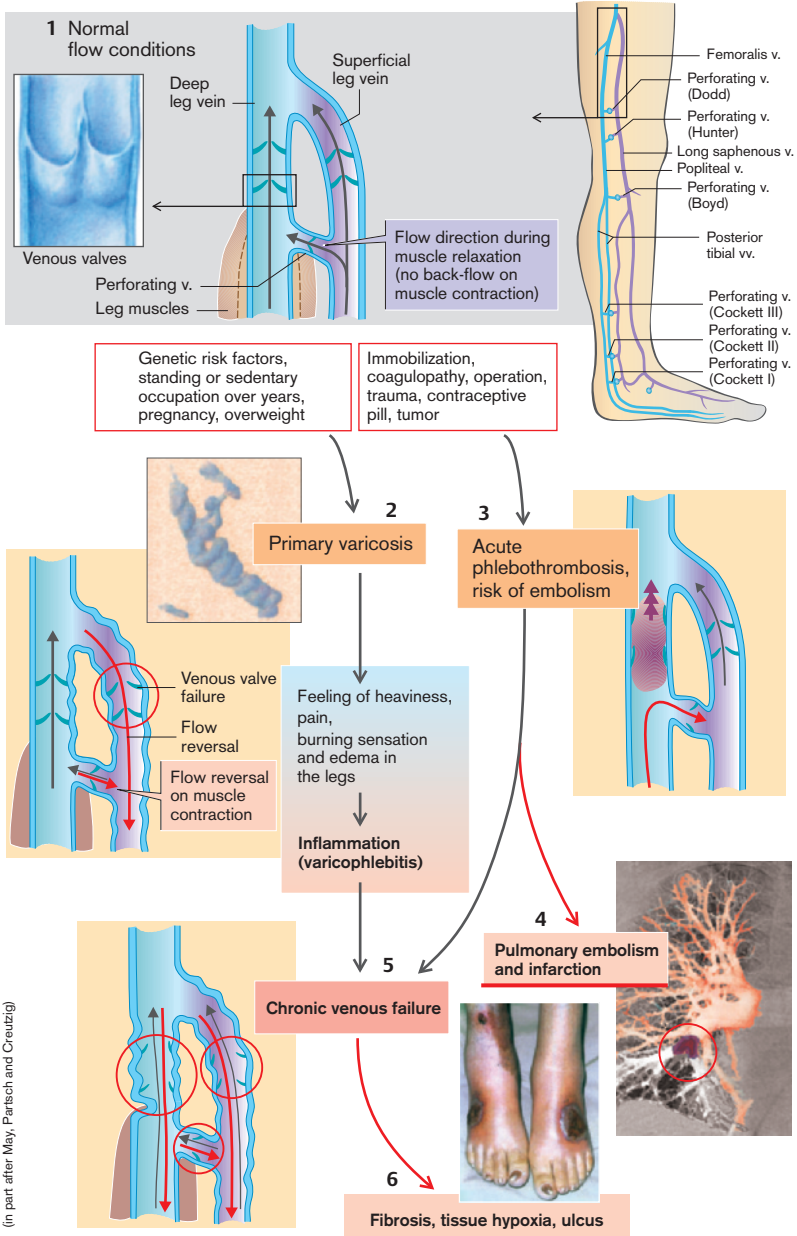
Venous Disease

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 (→ **A 1**).

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 varicosis**; → **A 2**). 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* (→ **A 5**).

Consequence: If a thrombus forms in the *deep veins of the legs* (**acute phlebothrombosis**; → **A 3**), the valves of the perforating veins are torn and blood will drain via the superficial veins, causing **secondary varicosis**. **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* (→ **A 4**). **In the long term** *chronic venous insufficiency* develops (→ **A 5**), 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* (→ **A 6**).

A. Varicosis and Phlebothrombosis



(in part after May, Partsch and Creutzig)

Photo: Siegenthaler W. Differentialdiagnose innerer Krankheiten. 16th Aufl. Stuttgart: Thieme; 1988.

Overview

Metabolic abnormalities are frequently caused by *faulty endocrine regulation* (e.g., diabetes mellitus; → p. 308 ff.), or *genetic defects* of *enzymes* (enzymopathies) or of *transport proteins*, the latter, for example, in cystic fibrosis (→ p. 176) and cystinosis (see below). The endocytosis and exocytosis of lipoproteins can also be affected by defects of apolipoproteins or membrane receptors (→ p. 264 ff.).

If there is an **enzyme defect** (→ **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; → p. 262);
- 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; → pp. 130 and 268);
- 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 (→ **A**, metabolite B). In glycogen storage disease, for example, it causes glucose or ATP deficiency (→ p. 262). A lack of metabolite B may additionally increase the metabolic rate of other enzyme reactions (→ **A**, enzyme Y).

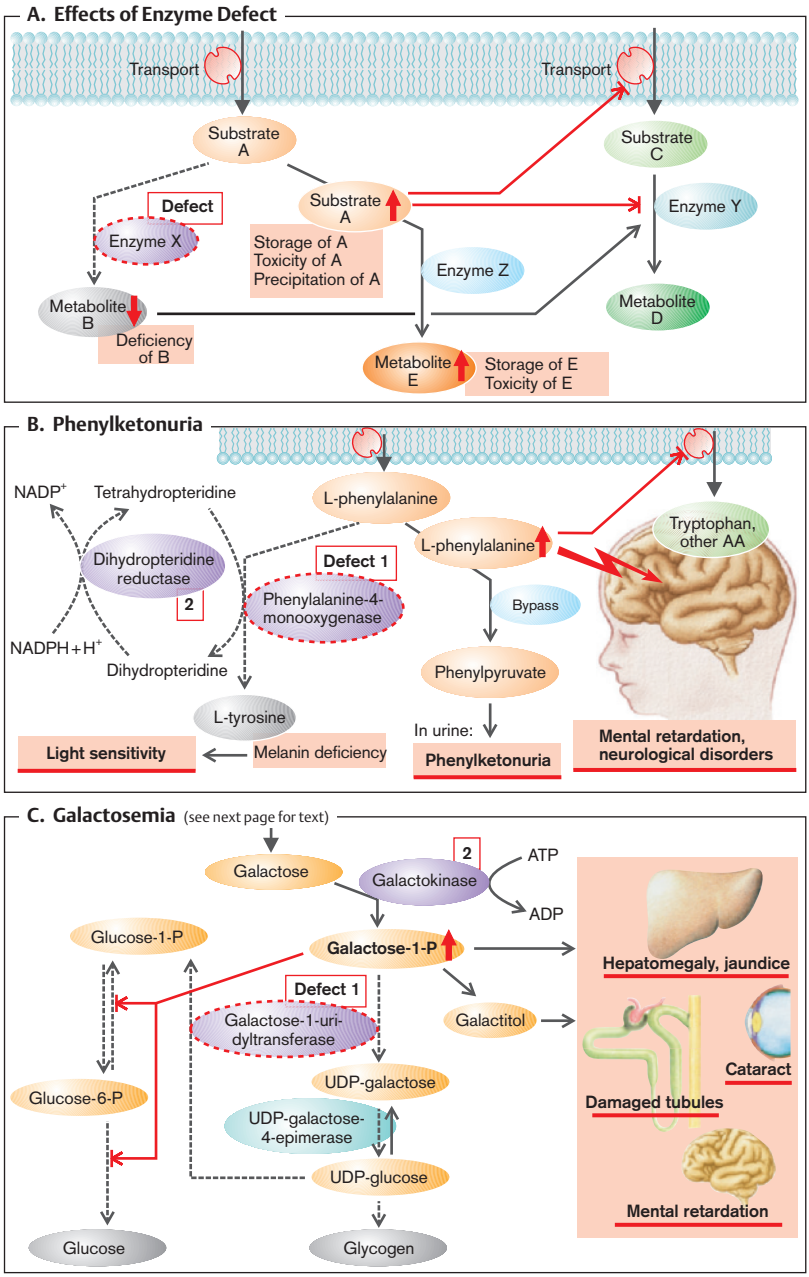
Metabolic disorders play a part in the processes dealt with in almost every chapter in this book. This chapter describes further examples of metabolic abnormalities, their selection made mainly according to the seriousness, treatability (on early diagnosis), and prevalence of the abnormalities.

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 can serve as energy sources. Ammonia, produced during catabolism, is mainly incorporated into urea and excreted in this form. Too many or too few amino acids, a carrier defect (→ e.g., p. 104 ff.), or abnormal formation of urea (→ p. 188) 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 (→ **B 1**). 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 other amino acids, so that these neither leave parenchymal cells (sequestration) nor are able to enter brain cells (→ **B**). Severe *developmental defects* in the brain are the result. A lack of *melanin* (→ **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 dihydropteridine reductase (→ **B 2**).

Further metabolic disorders of amino acids include (the corresponding enzyme defect is given in brackets): *hyperglycinemia* (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; → p. 38, A2), *cystinosis* (carrier defect ⇒ 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*.



Disorders of Carbohydrate Metabolism

Abnormalities of carbohydrate metabolism are usually caused by enzymopathies or abnormal regulation (see also *anemia*, → p. 34 ff. or *diabetes mellitus*, → p. 308 ff.).

In **galactosemia** (→ p. 261 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-uridyl transferase* deficiency (→ p. 261 C1), 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 *galactitol*, 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. 261 C2) 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 phosphorylase and fructose-1,6-diphosphate aldolase in the liver, thus causing *hepatogenic hypoglycemia*, *acute liver failure,* or *cirrhosis* (→ p. 186 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.

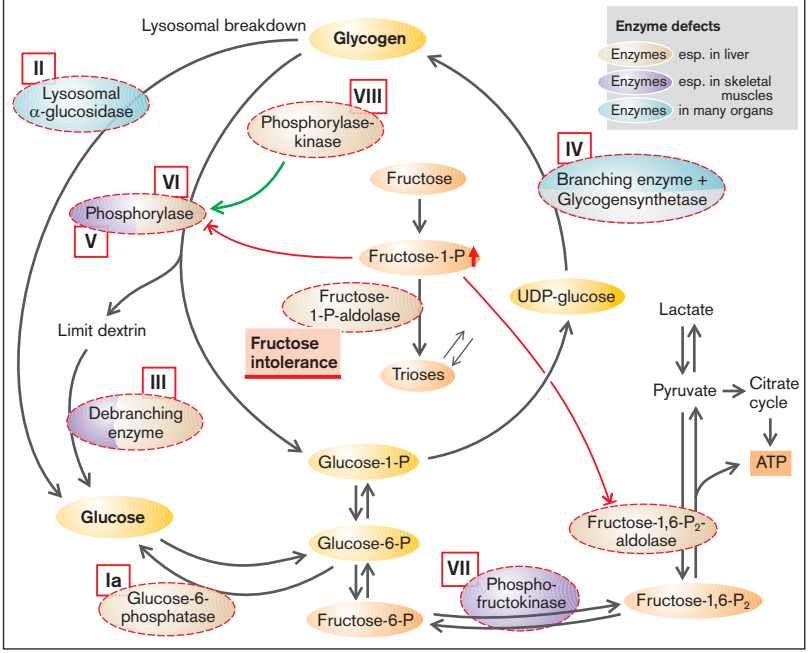
Depending on the primary **effects** of the enzyme deficiencies, one can simplify the classification by dividing the glycogen storage diseases into *liver types* (I, III, VI, VIII), *muscle types* (V, VII), and other types (II, IV) (→ **B**). In the liver types *hepatomegaly* (due to excess deposition 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

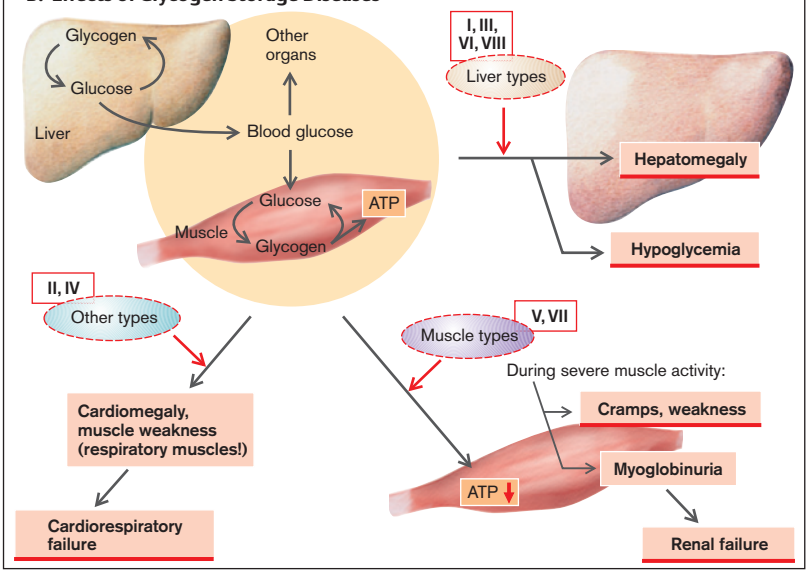
Lipidoses are disorders of fat metabolism, in which defects of enzymes and other proteins cause the accumulation (and thus deposition) of lipids.

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 **cholesterol-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



B. Effects of Glycogen Storage Diseases



Abnormalities of Lipoprotein Metabolism

Among the disorders of fat metabolism there are, in addition to the lipidoses (→ p. 262), 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., triacylglycerides (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., ApoAII and $ApoB_{48}$), as *ligands* (e.g., $ApoB_{100}$ and ApoE) for LP receptors in the membrane of the LP target cells, and as *enzyme activators* (e.g., ApoAI, 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 $ApoB_{100}$) 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 $ApoB_{100}$ 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 ApoAI 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**).

Lipoprotein-class*	% of TG	% of ChoL	Apolipoproteins	Formations in or [from]	Transport function
Chylomicr.	90	3	AI, B_{48}, CII + III, E	Gut	TG etc.: Gut ⇒ Periphery
Chyl. remnants				[Chylomicr.]	Lipids: Gut ⇒ Liver
VLDL	65	15	B_{100}, CII + III, E	Liver	TG etc.: Liver ⇒ Periphery
IDL			B_{100}, CIII, E	[VLDL,HDL]	Lipids: ⇒ Liver, LDL
LDL	10	45	B_{100}	[IDL]	Cholesterol: IDL ⇒ Liver, Periphery
HDL	5	20	AI,III + IV, CIII, D	Periphery	Cholesterol: Periphery ⇒ IDL

* 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, *overweight* 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 (→ **A 7**) 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 (→ **A 8**). Hypercholesterolemia is thus a risk factor for *atherosclerosis* (→ p. 252 ff.) and *coronary heart disease* (→ p. 232).

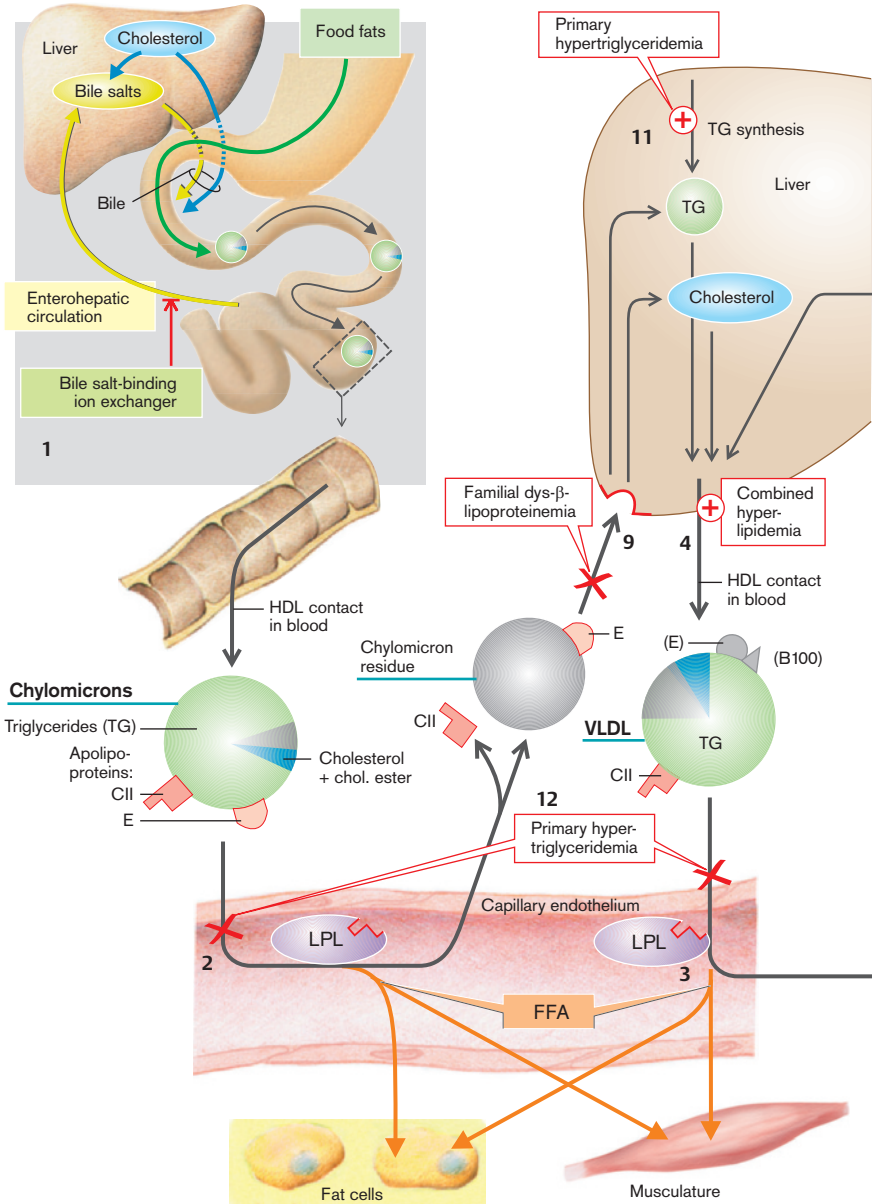
In **familial hypercholesterolemia** (hyperlipoproteinemia **type IIa**; incidence of homozygotes is $1:10^6$; of heterozygotes 1 : 500) the plasma cholesterol is markedly raised from birth (twice as high in heterozygotes; six times as high in homozygotes) so that myocardial infarction may occur even in children. The primary causes are *defects in the gene for the high-affinity LDL receptor* which prevents the cellular uptake of LDL (→ **A 7, 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 (→ **A 5**). *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 (→ **A 1**). 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 (→ **A 5**). However, it also stimulates cholesterol synthesis, but this in turn can be prevented by administering inhibitors of 3-HMG-CoA reductase (e.g., lovastatin) (→ **A 5**). The treatment of homozygotes includes the removal of LDL from plasma by *plasmapheresis*.

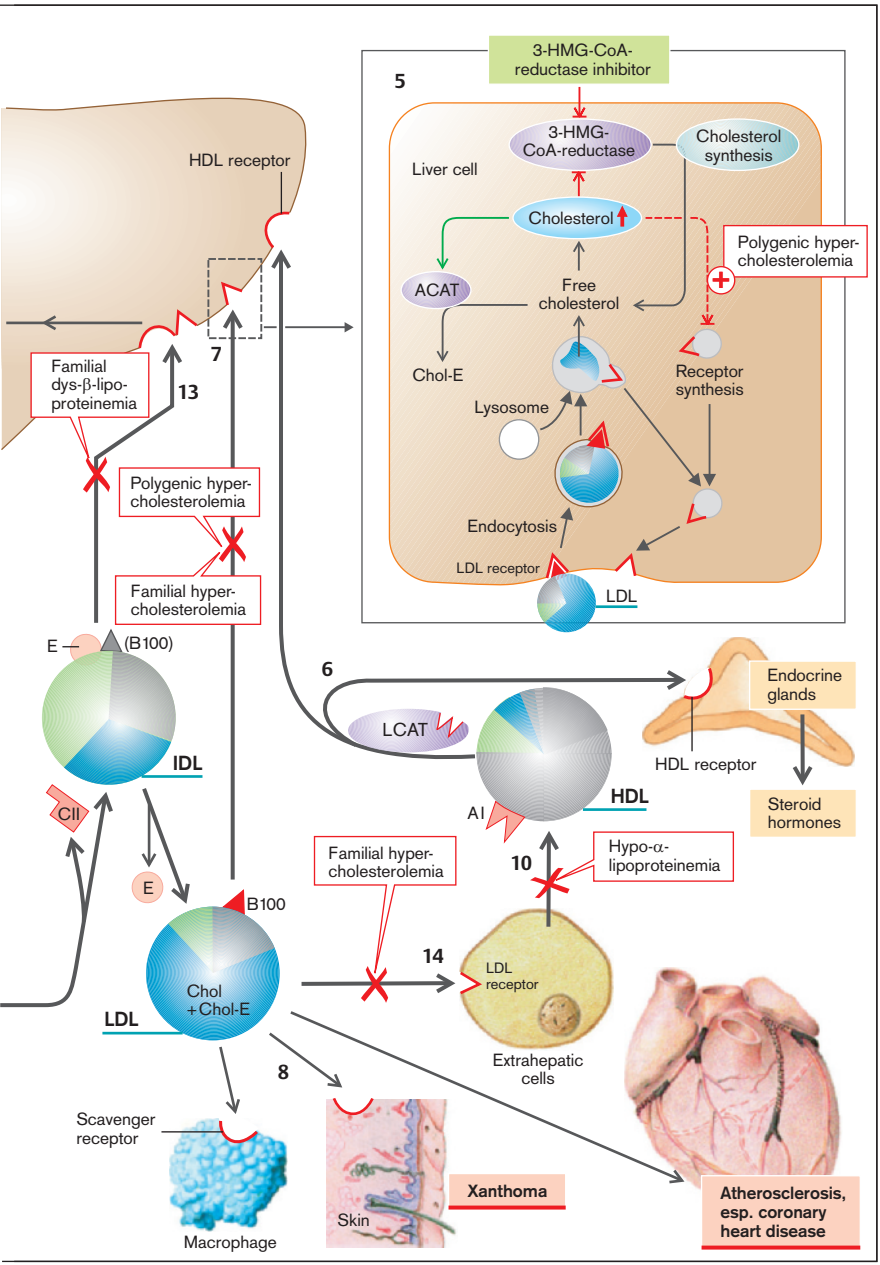
In another single-gene defect, **combined hyperlipidemia** (hyperlipoproteinemia **type IIb**), the TGs as well as cholesterol are slightly raised. The cause is possibly an overproduction of ApoB, so that an increased synthesis of VLDL occurs (→ **A 4**) and therefore more LDL is also formed. **Familial dys-β-lipoproteinemia** predisposes to hyperlipoproteinemia **type III**. In this condition, instead of the normal $ApoE_3$, an $ApoE_2$ variant is expressed that is not recognized by the E receptor. As a result, the hepatic uptake of chylomicron remnants and of IDL is disturbed (→ **A 9, 13**), so that their plasma concentration rises (high *risk of atherosclerosis*; → p. 252 ff.).

Primary **hypertriglyceridemia** is due to *increased TG synthesis* in the liver (→ **A 11**) or (rarely) to *abnormalities in the breakdown of chylomicrons and VLDL* (hyperlipoproteinemia **type I**), the result of a deficiency of LPL or ApoC-II (→ **A 2, 3**). They predispose a person to, for example, *pancreatitis* (→ p. 172 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 (→ **A 10**), increasing the atherosclerosis risk. In *A-β-lipoproteinemia* there are no LDLs in plasma (hypocholesterolemia). 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





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 reformed 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 (pK_a' of urate/uric acid ≈ 5.4), is the reason why gout develops from hyperuricema.

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, mussels, 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.

The solubility of urate is especially low in *synovial fluid* and at low temperature. As 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. 130).

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. 52 ff.), attracting neutrophils which phagocytoze the urate crystals. When the neutrophils subsequently break down, the phagocytozed urate crystals are released again, which maintains the process. A very painful, deepred 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. 118).

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

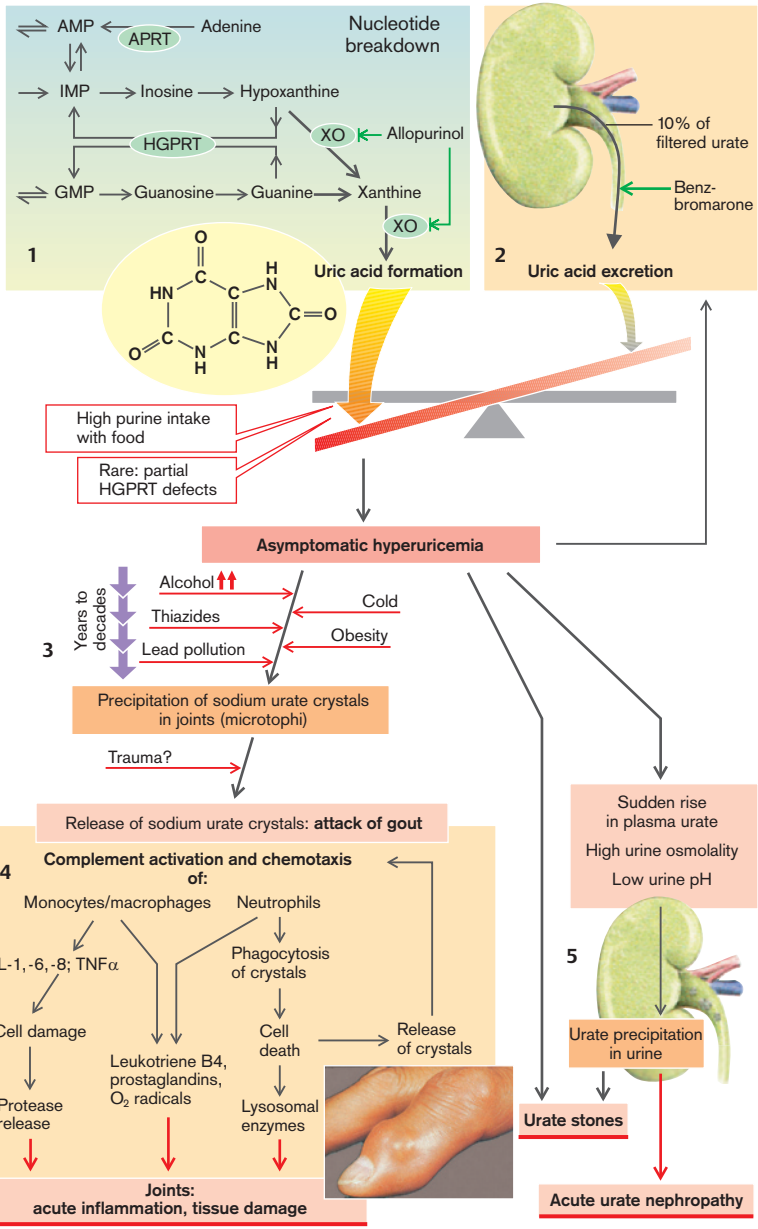


Photo: Siegenthaler W. Differentialdiagnose innerer Krankheiten.16th ed. Stuttgart: Thieme; 1988

Iron Metabolism, Hemochromatosis

Iron (Fe) is an essential element required for the O_2-binding molecules hemoglobin (Hb) in erythrocytes and myoglobin in muscle, as well as for cytochromes and further enzymes. Moreover, Fe plays an important role for the virulence of bacteria. The *sequestration* of Fe by proteins (lactoferrin, siderocalin, lipocalin, several acute phase proteins) thus participates in the defense against pathogens.

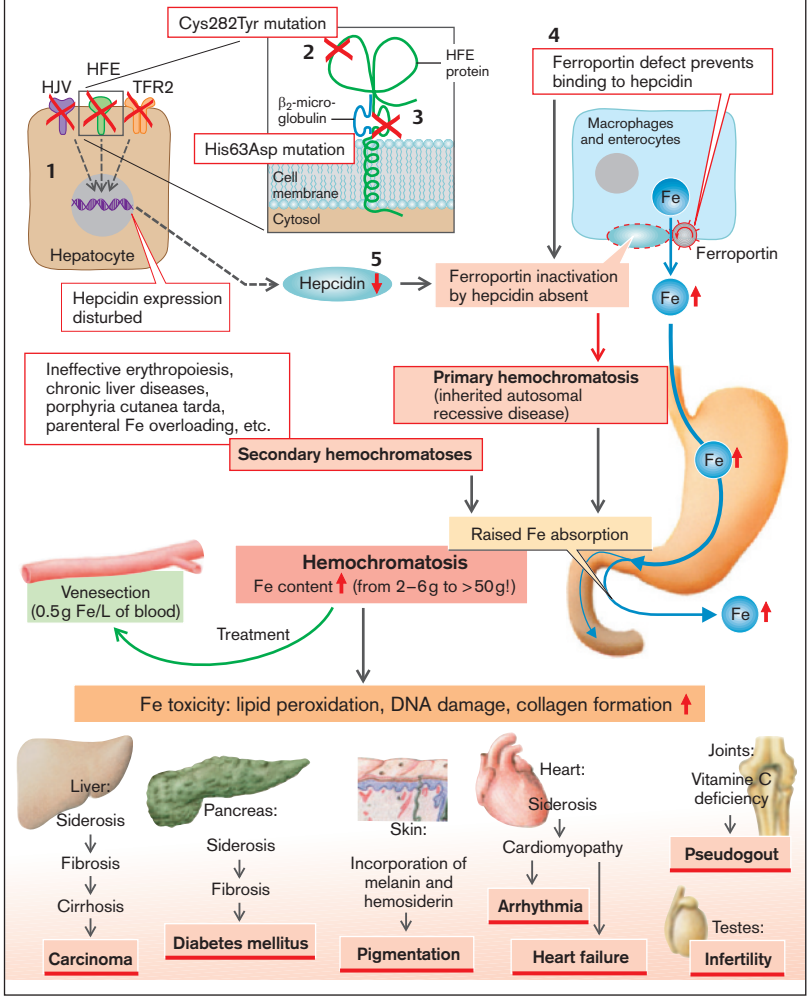
Some 25% of Fe is accumulated in stores (→ p. 42): *Ferritin* (in intestinal mucosa, liver, bone marrow, erythrocytes, and plasma), which has a "pocket" for 4500 Fe^{3+}-ions, provides rapidly available Fe (ca. 600 mg), while *hemosiderin* stores less rapidly recruitable Fe (250 mg Fe in macrophages from liver and bone marrow).

As *Fe deficiency leads to anemia* (→ p. 42) and excess *Fe* may cause oxidative cell damage, the **Fe homeostasis** is under tight regulation, which involves intestinal Fe absorption, recycling of Fe, and filling or emptying of the Fe stores. The hepatic peptide hormone **hepcidin** is the decisive regulator of those processes (→ p. 42). Its expression is enhanced at Fe excess and downregulated at Fe deficiency. The mechanisms involved in the regulation of hepcidin expression include HFE protein, transferrin receptor 2 (TFR2) and hemojuvelin (HJV) (→ **A1**). The *hepcidin production increases* during inflammation (stimulation by interleukin 6) and in Fe excess (stimulated by transferrin Fe) and is decreased by hypoxia (stimulated erythropoiesis) and Fe deficiency. The stimulation of hepcidin expression is accomplished by the cell membrane-bound serine protease matriptase-2 (= TMPRSS6), which cleaves HJV. **Hemachromatosis** is a condition with excessive progressive accumulation of iron (Fe) in the body, deposited in the parenchymal cells of the liver, pancreas, and other organs. Males are 5–10 times more frequently affected than females. **Primary** (= idiopathic, = hereditary) **hemachromatosis** (→ **A1**) is a common disease (1 in 500), and is inherited as an autosomal recessive trait. In 80–90% of cases the underlying cause is a homozygous Cys282Tyr mutation within the *HFE* gene (type 1; → **A2**), preventing the *synthesis of intact hepcidin*. Some 4–5% of patients with hemochromatosis are heterozygous for the Cys282Tyr mutation, but simultaneously heterozygous for a His63Asp mutation (→ **A3**) of the *HFE* gene (compound heterozygosity). Rarely, hemochromatosis results from genetic defects of *hepcidin* itself (type 2A), of the *HJV* gene (type 2B; → **A1**), of the *TRF2* gene (type 3; → **A1**), or of the hepcidin target molecule *ferroportin* (type 4; → **A4**). In each of the genetic defects the intestine absorbs excessive amounts of Fe, as the lack of hepcidin function mimics severe Fe deficiency (→ **A5, 6**). Serum Fe, ferritin and transferrin saturation are increased (→ p. 42). Following early diagnosis the excessive storage of Fe (some 25–50 g as compared with 2–5 g in healthy individuals) can be normalized by means of weekly *blood lettings* over 1 to 2 years (serum ferritin < 50 µg/L; transferrin saturation < 50%).

Secondary hemochromatoses (→ **A7**) occur if there is an *abnormal utilization of Fe* (e.g., increased Fe absorption with ineffective erythropoiesis in β thalassemia or sideroblastic anemia; → p. 40), in *liver disease* (e.g., alcoholic cirrhosis, portocaval shunt), in atransferrinemia (→ p. 42), and porphyria cutanea tarda (→ p. 276) 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).

A **consequence** of increased Fe deposition (especially in the form of hemosiderin [*siderosis*]) is **toxic cell damage** (→ **A3**). The underlying mechanisms include (a) Fe-mediated formation of O_2 radicals (lipid peroxidation of cellular membranes); (b) DNA damage; and (c) an increased formation of collagen, initiated by Fe. As soon as hepatic Fe accumulation approaches 20-fold of the normal value, fibrosis develops with subsequent *cirrhosis* (→ p. 186 ff.). Thereby the risk of death from hepatocellular carcinoma increases 200-fold. The siderosis induced pancreatic fibrosis results in damage of pancreatic β-cells, insulin deficiency, and *diabetes mellitus*; the accumulation of melanin and hemosiderin in (particularly sun-exposed) skin leads to marked *pigmentation* ("bronzed diabetes"). Siderosis in the heart causes a *cardiomyopathy*, which through arrhythmia and heart failure is a frequent cause of death in young patients. Fe accelerates the degradation of ascorbic acid (vitamin C); the vitamin C deficiency fosters the development of joint injury (*pseudogout*).

A. Hemochromatoses



Copper Metabolism, Wilson's Disease

Copper is an essential trace element that is incorporated in several enzymes (e.g., cytochrome *c* oxidase, tyrosinase, superoxide dismutase, etc.).

Copper (**Cu**) **metabolism** (→ **A**). Normal *Cu uptake* is ca. 2–5 mg daily, of which 40–60% are absorbed in the stomach and upper duodenum. In the liver, Cu is taken up by the *Cu transporter Ctr1*, bound to proteins or incorporated into the multicopper ferroxidase *ceruloplasmin* (**Cp**), which binds six Cu atoms relatively firmly. Bound to ceruloplamin, Cu is secreted into plasma (ca. 93% of plasma Cu; → **A1**), where it substantially contributes to the oxidation of Fe^{2+} to Fe^{3+} (→ p. 42). Only a little Cp-bound Cu is released into the tissues. The Cu excretion into bile is accomplished by the P-type ATPase **ATP7B**. Aged (desialysed) Cp is degraded in the liver and the liberated Cu is excreted, firmly bound to biliary proteins (→ **A2**), into bile and feces (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 of the Cu-transporting *Cu-ATPase ATP7B*. 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 (→ **A**). 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 (→ **A3**). In this form it is cytotoxic because it binds to proteins, especially the sulfhydryl groups, and promotes the formation of oxygen radicals (lipid peroxidation). Cu^{2+} also triggers apoptosis of hepatocytes as it activates the acid sphingomyelinase (Asm) and thereby sets free ceramide (→ p. 14).

The **effects** (→ **A4**) are *hemolytic anemia* and *chronic active hepatitis*, which can later change to *cirrhosis*. If the hepatitis takes a fulminant course, large amounts of Cu are suddenly released from the necrotic liver, possibly triggering 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. As the underlying cause of the Cu overload is the defective hepatic ATP7B, Wilson's disease can be cured by liver transplantation.

α_1-Antitrypsin Deficiency

α_1-Antitrypsin (AAT) belongs to the "*positive acute-phase-proteins*," i.e., to those proteins whose production is stimulated by acute inflammation (acute phase response, → pp. 54 and 274). AAT is a serine protease inhibitor (serin-PI = serpin), which is synthesized in liver and lung but found in all tissues and in plasma. In serum electrophoresis AAT is the major component of the α_1-peak. AAT inhibits the action of trypsin and the elastase of neutrophils. It is particularly important in the lung, where it protects the tissue from degradation by the elastase from neutrophils.

AAT-deficiency (= Laurell–Eriksson syndrome) results from mutations in the AAT-gene on chromosome 14 (→ **B**). It results in an autosomal recessive disorder, in which instead of the normal allele M (phenotype PI*MM) the pathological alleles S or Z are produced (prevalence of the homozygous form: 1 : 1500 down to 1 : 5000). The form with the highest risk is the homozygous phenotype PI*ZZ. The AAT deficiency results in an excessive pulmonary proteinase activity leading to tissue destruction (emphysema, bronchiectases) and eventually to respiratory insufficiency with hypoxemia and hyperkapnia. *Smoking* and recurrent infections accelerate the deterioration of lung function (→ **B**). The hepatic synthesis of the most common AAT variant (PI*ZZ) results in aggregation of the defective protein to polymers with subsequent accumulation in the hepatocellular endoplasmic reticulum (ER). Consequences include **liver injury** with cholestatic jaundice in infants, chronic hepatitis, liver cirrhosis, and frequent development of hepatocellular carcinoma (→ **B**). As with Wilson's disease, liver transplantation cures the AAT deficiency.

A. Wilson's Disease

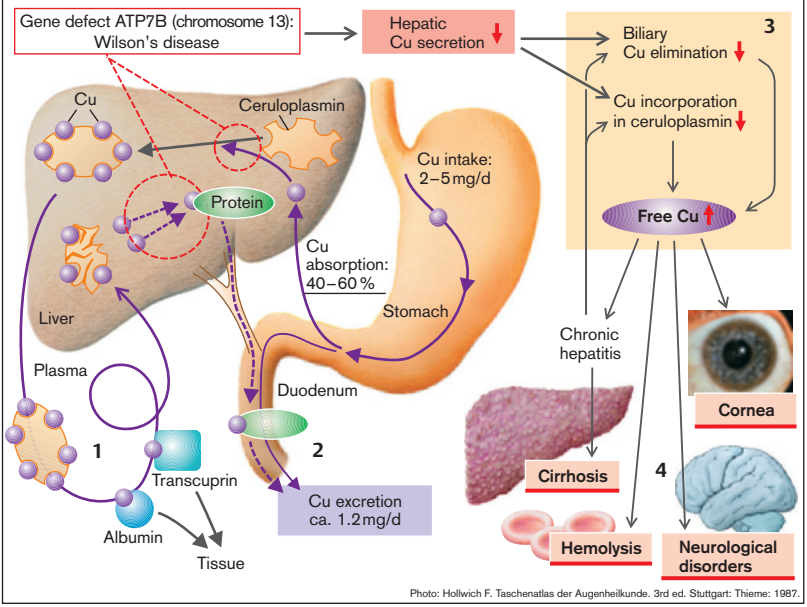
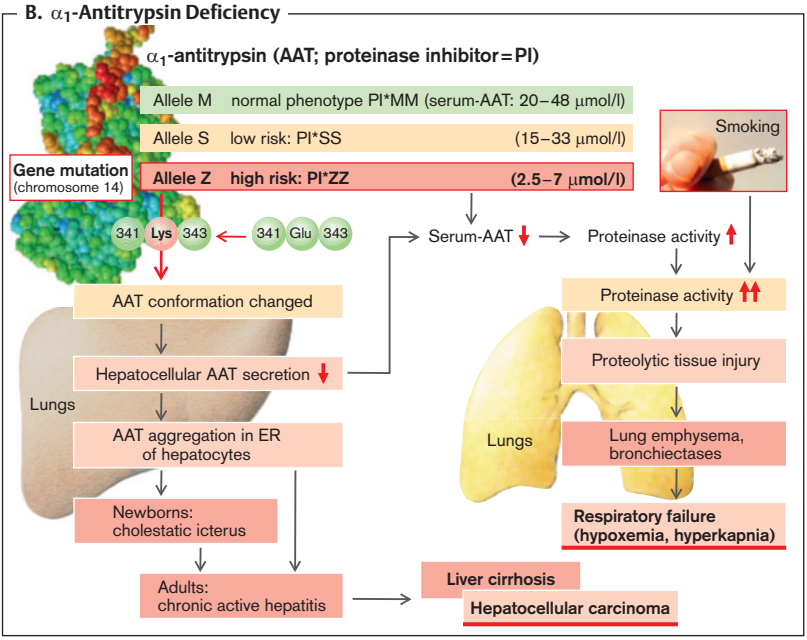


Photo: Hollwich F. Taschenatlas der Augenheilkunde. 3rd ed. Stuttgart: Thieme: 1987.

B. α_1-Antitrypsin Deficiency



Dysproteinemias

Acute-phase proteins. *Acute* and acutely recurring chronic *infections* as well as *burns and traumatic injury trigger an* **acute-phase reaction** (see also p. 54), whereby the plasma concentrations of some 30 distinct **acute-phase proteins (APP)** *increase* within 5 hours to 2 days (→ **A** left). APPs include α_1-antitrypsin (→ p. 272), serum amyloid A (see below), C-reactive protein (CRP), ceruloplasmin (→ p. 270), haptoglobin, ferrin (→ p. 42), plasminogen, and fibrinogen (→ p. 64 ff.). During an acute phase reaction the plasma concentration of other APPs *decreases* (→ **A** right) including albumin, transthyretin ("prealbumin", a thyroxin-binding protein), transferrin (→ p. 42), and antithrombin III (→ p. 64). The serum protein electrophoresis (→ **B1**) yields during the acute phase reaction an increased α-globulin peak (→ **B2**, "positive APPs"), whereas the albumin- and transferrin-peaks are decreased ("negative APPs"). The alterations of APP abundance result from cytokin release (interleukin 1 and 6, tumor necrosis factor α, etc.), from tissue macrophages. The inflammatory cytokines regulate the hepatic formation of APPs by binding to specific receptors and triggering the activation of STAT transcription factors (→ **A**).

The **functional significance of the APPs** (→ p. 54) lies in their anti-infectious efficacy. They counteract the spread of inflammation and support the immune system in the clearance of the inflammatory tissue. CRP, for instance, opsonizes pathogens (→ p. 48), the antiproteases limit the proteolytic activity of proteases released in the inflamed tissue (→ p. 272), and the decrease of transferrin decreases the iron availability for the pathogens in blood (→ pp. 42 and 270) etc. (→ **A**).

Paraproteins. Paraproteins are homogenous *immune globulins* (or their L- or H-chains), which are produced excessively by a single clone of uncontrolled B-lymphocytes and appear in the serum protein electrophoresis as a slim band, mostly within the β- or γ-globulins (→ **B3**). Paraproteins appear in plasma following malignant transformation of plasma cells, such as:

- in *plasmocytoma* (= *multiple myeloma*), an uncontrolled proliferation of a single plasma cell clone in bone marrow with multiple bone defects and synthesis of pathological immune globulins without antibody function;
- in *Waldenström's disease,* a malignant lymphoma of B-lymphocytes with excessive formation of a monoclonal IgM-macroglobulin;
- in the relatively rare *heavy (or H-)chain disease* with enhanced formation of incomplete heavy chains of IgG, IgA, or IgM.

L-chain paraproteins are so small as to be largely filtered at the renal glomerular filter and subsequently excreted with the urine (*Bence–Jones proteinuria*). They accumulate in plasma only in advanced renal failure.

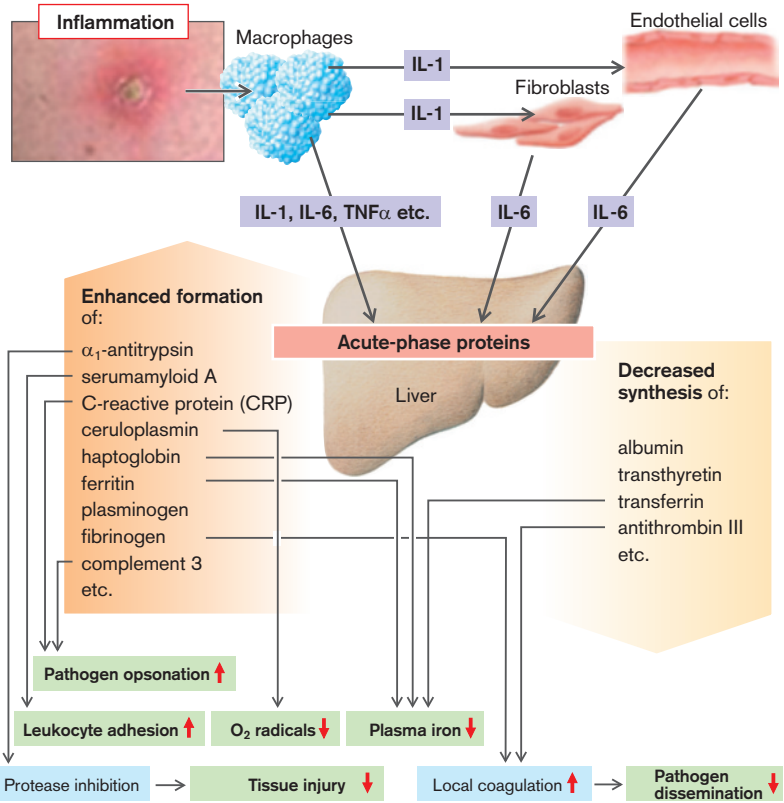
Cryoglobulins. Cryoglobulins are immune globulins or fragments thereof in plasma, which at *decreasing temperature* form reversible gels or reversibly precipitate as (cryo-)precipitates or crystals.

Type I is caused by monoclonal nonfunctional antibodies and is encountered in plasmocytoma (see above) and further malignant lymphomas; *Type II* is due to monoclonal functional antibodies against the Fc region of immune globulins, whereas the most common *type III* is due to polyclonal antibodies. Type III is encountered in rheumatoid arthritis, systemic lupus erythematodes, and chronic infections (e.g., hepatitis C).

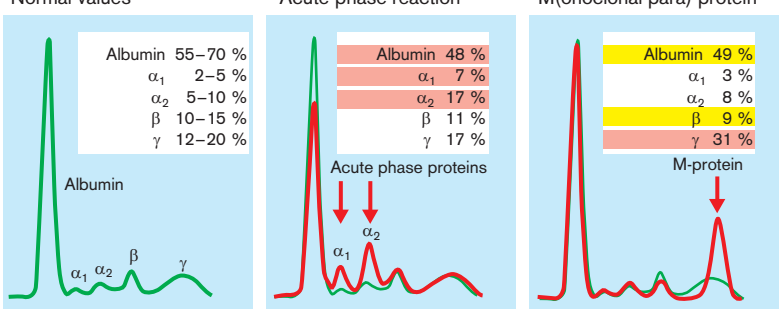
In blood, cryoglobulins (*cryoglobulinemia*) enhance the viscosity, aggregate erythrocytes, derange thrombocyte function, alter the permeability of the vascular wall, and cause glomerular injury. **Consequences** include periodical cold-induced vascular cramps mostly affecting the fingers (secondary Raynaud's syndrome) with pallor, cyanosis, and painful reactive hyperemia, infarcts of internal organs, petechial bleeding, retinal vascular thrombosis, etc.

Amyloidosis. The aggregation of proteins with β-sheet structure to insoluble fibrils (*amyloid*) leads to amyloidosis. The involved proteins include the APP *serum amyloid A* (*AA amyloidosis*) in chronic inflammatory processes, *L-chains of immune globulins* (*AL-amyloidosis)* at monoclonal paraproteinemia or prealbumin (*AH-amyloidosis*) in patients with hereditary variants of this protein, which contains ample β-sheet structures. Prolonged treatment with hemodialysis may be paralleled by β_2-microglobulin deposition (*AB-amyloidosis*). The consequences of amyloidosis depend on the tissue and localization of the deposits and include cardiomyopathy, renal insufficiency, polyneuropathia, hepatomegaly, etc.

A. Acute-Phase Proteins



B. Serum Protein Electrophoresis at Dysproteinemias



Values: % of total plasma proteins

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. 40), heme is synthesized in practically all organs and built into myoglobin, cytochrome P_{450}, 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. 40).

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 porphinogens; 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).

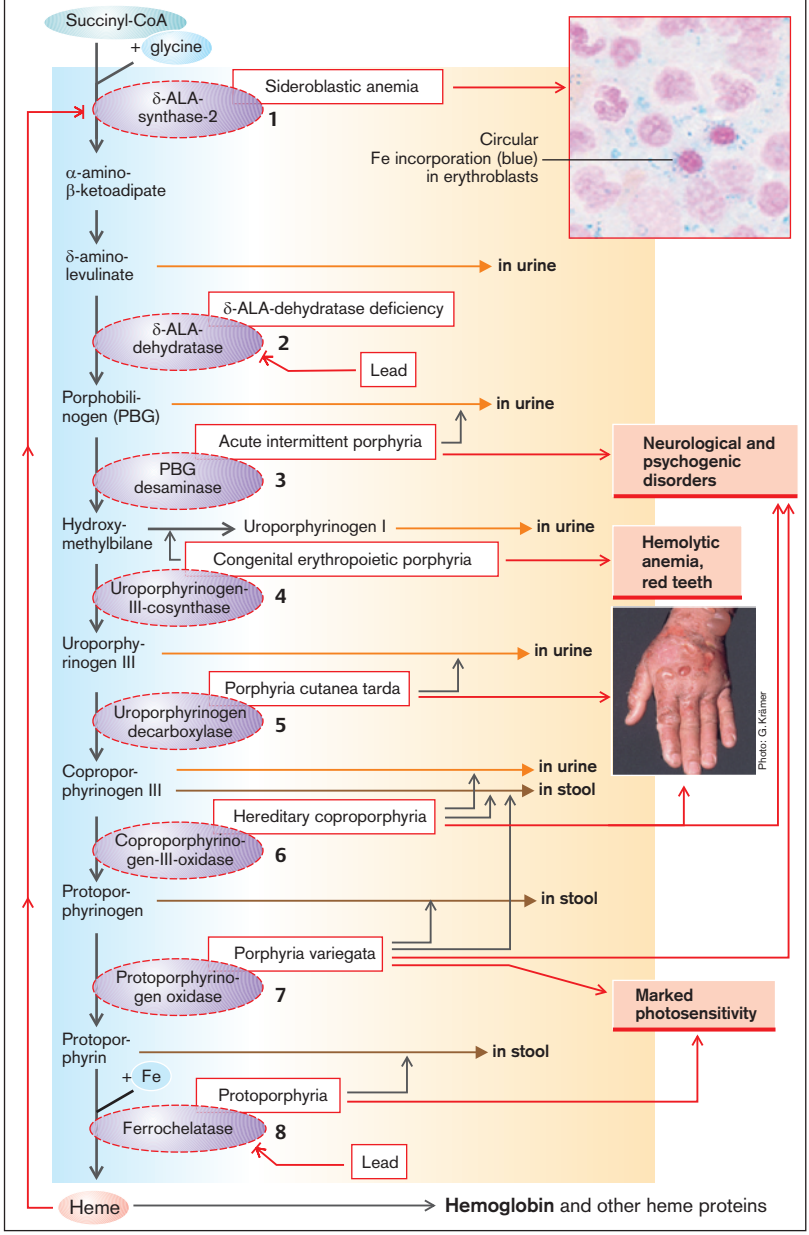
In **congenital erythropoietic porphyria** (→ **A4**) uroporphyrinogen will be formed non-enzymatically from hydroxymethylbilane, and converted enzymatically to coproporphyrinogen I (analogously to A5). Coproporphyrinogen I can no longer be used metabolically and, excreted in the urine, in infants it 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). *O_2 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



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** (→ p. 6 ff.). 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 enhance their 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* (e.g., due to a genetic defect). 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**), for instance due to destruction by autoimmune disease, infections, or ischemia.

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 or inhibited [e.g., by antibodies] hormone receptors or faulty intracellular transmission) or *functional incapacity of the target cells* or *organs* (→ **A9**).

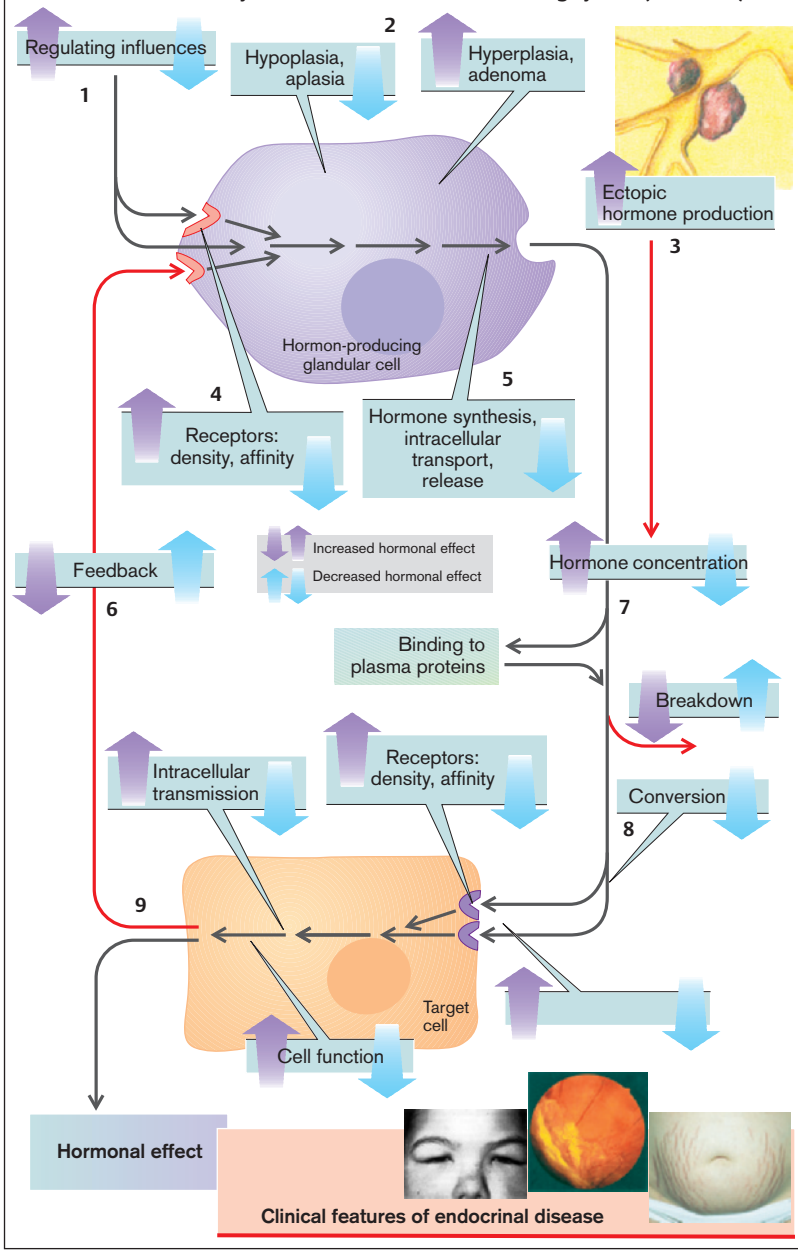
Causes of **increased hormone effects** (violet arrows) include, first of all, *increased hormonal release*. This may be due to an excessive influence of individual stimuli (→ **A1**), increased sensitivity (→ **A4**), or too large a number of hormone-producing cells (hyperplasia, adenoma; → **A2**). 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**). For instance, hormone receptors may be stimulated by antibodies.

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)



Abnormalities of Endocrinal 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 influence of the hormone on the target organs typically leads to a reduction in the stimuli of 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 concentrations 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 subsequent stimulation of 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 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 by corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) (→ **B1**).

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. 278 A3) of liberins, tropins, or peripheral hormones.

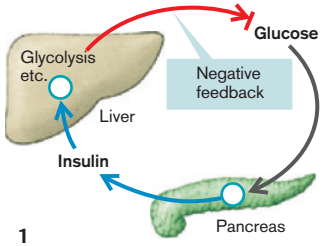
If there is an **increase in liberin release** (→ **B2**), liberin, tropin, and peripheral hormone concentrations are raised.

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**).

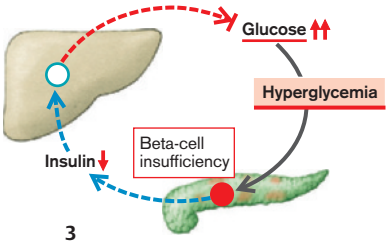
If there is a primary **rise in peripheral hormone release**, the release of liberins and tropins is suppressed (→ **B4**).

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.

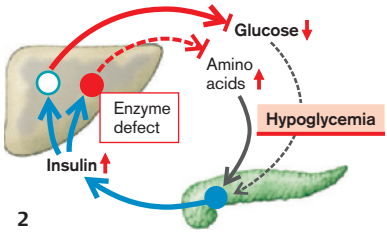
A. Abnormalities of Simple Endocrinal Regulatory Circuit



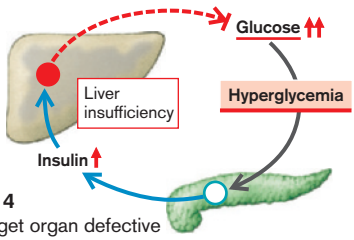
1
Normal regulation



3
Defect in hormonal gland

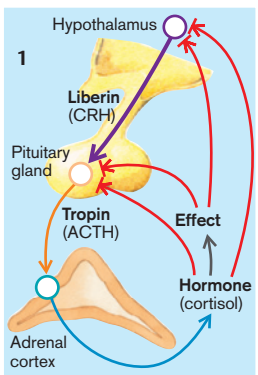


2
Increased secretion in the intertwined regulatory circuit

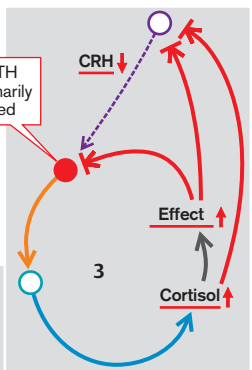


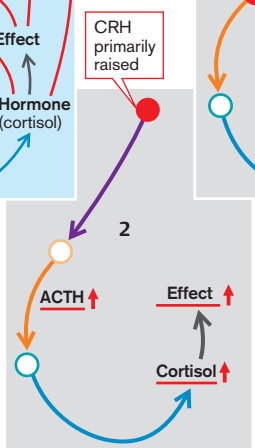
4
Target organ defective

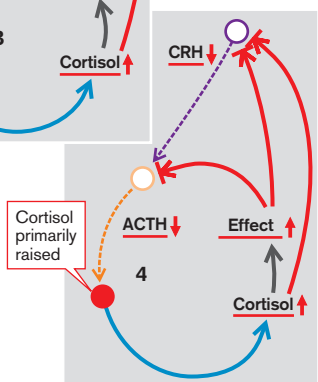
B. Abnormalities of Hypothalamus-Regulated Hormones



Normal regulation







The Antidiuretic Hormone

The **antidiuretic hormone** ([**ADH**] **adiuretin**, **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 release ist stimulated by extracellular hyperosmolarity (or cell shrinkage), decreased filling of the cardiac atria (hypovolemia), arterial hypotension, nausea, hypoglycemia, lack of glucocorticoids, pain, fear, stress, (sexual) arousal, 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 causes the incorporation, via V_2-receptors and cAMP, of water channels (aquaporin 2) into the luminal membrane of renal distal tubules and collecting duct and thus promotes *water reabsorption* in the kidney. ADH further stimulates the tubular absorption of Na^+ and urea. A high ADH concentration also leads to *vasoconstriction, hepatic glycogenolysis*, and *corticotropin (ACTH) release* (via V_1-receptors).

ADH excess (→ **A 1**) 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 soluble 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. 380). ADH further contributes to volume retention and edema formation (→ p. 250), for example in pregnancy (→ p. 126), cardiac insufficiency (→ p. 238), and liver cirrhosis (→ p. 128).

ADH deficiency (→ **A 2**) 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 genetically defective receptors or water channels, or if the concentrating capacity of the kidney is otherwise impaired (→ p. 100), 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. 132), 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 hypodipsia, 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*.

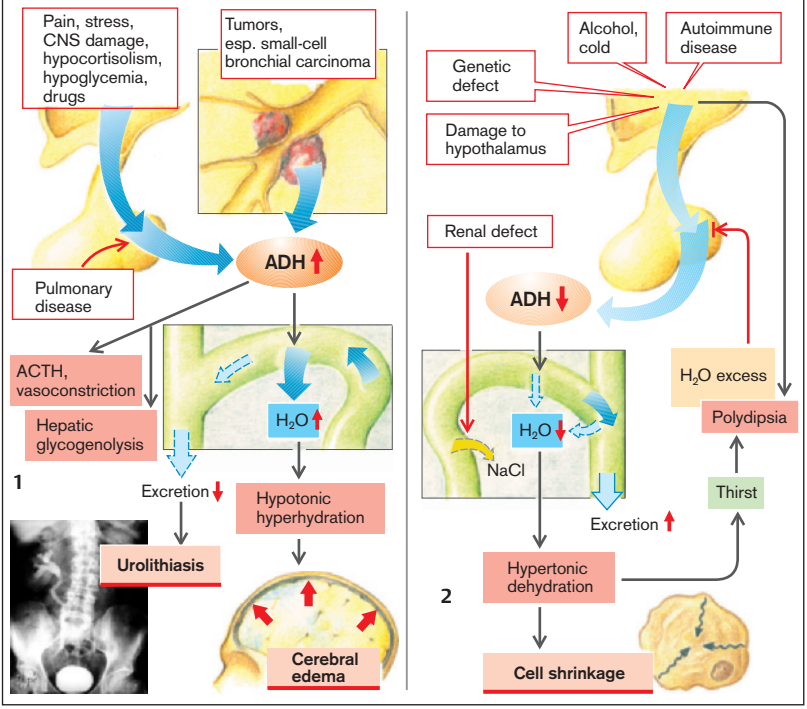
Prolactin

Prolactin (→ **B**) is formed in the anterior lobe of the pituitary gland. Prolactin release is stimulated by touching the nipple of a lactating woman, orgasm, estrogens (pregnancy), 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 (D_2 receptors) inhibits prolactin release. As prolactin increases dopamine metabolism in the hypothalamus, it inhibits its own release ("short" negative feedback). Glucocorticoids and T_3/T_4 are weak inhibitors of prolactin release.

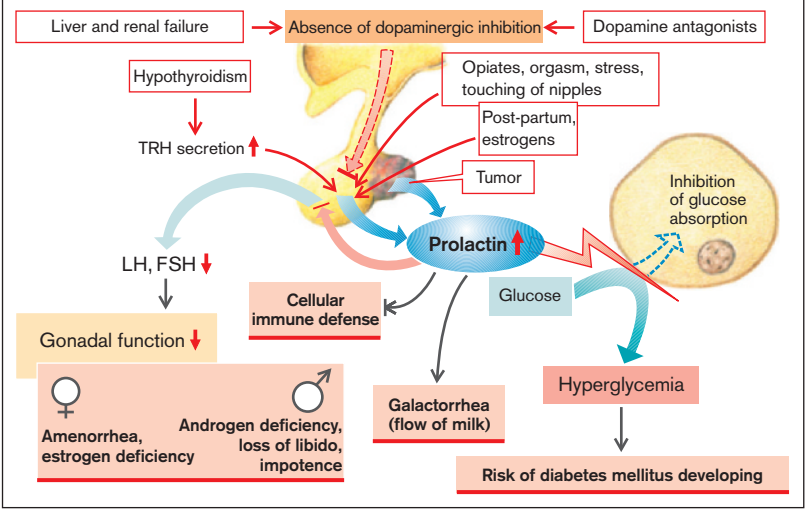
Prolactin stimulates growth and differentiation of the mammary gland as well as *milk production*. It inhibits the pulsatile, but not the basal, release of the gonadotropins (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]; → p. 296). It also inhibits cellular glucose uptake and the cellular immune defense.

Excess prolactin (→ **B**) can be caused by hormone-producing *tumors*, stress, or by administration of *antidopaminergic drugs*. Renal insufficiency (impaired degradation) and liver cirrhosis (dopamine depletion) can also result in an excess of prolactin. *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



B. Prolactin Excess



Somatotropin

The normally pulsatile release of **somatotropin** (**growth hormone** [**GH**]) from the anterior lobe of the pituitary gland is stimulated by *somatoliberin* (GHRH) and inhibited by *somatostatin* (SRIF). The release of somatotropin is stimulated by amino acids (particularly arginine), hypoglycemia, ghrelin, glucagon, estrogens, dopamine, α-adrenergic stimulation, and stress. It is inhibited by hyperglycemia, hyperlipidacidemia, glucocorticoids, β-adrenergic stimulation, IGF1 (insulin-like growth factor 1), obesity, and cold. The somatotropin release sharply declines in advanced age.

Somatotropin is in part effective by stimulating the release of insulin-like growth factor IGF-1 (mainly in the liver). Somatotropin stimulates protein synthesis and lipolysis and *inhibits the uptake of glucose* in fat and muscle cells. It stimulates the *formation of erythropoietin* and the renal retention of Na^+ and K^+ and increases the plasma phosphate concentration. It stimulates 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 the immune defense. Estrogens inhibit the formation of IGF1, thus reducing the effects of somatotropin.

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. Uncontrolled *therapeutic administration of somatotropin* can also result in an iatrogenic excess of somatotropin (→ **A 1**).

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** (→ **A 2**). 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 (→ **A 3**). 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. 232). **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** (→ **A 4**), in some cases of *diabetes mellitus*. Increased intestinal absorption results in **calcium excess** followed by *hypercalciuria* (→ **A 5**). The latter may cause precipitation of calcium salts in urine (nephrolithiasis; → p. 130). Somatotropin excess also promotes the development of colon polyps and **tumors**.

A somatotropin-producing pituitary tumor often causes enlargement of the sella turcica; pressure on the optic chiasma (→ **A 6**) can give rise to **visual field defects** (typically bitemporal hemianopia, as though the patient were wearing blinkers; → p. 348). Displacement of other endocrine cells can lead to gonadotropin deficiency, and thus to amenorrhea as well as loss of libido, and impotence (→ **A 7**). Conversely, somatotropin-producing tumors can also release other hormones, such as prolactin (→ p. 282).

Somatotropin deficiency can be *genetically determined* (e.g., defects of the GH-regulating transcription factors Pit-1 and Prop-1) 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, malnutrition, hypoinsulinism, renal insufficiency*, and *inflammatory mediators*. It may be abolished by genetic defects of the receptor (*Laron syndrome*). If somatotropin deficiency occurs before epiphyseal fusion, **pituitary dwarfism** with high-pitched voice, micropenis, increased fat, and propensity to hypoglycemia will result. A deficiency occurring after the completion of longitudinal growth results in decreased muscle mass, increased fat tissue, hyperlipidemia, arteriosclerosis, *weakening of the immune system*, demineralization of bone, and psychological disorders (depression, social isolation).

A. Somatotropin Excess

Magnetic resonance image kindly supplied by R. Santen, Düsseldorf Univ., Endocrinology Clinic

Pituitary adenoma

Age, obesity, cold, glucocorticoids, β-agonists

Stress, ghrelin NREM sleep, hypoglycemia, amino acids, α-agonists

Rare: Ectopic adenoma

6 Compression of optic chiasma → Visual field defects

7 Gonadotropin deficiency → Amenorrhea, loss of libido and impotence

1 Iatrogenic

Somatotropin

Tumors

Before epiphyseal fusion: Gigantism

4 Glucose absorption reduced → Hyperglycemia

Hyperphosphatemia

5 → Calciuria

Visceromegaly → Carpal tunnel syndrome → Risk of angina pectoris → Hypertension

3 Secretion of sweat and sebum

2 Acromegaly

Macroglossia

Enlargement of cheek bones, hands and feet

Adrenocortical Hormones: Enzyme Defects in Formation

Adrenocortical hormones (*corticoids*) include the **glucocorticoids** (mainly cortisol, produced in the zona fasciculata), **mineralocorticoids** (mainly aldosterone from the zona glomerulosa), **androgens** (mainly dehydroepiandrosterone), **progestogens**, and **estrogens** (produced in the zona reticularis). The hormones are degraded mainly in the liver.

All adrenocortical hormones (see also p. 294 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.

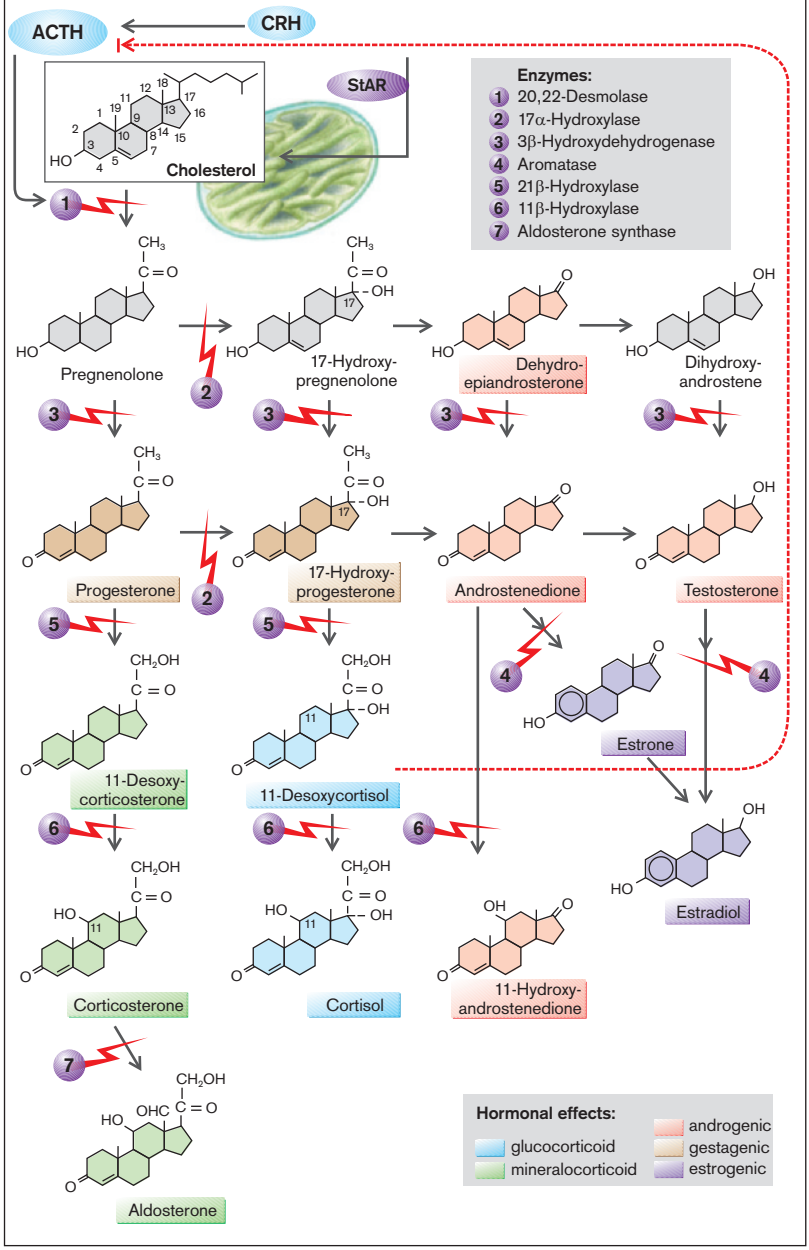
Enzyme defects lead to decreased synthesis of enzyme products, and thus also of the hormones formed through their action. However, reduced glucocorticoid synthesis **disinhibits the formation of corticoliberins** (CRH) **and of corticotropin** (adrenocorticotropic hormone [ACTH]). Corticotropin, in turn, 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, i.e. of steroids which are 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 adrenocorticoid hormone production, glucococorticoid production can be (practically) normalized, in spite of an enzyme defect. More frequently, though, the glucocorticoid action decreases (→ p. 292). If there is an excess of gestagenic metabolites, their weak antimineralocorticoid effect can trigger natriuresis (→ p. 298). Some enzyme defects increase concentrations of androgenic metabolites, with the corresponding consequences for sexual development (→ p. 294 f.). If there is a 3β-hydroxydehydrogenase defect (→ **A 3**), 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-desoxycortisol (→ **A 5**). 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. 294). These effects can already be detected at birth, since the excess androgens are formed intrauterinely. An 11β-hydroxysteroid dehydrogenase (11β-HD) type I in the periphery (mainly liver) may convert inactive cortisone to active cortisol. Conversely, an 11β-HSD type II may inactivate cortisol to cortisone. The 11β-HSD type II normally prevents an activation of mineralocorticoid receptors by corticol. If it is defective, cortisol exerts mineralocorticoid effects (→ p. 292).

Enzyme Defect (→ **A 1 – 8**)	Androgenic Action	Glucocorticoid Action	Mineralcorticoid Action
❶ 20,22-Desmolase (CYP11A1, StAR)	↓	↓	↓
❷ 17α-Hydroxylase (CYP17)	↓	↓	↑
❸ 3β-Hydroxydehydrogenase (3β-HSD2)	↑ (♀) ↓ (♂)	↓	↓
❹ Aromatase (CYP19)	↓	–	–
❺ 21β-Hydroxylase (CYP21A2)	↑	↓	↓
❻ 11β-Hydroxylase (CYP11B1)	↑	↓	↑
❼ Aldosterone synthetase (CYP11B2)	–	–	↓

A. Enzyme Defects in Formation of Adrenocortical Hormones



Adrenocorticoid Hormones: Causes of Abnormal Release

The **glucocorticoids** serve, in the first instance, in the adaptation of metabolism, circulation, blood, immune system, etc. to physical and emotional stress. The **mineralocorticoids** act on mineral and water balance (for mechanism of action see p. 290) 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 corticoliberin (corticotropin-releasing hormone [CRH]) from the hypothalamus (→ **A**). The most important stimulus for the release of CRH, ACTH and cortisol, is stress. Other stimuli are epinephrine, ADH, histamine, pyrogens, pain, fall in blood pressure, and hypoglycemia (→ **A 1**). Release of cortisol is highest in the early morning hours and then slowly falls during the day (→ **A 2**). The release is inhibited by morphine.

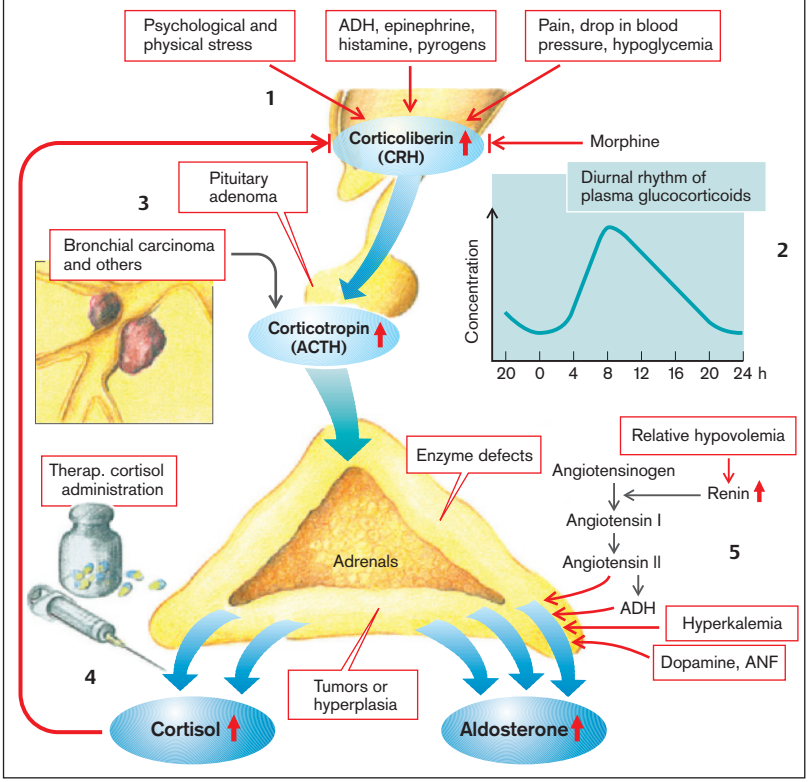
An **excess of glucocorticoids** may result from therapeutic administration of glucocorticoids for immunosuppression (→ **A 4**), a hormone-producing *tumor* in the adrenal gland or other organs (especially small-cell bronchial carcinoma; → **A 3**) (Cushing's disease; → p. 290) or an excess *stimulation of the adrenal* by ACTH (secondary Cushing syndromes, for example, due to a pituitary tumor, other causes of CRH release, or ectopic formation of ACTH or, rarely, of CRH).

The most important stimulus for the **release of the mineralocorticoid** aldosterone is angiotensin II, which is formed by the renin–angiotensin system when the renal perfusion pressure is reduced (e.g., in hypovolemia; → **A 5**). Aldosterone release is also stimulated by ADH, whose secretion is stimulated by angiotensin II. Aldosterone release is increased by hyperkalemia, and to a lesser extent by ACTH, serotonin, and endothelin. It is decreased by dopamine and the atrial natriuretic factor (ANF).

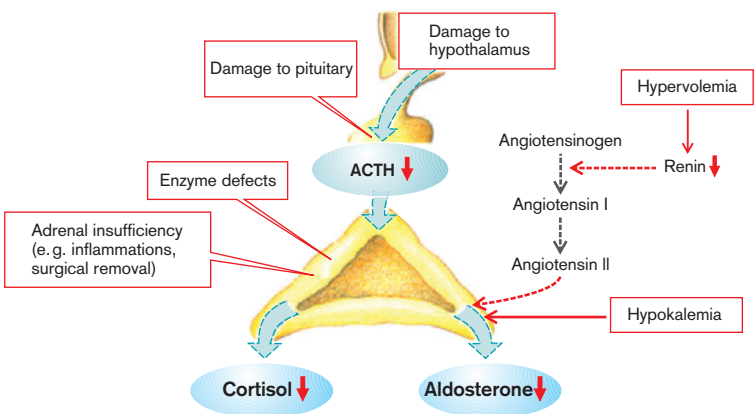
A selective **excess of mineralocorticoids** results in the majority of cases from increased renin release (*secondary hyperaldosteronism*). In hypovolemia (e.g., in dehydration) the increased release of aldosterone is adequate for controlling volume, but usually too high for K^+ balance. If hypovolemia occurs, the resulting "intertwining" of the regulatory circuits for plasma volume and potassium (→ p. 280) regularly leads to hypokalemia. Even if blood volume is normal or increased, renal perfusion may be impaired and thus renin release increased in several renal diseases (→ p. 124). If the pumping action of the heart is reduced (→ p. 238), or in peripheral vasodilation (e.g., in sepsis or liver failure; → p. 128) the blood pressure can be maintained only by massive activation of the sympathetic nerve 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 genetic defect of 11β-hydroxysteroid dehydrogenase (*apparent mineralocorticoid excess*; → p. 124) 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 (110-HSD) is defective. Excessive cortisol concentrations saturate the 11β-HSD and the incomplete degradation of cortisol leads to stimulation of the mineralocorticoid receptor. 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. 292; e.g., in genetic defects, autoimmune adrenal disease, tuberculosis, metastases, surgical removal) or of enzyme defects in adrenal hormone synthesis (→ p. 286). 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



B. Causes of Cortisol and Aldosterone Deficiency



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, coagulation factors) in the liver. They increase the number of neutrophils and thrombocytes, decrease the number of eosinophils and monocytes, and stimulate the apoptosis of T lymphocytes. Partially by suppressing the transcription factors AP1 and NFκB they inhibit the release of inflammatory mediators, such as interleukin 1 and 6, tumor necrosis factor (TNF)-α, bradykinin, serotonin, histamine, and platelet activating factor (PAF). By inhibiting phospholipase A_2 they suppress the formation of prostaglandins and leukotrienes. They inhibit the migration of leukocytes and macrophages. They are thus *immunosuppressive* and *anti-inflammatory*, but at the same time impede collagen synthesis and repair. They stimulate coagulation and pulmonary surfactant production. They simulate the secretion of acids and pepsin in the stomach and slow down mucus production. In the eye they stimulate secretion of fluid and intraocular pressure. They decrease intestinal calcium absorption and favor bone resorption. They also sensitize blood vessels and the heart to catecholamines, partly by inhibiting prostaglandin synthesis; they stimulate the release of norepinephrine, increase the excitability of the nervous system, and influence emotions.

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^+, Mg^{2+}, and H^+ and simultaneously the cellular uptake of potassium. At simultaneous salt excess, mineralocorticoids stimulate the formation of TGF-β and PAI-1 (plasminogen activator inhibitor 1) and thus stimulate matrix protein formation. 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. 288).

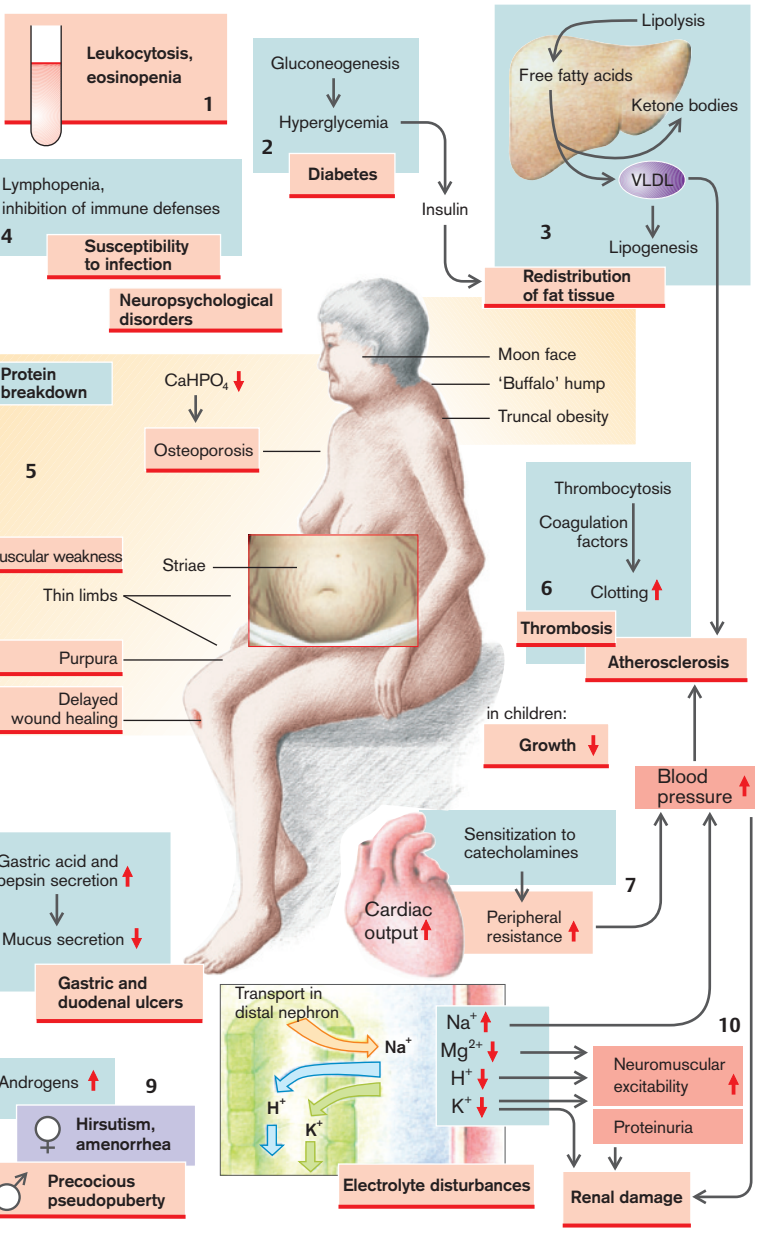
Dehydro-epiandrosterone (**DHEA**), a weakly androgenic precursor of the steroid sex hormones, is also formed in the adrenals, in addition to mineralocorticoids and glucocorticoids.

The metabolic effects of **glucocorticoid excess** favor the development of diabetes mellitus (→ p. 308 ff.), i.e., **steroid diabetes** (→ **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 $CaHPO_4$ deficiency and inhibition of somatotropin release. In children it results in **delayed growth**. The effects on blood increase **coagulability** (→ **A6**). Weakened immune defenses encourage **infections** (→ **A4**). Sensitization of the circulation to catecholamines causes an increase in cardiac contractility as well as peripheral vasoconstriction, 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 mineralcorticoid effect** causes hypervolemia, which in turn leads to *hypertension*; it also causes hypokalemia, hypomagnesemia, and alkalosis, which in turn lead to *increased neuromuscular and cardiac excitability* (→ **A10**). Excessive formation of TGF-β and PAI-1 damage the renal glomerula (proteinuria) and stimulate renal and cardiovascular fibrosis.

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. 294).

A. Effects and Symptoms of Adrenocortical Hormone Excess



Deficiency of Adrenocorticoid Hormones: Addison's Disease

For the effects of the adrenocorticoid hormones, see p. 290.

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. 284). 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, resulting in loss of body weight. 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 *neutropenia, eosinophilia,* and *lymphocytosis* (→ **A4**). Other symptoms are fatigue and weakness. However, while cortisol deficiency persists, sensitivity of the target cells is raised and they thus delay the onset of symptoms.

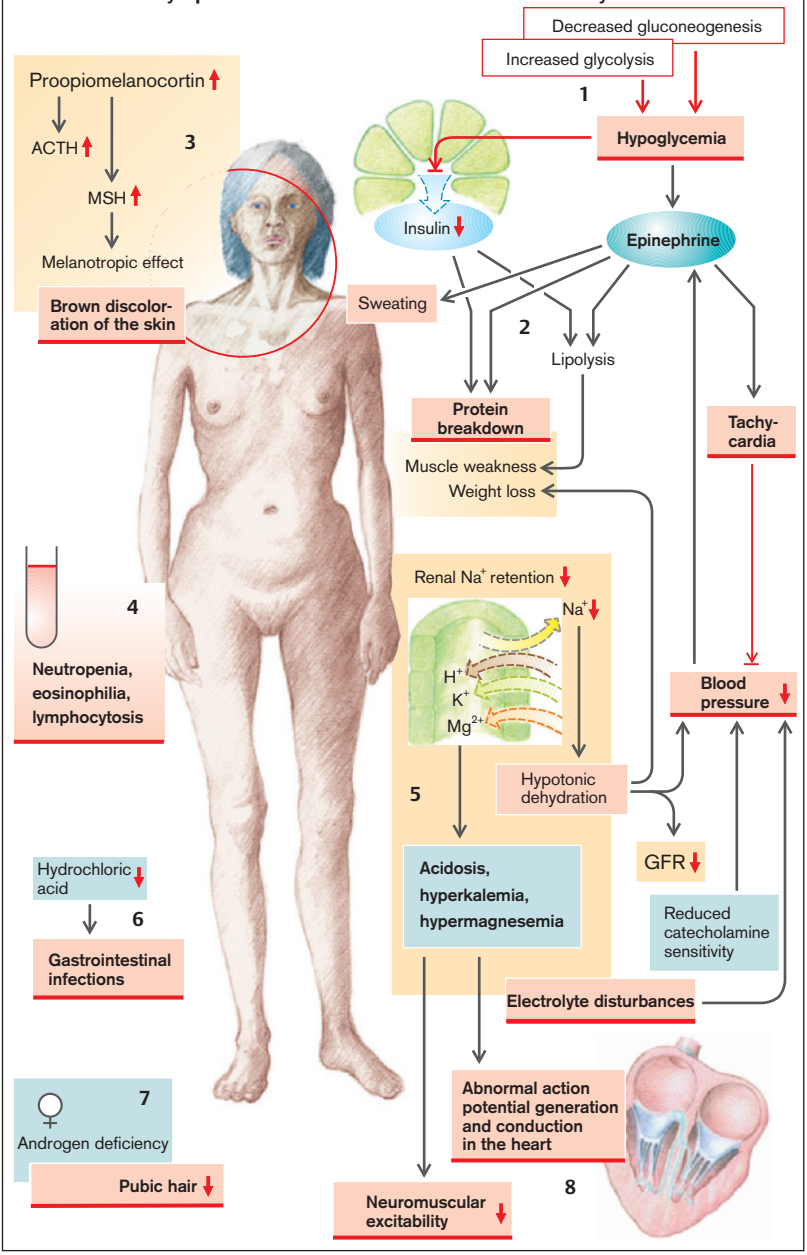
In **primary adrenocorticoid insufficiency** (**Addison's disease**) the diminished negative feedback from cortisol leads to a massive rise in the synthesis of *pro-opiomelanocortin* (*POMC*), the precursor of ACTH. This increases formation not only of ACTH, but also of α-melanotropin (α-MSH or melanocortin). 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 adrenocorticoid 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^+, Mg^{2+}, 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. 132 ff.). 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 hypoosmolarity. The retention of K^+, Mg^{2+}, 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. 134 ff.). The fluid depletion causes **weight loss,** and the arterial hypotension reduces 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



Causes and Effects of Androgen Excess and Deficiency

Follitropin (FSH) and *lutropin* (LH) are released in the anterior pituitary, stimulated by pulsatile release of gonadoliberin (gonadotropin-releasing hormone, GnRH) (→ **A1**). The pulsatile secretion of these gonadotropins is stimulated by leptin and inhibited by *prolactin* (→ p. 282). 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 (→ **A2**). Testosterone can be converted by a 5α-reductase into dihydrotestosterone (5α-DHT) and by an aromatase into estradiol. 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 (→ **A3**).

Testosterone stimulates the development of *seminiferous tubules,* dihydrotestosterone (5-α-DHT) promotes the *growth of prostate, penis, urethra, and scrotum* (→ **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 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*. It stimulates the renal retention of electrolytes, reduces the concentration of high density lipoprotein (HDL) in blood (→ p. 264 f.), and influences fat distribution. By promoting muscle and bone growth (protein anabolism), longitudinal growth, and bone mineralization as well as fusion of the epiphyseal plates, it influences *height and stature*. Its effect on bone is partially mediated by estradiol and requires aromatase (→ p. 286).

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, inflammation, ischemia, genetic defects) as well as psychological or physical stress. Malnutrition abrogates the stimulation of gonadotropins by leptin. In liver insufficiency the delayed degradation of androstendion enhances formation of estrogens, which inhibit the release of LH and thus of testosterone. 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 (→ p. 286), by a *defect of the testosterone receptors*, or by a lack of aromatase.

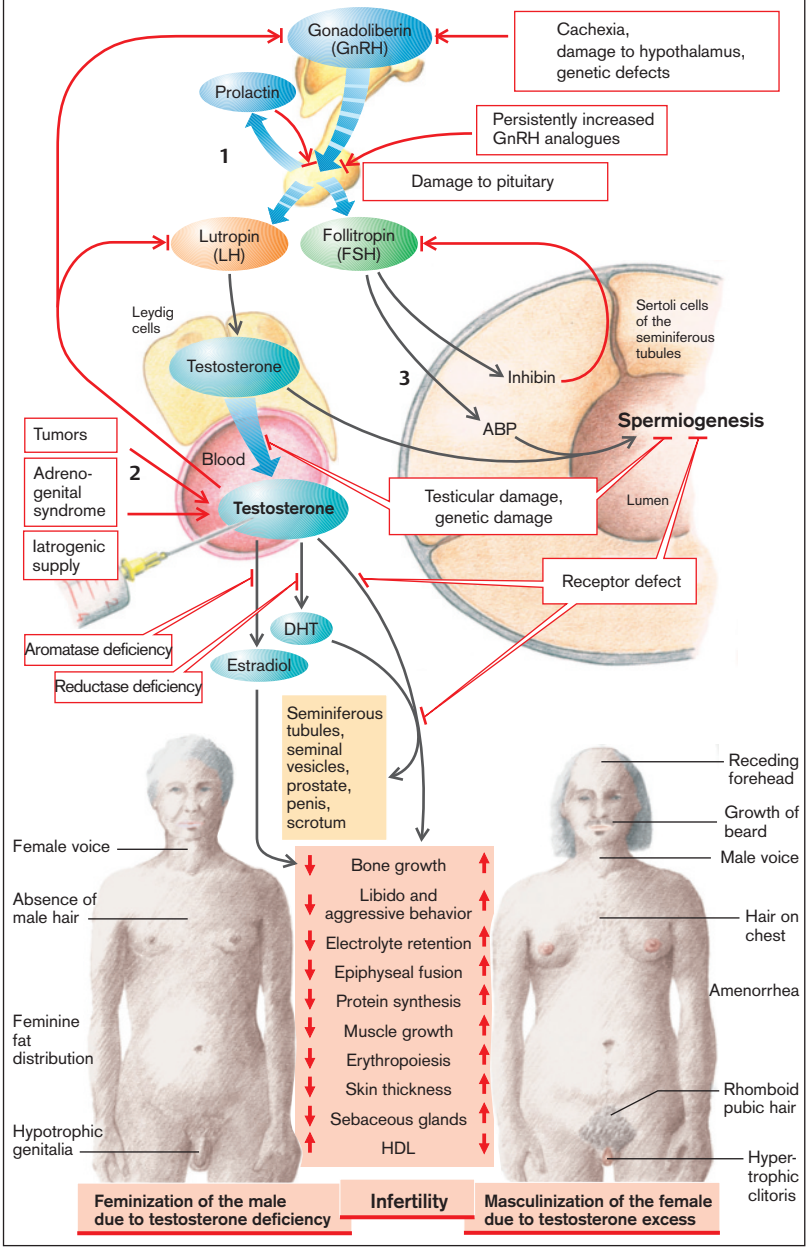
Effects of deficient testosterone action in the male fetus are **absent sexual differentiation** (→ p. 300); in juveniles they are failure of the voice to break and absence of adult body hair, delayed bone growth, but also ultimately excess longitudinal growth of the limbs due to delayed epiphyseal fusion. 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* (→ p. 286), a *testosterone-producing tumor*, or *iatrogenic androgen supply* (→ **A2, 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 (♀) and **impaired fertility** (♂ and ♀) 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



Release of Female Sex Hormones

The gonadotropic hormones FSH and LH are released from the anterior lobe of the pituitary gland in a pulsative manner (every 60 to 90 min for 1 min) after pulsatile stimulation by GnRH from the hypothalamus at the same frequency (→ **A1**; see also p. 294). FSH and LH are essential for the maturing of the follicles and for the temporal coordination of the production of female sex hormones (→ **A2**). The **estrogens** (mainly estradiol, but as well estrone and 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 theka cells form the androgens *androstenedione* and *testosterone* (→ p. 294). Activin promotes gonadotropin release, while inhibin suppresses it. The ovary further produces relaxin (softens uterine cervix and symphysis) and oxytocin (is similarly released from the neurohypophysis; promotes affection and stimulates contractions of uterine muscle and myoepithelial cells in mammary glands). *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 gonadotropins or sex hormones, cerebral inflammation may lead to stimulation of gonadotropin release and the FSH receptor may be stimulated by excessive TSH concentrations (→ p. 302). Delayed degradation increases estrogen plasma levels in liver insufficiency.

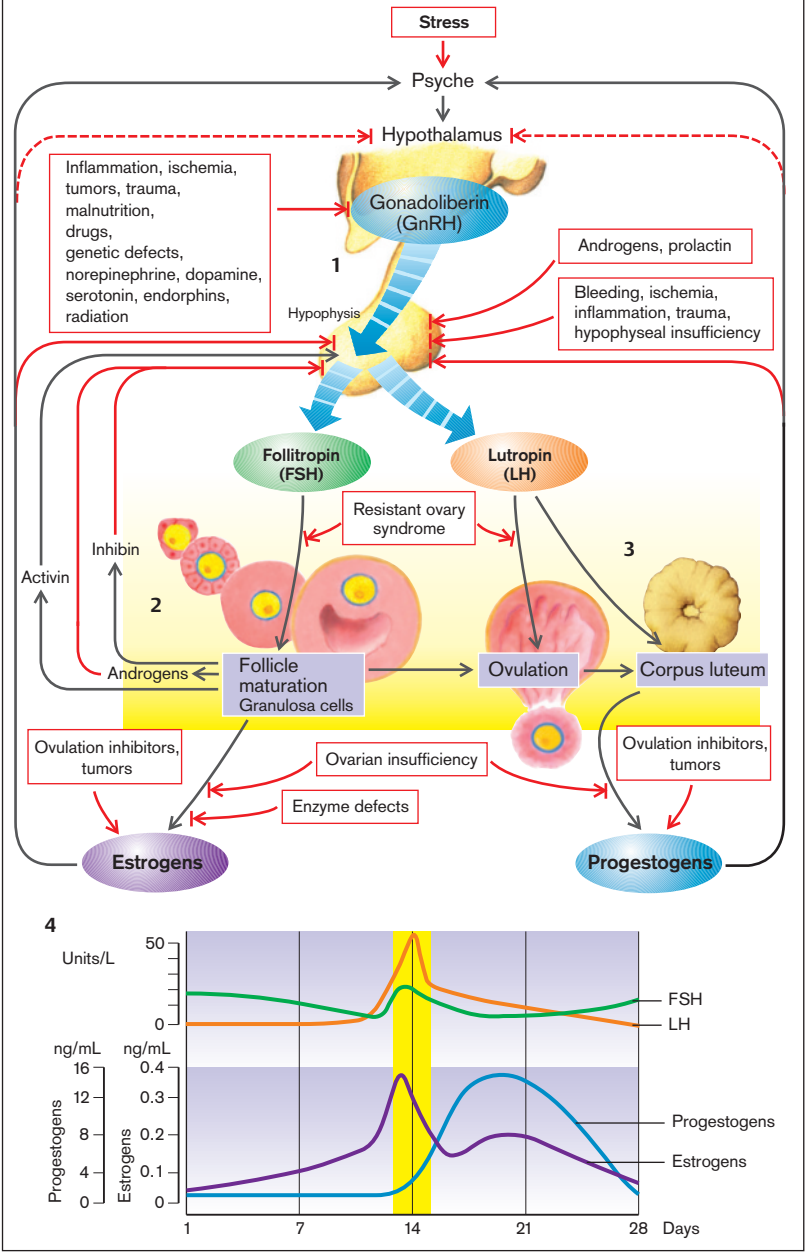
A **lack** of estrogens and progestogens is frequently the result of a *decreased GnRH release* in severe psychological or physical stress (e.g., malnutrition, malabsorption, renal insufficiency, further serious systemic disease, high-performance sport). GnRH release can also be reduced through the influence 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 receptors). 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, adrenogenital syndrome; → p. 286).

If androgen production is raised, the release of FSH is inhibited and follicle maturation is thus interrupted. *Polycystic ovaries* are formed. Lack of FSH promotes the accumulation of androgens and gestagens. In obesity androgens may be transformed into estrogens which, via stimulation of LH release, promote further formation of ovarian androgens.

Gonadotropin release is inhibited at excessive *prolactin secretion*, which may occur following treatment with antidopaminergic drugs (→ p. 282). Gonadotropin release can be further 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. 300) 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. At age 50, the ovarian function gradually ceases, leading to irregular, partially anovulatory cycles, decline of ovarian estradiol formation (at enhanced gonadotropin release), and eventual discontinuation of menses (menopause).

A. Release of Female Sex Hormones



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 development of the secondary sexual characteristics (e.g., 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.

In the fertile female, estrogens promote the proliferation of the **uterine** mucosa. In the **cervix** and **vagina** they reduce the viscosity of the cervical mucus and accelerate the proliferation and 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 formation 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 formation and mineralization of the **bones** (→ p. 142). In children they promote bone growth and maturation and accelerate epiphyseal fusion.

Progesterone

In the **uterus** progesterone 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**.

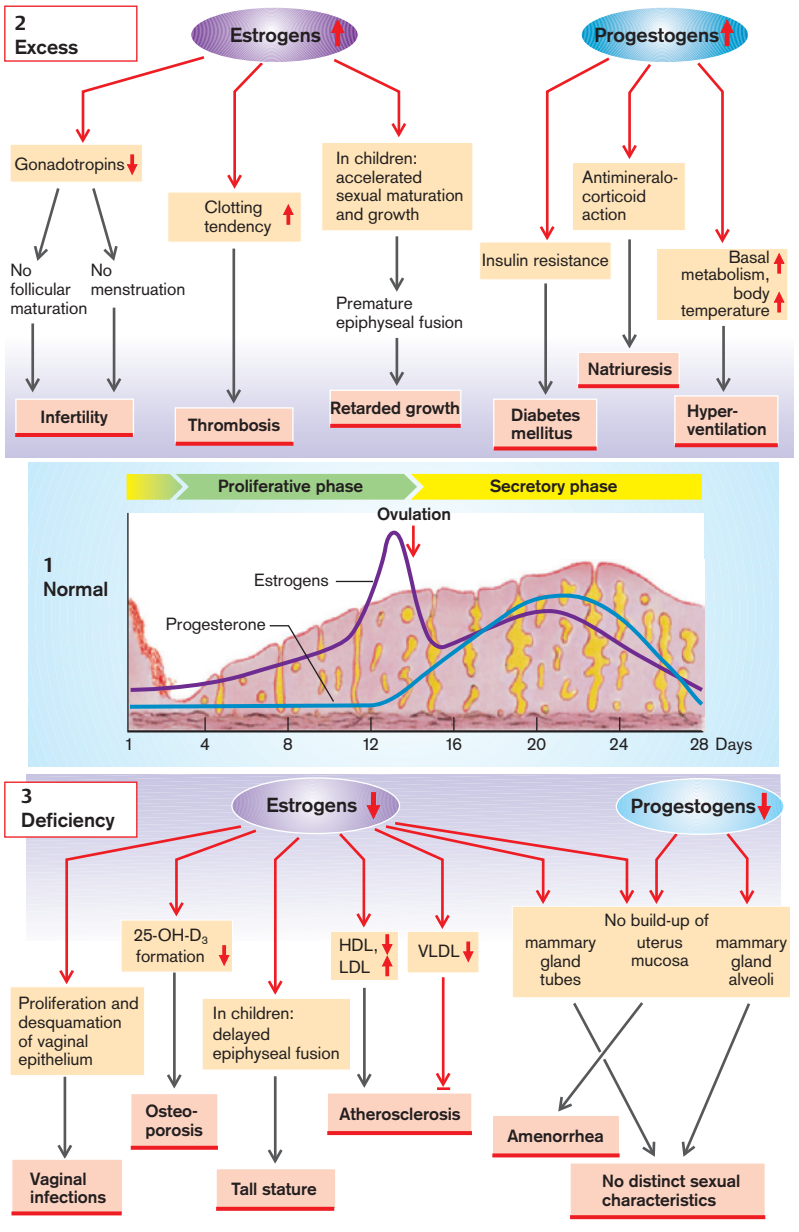
Effects of Excess and Deficiency

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 (e.g., in postmenopause) 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*. The hormonal change in the menopause leads to vasomotor symptoms (e.g., hot flushes), alterations of skin and hair (e.g., wrinkling), as well as emotional changes (e.g., sleeping disorders, anxiety, depression). 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



Intersexuality

The **development of the gonadal anlagen** to ovaries and testes is fixed by the presence or absence of the sex determining region of the Y chromosome (SRY) and is responsible for testicular development (→ **A1**). SRY governs the formation of the transcription factor SOX9 (SRY-related HMG-box 9) and inhibits the expression of DAX1 (dosage sensitive sex-reversal, adrenal hypoplasia congenita on the X chromosome gene 1). SOX9 stimulates, DAX1 inhibits the development of testes. Ovaries develop if SRY 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. 294), 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.

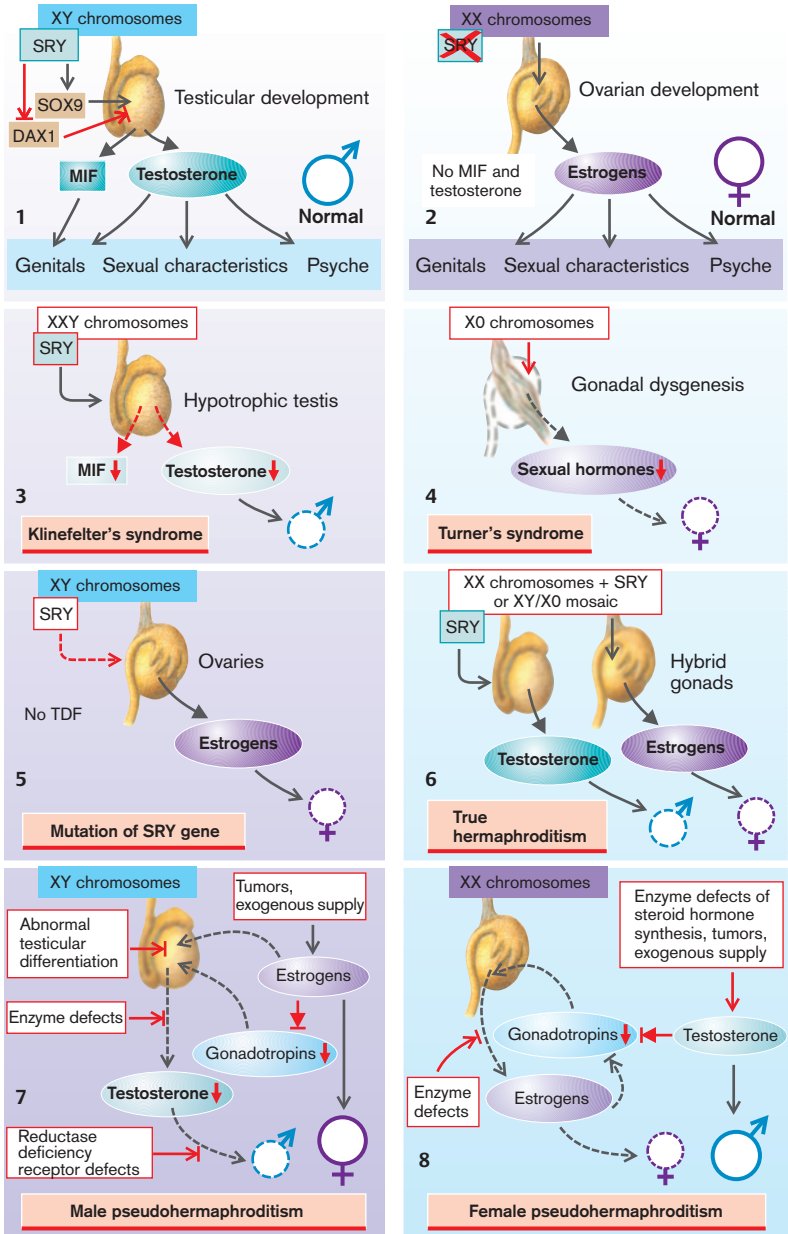
An abnormal chromosome set occurs, for example, in **Klinefelter's syndrome** (**XXY**), in which the testes are formed in such a way that spermatogenesis is possible, but androgen production is impaired (→ **A3**). The androgen deficiency then leads to an inadequately male appearance. Only mild clinical symptoms are present in the XYY syndrome. A translocation of an SRY-containing Y chromosome fragment onto an X chromosome may trigger the development of testes in individuals with XX. 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 testis 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/XX mosaic can be a cause. Translocation of some parts of the Y chromosome, including of the SRY gene, onto an X chromosome 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. 286), defective testes, absent conversion of testosterone into dihydrotestosterone (reductase deficiency), or defective androgen receptors (→ p. 294). 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. 286).

A. Intersexuality



Causes of Hypothyroidism, Hyperthyroidism, and Goiter

The hormones thyroxine (T_4) and triiodothyronine (T_3) 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. Dietary iodine (→ **A1**) is taken up from the blood into the follicular epithelial cells by means of a Na^+, J^- cotransporter$^+$ (→ **A2**), secreted across the apical membrane of the cells into the follicular lumen (→ **A3**) by an anion exchanger (pendrin) and oxidized in the lumen by an oxidase (→ **A4**).

A tyrosine-rich protein (thyroglobulin, TG) is formed in the epithelial cells (→ **A5**) and secreted into the follicular lumen, too. Here the tyrosine residues of the globulin are iodized to the residues of diiodotyrosine (DIT) or of monoiodotyrosine (MIT) (→ **A6**). Two of those residues are subsequently coupled (→ **A7**). The thyroid hormones are stored as thyroglobulin colloid in the follicular lumen. When stimulated by the thyroid-stimulating hormone (TSH; see below), the follicular epithelial cells take up globulin from the lumen and split off thyroxine and to a lesser extent triiodothyronine (→ **A8**). J^- is retrieved from uncoupled DIT or MIT by a halogenase (→ **A9**). In blood T_4 (99.98%) and T_3 (99.7%) are largely bound to plasma proteins (thyroxin-binding protein, transthyretin, albumin). In the periphery one iodine is removed from T_4 by deiodinating enzymes (deiodinase type I [low affinity] and type II [high affinity]) and thus converted into the more active T_3 (→ **A10**). During starvation and severe disease T_4 and T_3 are inactivated by a deiodase type III yielding the inactive reverse T_3 (rT_3). T_3 and T_4 stimulate TRα and TRβ receptors (→ **A11**), which are 10-fold more sensitive to T_3 than to T_4.

Formation and release of T_3 and T_4 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, while glucocorticoids, somatostatin, and dopamine inhibit TSH release.

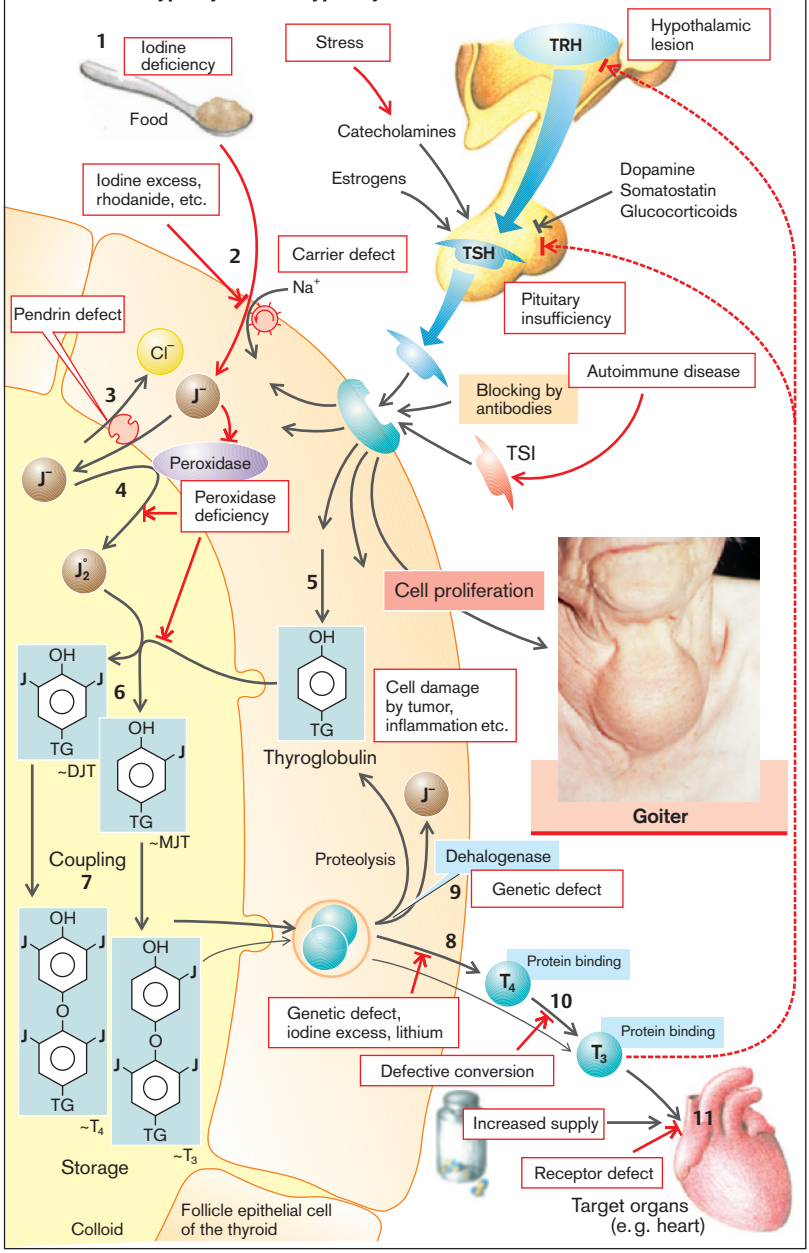
The causes of a **lowered release of thyroid hormone** (**hypothyroidism**) are usually found in the thyroid itself. *Abnormal synthesis or action of thyroid hormones* may result from: 1. Decreased iodine intake in food; 2. Impaired iodine uptake in the thyroid cells (genetically defective carrier or inhibition of transport by perchlorate, nitrate, thiocyanate (rhodanate); 3. Defective pendrin (genetic defect simultaneously leading to deafness [Pendred's syndrome]); 4. Peroxidase deficiency (genetic defect) or peroxidase inhibition by thiouracil or iodine excess (inhibition of H_2O_2 formation by excessive I^-); 5. Abnormal thyroglobulin; 6. Defective iodine incorporation (peroxidase is involved in this, too); 7. Defective coupling of two iodinated tyrosine residues; 8. Inability to release thyroxine and triiodothyronine, from thyroglobulin (genetically determined or lithium); 9. Defective halogenase; 10. Inadequate conversion into the more effective T_3 decreases T_3/T_4 effectiveness even if T_3/T_4 release is normal or even raised; 11. Defective TSH receptor or signaling, (e.g., G-protein Gsα in Albright's syndrome, transcription factors TTF-1, TTF-2, or PAX-8).

However, genetic defects of receptors and enzymes of T_3/T_4 synthesis are rare. Common causes of hypothyroidism are iodine deficiency, *inflammatory damage* to the thyroid gland (e.g., autoimmune Hashimoto thyroiditis), radiation, or *surgical removal* of the gland (due to thyroid cancer). Less common is hypothyroidism due to a deficiency of TSH (e.g., in pituitary insufficiency) or of TRH (e.g., in damage to the hypothalamus). In rare cases the TSH receptor may be blocked by antibodies.

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**). Effects include stimulation of hormonal release and thyroid enlargement. TSH release is suppressed by a high T_3/T_4 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 (goiter) 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 Goiter



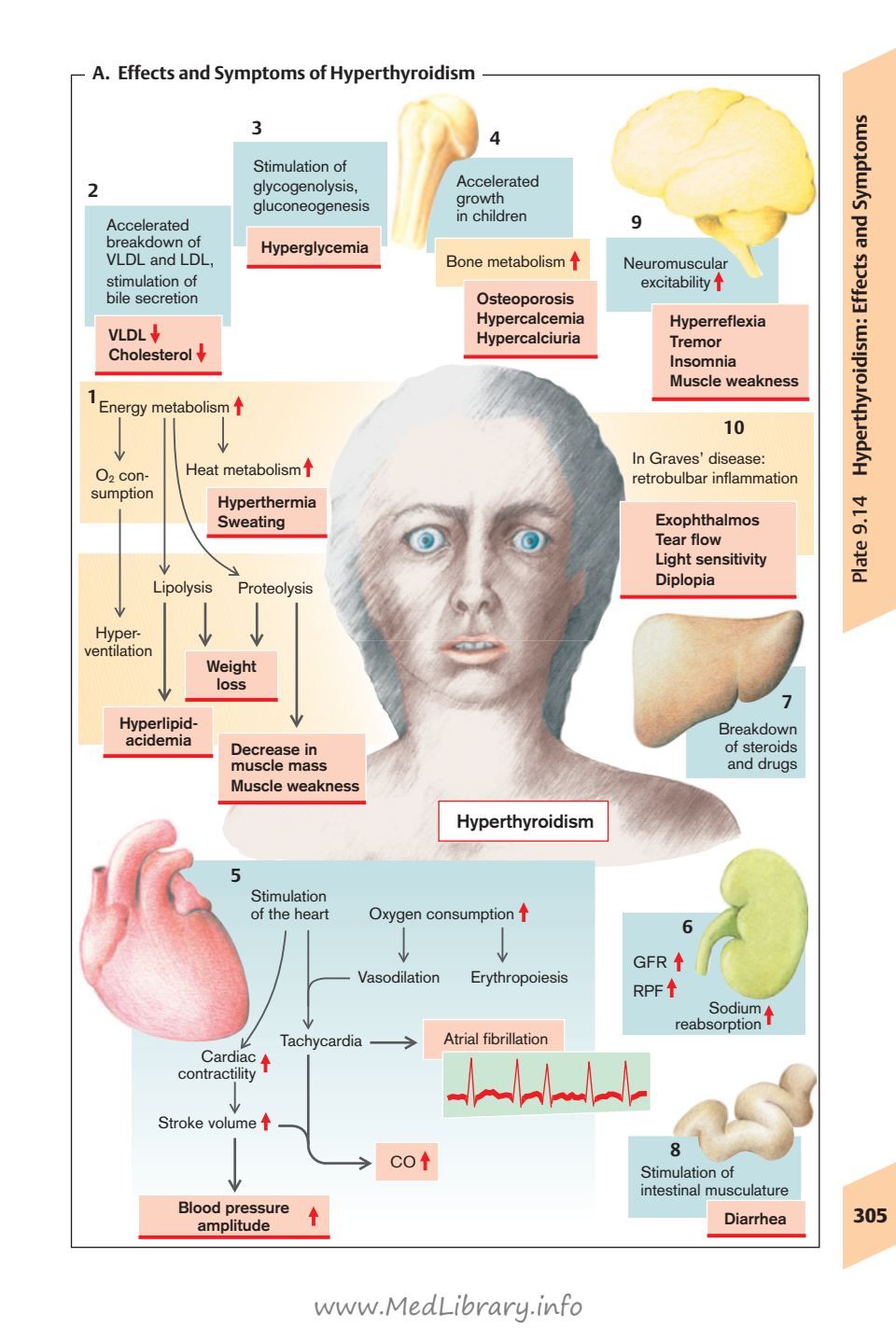
Effects and Symptoms of Hyperthyroidism

In many tissues the **thyroid hormones** (T_3, T_4) 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 glycogenolysis 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 O_2 affinity and thus favors the peripheral release of O_2. 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. T_3 and T_4 stimulate the restructuring of bone and muscle, the catabolic effect predominating and increase neuromuscular excitability. T_3 and T_4 act mainly through enhanced gene expression, which takes several days. Beyond this their prolonged action is due to the long half-life in blood (T_3 = one day; T_4 = seven days). Maternal T_3 and T_4 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 O_2 demand requires hyperventilation and stimulates erythropoiesis. The raised lipolysis leads to **weight loss**, on the one hand, and to **hyperlipidacidemia**, 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 (→ **A1**). 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 (→ **A7**). Stimulation of the intestinal musculature (→ **A8**) leads to **diarrhea** and steatorrhea; the increase in neuromuscular excitability to **hyperreflexia, tremor, muscular weakness,** and **insomnia** (→ **A9**). In females, amenorrhea may occur. In children, **growth may** be accelerated (→ **A4**). T_3 and T_4 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. 302) **exophthalmos** may be added to the increased effects of thyroid hormones (→ **A10**); 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 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 swelling is found in the skin (dermatopathy particularly in the pretibial region).

A. Effects and Symptoms of Hyperthyroidism



Effects and Symptoms of Hypothyroidism

For a description of the functions of the thyroid hormones, see p. 304. 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 **moderate weight gain** 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 the water-binding 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**). Carpal tunnel syndrome may occur. Typically, the eyelids are swollen. Swelling of the vocal cords leads to hoarseness; swelling of the tongue affects articulation. In addition, fibronectin, collagen, and plasma albumin are deposited in the skin. Reduced transformation of carotene into vitamin A causes **hyperkeratosis**. The skin may appear yellowish due to carotin deposition. The patients may suffer from hair loss. Also, because of reduced sweat and sebaceous secretion, the skin is dry and the reduced heat production makes it feel cold.

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, hearing loss, 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.

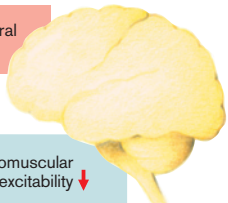
A T_3/T_4 deficiency disinhibits the formation of TRH and TSH (→ p. 302). TSH not only stimulates the formation of TSH, but also of prolactin, and can thus trigger **hyperprolactinemia** (→ p. 282) with subsequent galactorrhea, inhibition of gonadotropin release, and reduced fertility. TSH also promotes the growth of the thyroid gland, causing **goiter** (→ p. 302). Lastly, abnormal release of **gonadotropins** can impair fertility.

A. Effects and Symptoms of Hypothyroidism

Depostion of glycosamineglycans (mucin)

Filtration of albumin
Na^+ retention ↓
↓
Edema

Impaired cerebral development



7

Neuromuscular excitability ↓

Sensory disturbances

Hearing loss
Hyporeflexia
Lack of drive
Depression
Clouded consciousness
Coma

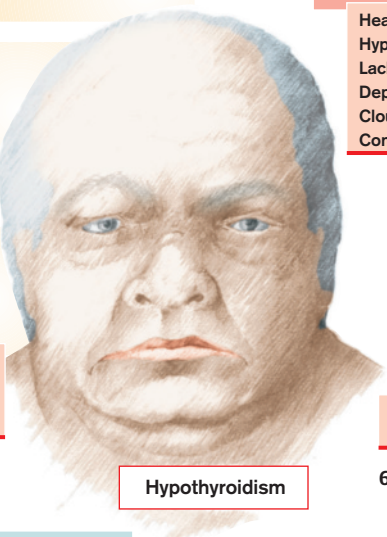
4

Effusions
hoarse voice
speech difficulties
puffed-up face
carpal tunnel syndrome

Myxedema

Vitamin A ↓
Sebaceous and sweat gland activity ↓
Hair loss

Dry, scaly skin



1

Energy metabolism ↓
↓
Heat metabolism ↓

Sensitivity to cold
Appetite ↓
Erythropoiesis ↓

Renal blood flow ↓
Glomerular filtration ↓
Transport ↓

Salt and water retention

Hypothyroidism

Delayed breakdown of VLDL
Reduced bile secretion

VLDL ↑
Cholesterol ↑

↓

Atherosclerosis

2

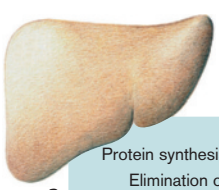
Reduced lipolysis

Overweight

6

Intestinal motility ↓

Obstipation
Reflux esophagitis



3

Protein synthesis ↓
Elimination of drugs ↓
Glycogenolysis ↓
Gluconeogenesis ↓

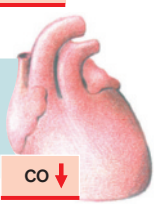
Hypoglycemia

8

In children:
retarded longitudinal growth and delayed epiphyseal fusion
somatotropin release ↓

Small stature
Cretinism

5



Cardiac contractility ↓
Bradycardia

CO ↓

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 (→ p. 310). The disease was given its name because of the glucosuria. 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** (previously called juvenile diabetes; → **A**) there is an *absolute lack* of insulin. The condition is caused by a lesion in the beta cells of the pancreas, as a rule produced by an autoimmune reaction (type IA) of T-lymphocytes against beta cell antigens. The beta cells, however, remain unrecognized as long as they do not express MHC. The autoimmune reaction is frequently triggered by a viral infection, which leads to activation of Toll-like receptors with subsequent release of interferon α (IFN-α). IFN-α stimulates the expression of MHC molecules in the beta cells and thus renders the cells visible for the T-lymphocytes. Autoantibodies against islet tissue (islet cell antibodies [ICA]) and insulin (insulin autoantibodies [IAA]) can be detected in some cases 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*. In some patients no evidence is found for autoimmune disease (type IB).

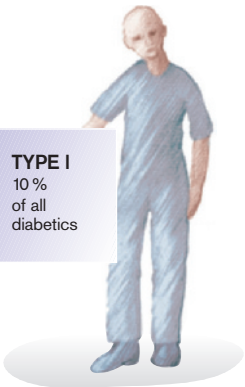
Type II (formerly called maturity-onset diabetes; → **B**) is by far the most common form of diabetes. In type II genetic disposition is even more important than in type I diabetes. However, there is a *relative insulin deficiency*. Insulin release can be normal or even increased, but the target organs have a diminished sensitivity to insulin. For instance, the PKB/Akt (→ p. 10) mediated stimulation of the glucose carrier GLUT4 in skeletal muscle or adipocytes may be impaired, thus compromising cellular glucose uptake. Moreover, excessive hepatic glucose production may contribute to hyperglycemia.

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 been abnormal prior to overt disease. Several genes have been defined that promote the development to obesity and type II diabetes such as gene variants of glucokinase, insulin or elements of cellular signal transduction (e.g., IRS [insulin receptor substrate], PPARγ [receptor], SGK1 [kinase], KCNQ1 [K^+ channel]). They may not only predispose to diabetes but also to obesity, dyslipidemia, hypertension, and arteriosclerosis ("metabolic syndrome" (→ p. 256). Type II diabetes may already occur at a young age (maturity-onset diabetes of the young [MODY]), as in patients with genetic defects of glucokinase or of hepatocyte nuclear transcription factor (HNF).

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* (**pancreas-deprived diabetes**; → **C**), or by toxic damage to beta cells. The development of diabetes mellitus is promoted by an *increased release of antagonistic hormones*, such as somatotropin (in acromegaly), ACTH, glucocorticoids (in Cushing's disease or stress [so-called **steroid diabetes**]), epinephrine (in stress), progestogens and choriomammotropin (in pregnancy), thyroid hormones and glucagon. In most patients with newly discovered diabetes during pregnancy the hyperglycemia disappears following birth. However, half of those patients develop diabetes later in life. *Severe infections* increase the release of several of the above hormones and thus the manifestation of diabetes mellitus (→ **C**). A somatostatinoma can cause diabetes by inhibition of insulin release.

A. Diabetes Mellitus: Type I



TYPE I
10 %
of all
diabetics

Viral infection → Autoimmune disease

Genetic disposition

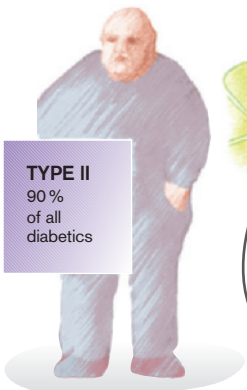
Destruction of beta cells

Beta cells (pancreas)

Absolute insulin deficiency

Lipolysis ↑ **Hyperglycemia** Protein breakdown ↑

B. Diabetes Mellitus: Type II



TYPE II
90 %
of all
diabetics

Familial disposition → Substrate uptake / Substrate consumption ↑

Lipolysis ↓

Fatty acids ↑

Obesity

Ketone bodies ↑

Insulin

Target cell

Insulin insensitivity

Relative insulin deficiency

esp. **Hyperglycemia**

C. Other Causes of Diabetes Mellitus

Abnormal insulin release
Removal of pancreas
Pancreatic disease

Insulin

Unresponsive receptor

Postreceptor defect

Target cell

Antibodies

Severe infections

Antagonistic hormones (e.g. in pregnancy)

Hyperglycemia

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 other cell types) insulin stimulates protein synthesis and inhibits protein breakdown; in the liver and muscles it promotes glycogen synthesis, inhibits glycogen 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 antiproteolysis) and intracellular alkalosis (stimulation of glycolysis, increased cardiac contractility). Insulin achieves these effects by activating the Na^+/H^+ exchanger (cell swelling and alkalinization), the Na^+-K^+-2 Cl^- cotransporter (cell swelling), and the Na^+/K^+-ATPase. This results in K^+ uptake by the cell and hypokalemia. The cell swelling is attenuated by activation of cell volume regulatory K^+ channels (KCNQ1). 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 paracrinally inhibits the release of glucagon and thus diminishes its stimulating action on glycogenolysis, gluconeogenesis, lipolysis, and ketogenesis.

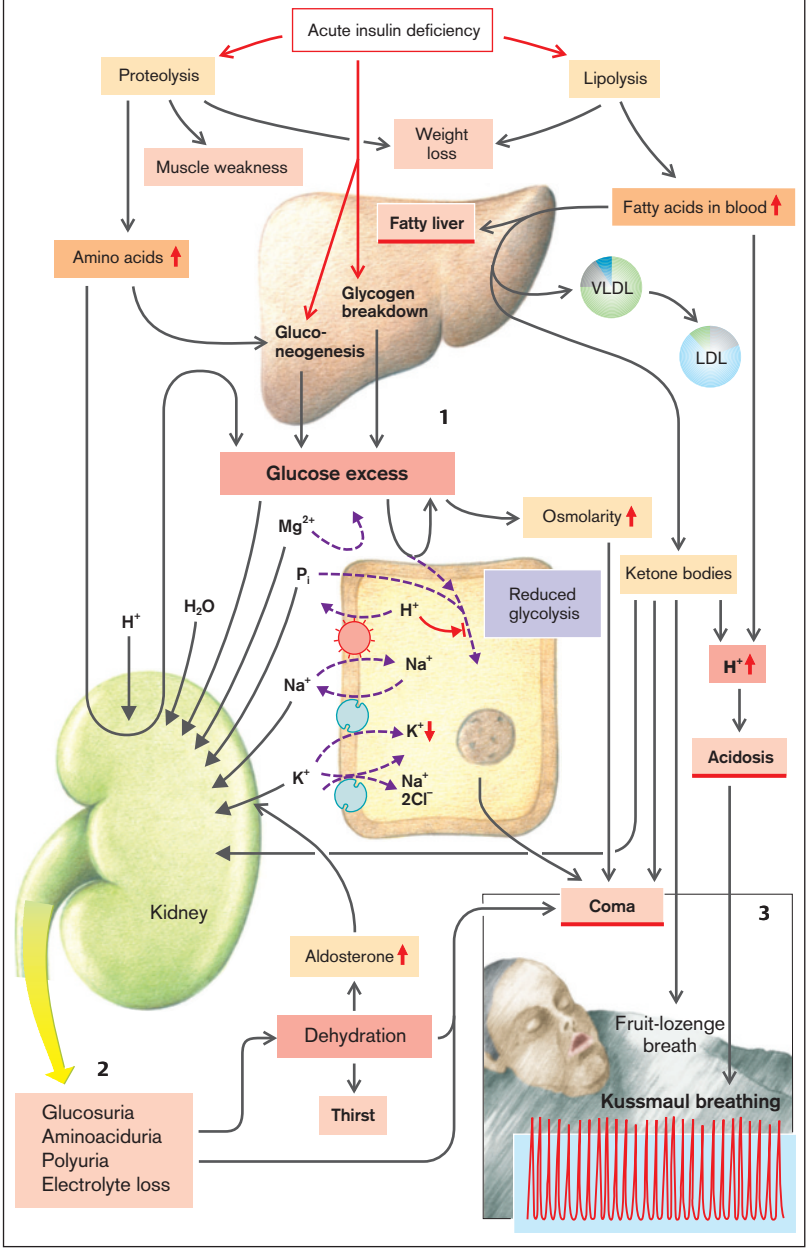
In **acute insulin deficiency** the absence of its effect on glucose metabolism results in **hyperglycemia** (→ **A 1**). The extracellular accumulation of glucose leads to **hyperosmolarity.** The transport maximum of glucose is exceeded in the kidney so that glucose is excreted in the urine (→ **A 2**). 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 frequently no hypokalemia because the cells release up K^+ as a result of reduced activity of Na^+-K^+-2 Cl^- 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. 134). 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 (**hyperlipidacidemia**). In the liver, the fatty acids are utilized for the production of acetoacetic acid and β-hydroxybutyric acid, a process stimulated by glucagon. Accumulation of these acids leads to acidosis, which forces the patient to breathe deeply (**Kussmaul breathing**; → **A 3**). 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. The hypertriglyceridemia favors the development of pancreatitis. 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** or type II diabetes are *hyperglycemia* and *hyperosmolarity*, while ketoacidosis is observed primarily (but not exclusively) in **absolute insulin deficiency** or type I diabetes.

A. Acute Effects of Diabetes Mellitus



Late Complications of Prolonged Hyperglycemia (Diabetes Mellitus)

The metabolic abnormalities of inadequately treated relative or absolute insulin deficiency (→ p. 308) 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 aldosereductase. This hexahydric alcohol cannot pass across the cell membrane, as a result of which its cellular concentration increases and the cell swells (→ **A1**). Accumulation of sorbitol in the lens of the eye osmotically attracts water with lenticular swelling and loss of transparency (clouding of the lens [**cataract**]; → **A2**). Hyperglycemia further damages the Schwann cells and neurons and thus impedes nerve conduction (**polyneuropathy**), affecting mainly the autonomic nervous system, reflexes, and sensory functions (→ **A3**).

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. 308).

Hyperglycemia promotes the formation of sugar-containing plasma proteins such as fibrinogen, haptoglobin, α_2-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. Hyperglycemia fosters the formation of diacylglycerol (DAG) and stimulates the release of PAI-1 (plasminogen activator inhibitor 1), TGF-β, and further growth factors (e.g., PDGF, EGF). DAG and particularly TGF-β foster the expression of extracellular matrix proteins such as collagen, which may in turn be modified by glycation. The deposition of collagen fibers contributes to the development of **glomerulosclerosis** (Kimmelstiel–Wilson) leading to proteinuria, loss of nephrons (decline of GFR), hypertension, and renal insufficiency (→ **A7**). The high plasma amino acid concentrations lead to hyperfiltration in the residual intact glomeruli, which are thus similarly damaged. The hyperglycemia leads to thickening of the basement membrane with decreased permeability and narrowing of the lumen (**microangiopathy**; → **A8**). The tissue hypoxia stimulates the formation of VEGF (vascular endothelial growth factor) with subsequent angiogenesis. The microangiopathy in the retina may ultimately lead to blindness (**retinopathy**; → **A9**).

Together with a rise of VLDL in blood (→ p. 310) 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 (HbA) to form **HbA_{1c}**, whose increased concentration in blood points to a hyperglycemia that has been present for some time. HbA_{1c} 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

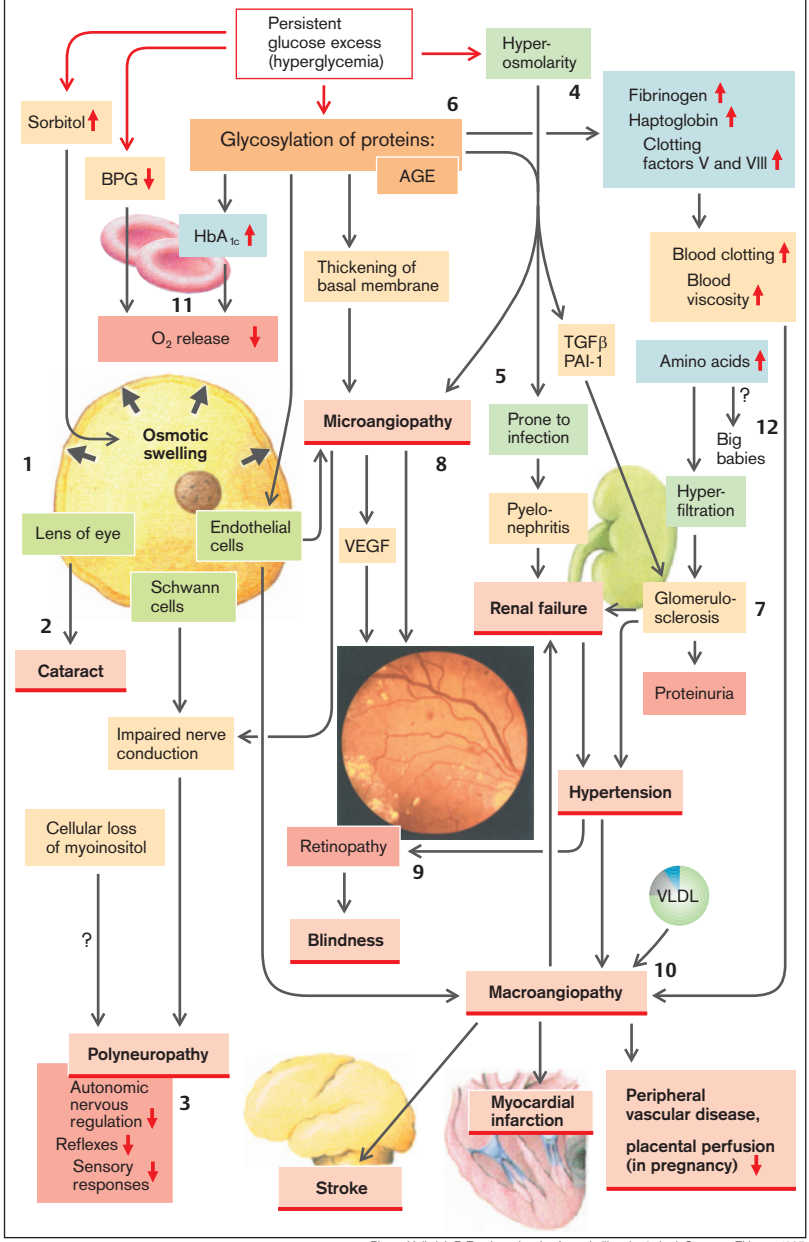


Photo: Hollwich F. Taschenatlas der Augenheilkunde. 3rd ed. Stuttgart: Thieme; 1987

Hyperinsulinism, Hypoglycemia

Insulin release is, first and foremost, regulated by glucose (→ **A1**). Glucose is taken up by the beta cells of the pancreas via the carrier GLUT2. The subsequent glucose metabolism yields ATP, which inhibits the ATP-sensitive K^+ channels. Subsequent depolarization opens voltage-dependent Ca^{2+} channels so that Ca^{2+} enters the cell. The rise in intracellular Ca^{2+} concentration then triggers insulin release. The sulfonylureas used as oral antidiabetic drugs stimulate the release of insulin by binding to the SUR subunit and subsequent inhibition of the ATP-sensitive K^+ channels.

Insulin release is stimulated not only by glucose but also by amino acids (→ **A3**), somatotropin (growth hormone) and several gastrointestinal hormones (glucagon, secretin, gastrin, glucose-dependent insulin-releasing peptide [GIP], cholecystokinin [CCK]). 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** (→ **A4**) or of **an oral antidiabetic drug** (sulfonyl ureas, → **A2**) during treatment of diabetes mellitus. As a rule overdosage becomes manifest when insulin requirement falls on physical activity. Insulin excess also often occurs in **newborn babies of diabetic mothers** (→ **A5**). The high glucose and amino acid concentrations in the mother's blood will lead intrauterinely 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 concentrations of amino acids in blood are markedly raised (e.g., in hyperleucinemia). The insulin release stimulated by the amino acids is then too high for the particular glucose concentration and hypoglycemia results. In **liver failure** the reduced breakdown of amino acids can cause hypoglycemia (→ **A3**). **Abnormalities of carbohydrate metabolism** (→ p. 262), such as some glycogen storage diseases, fructose intolerance or galactosemia, can also bring about hypoglycemia.

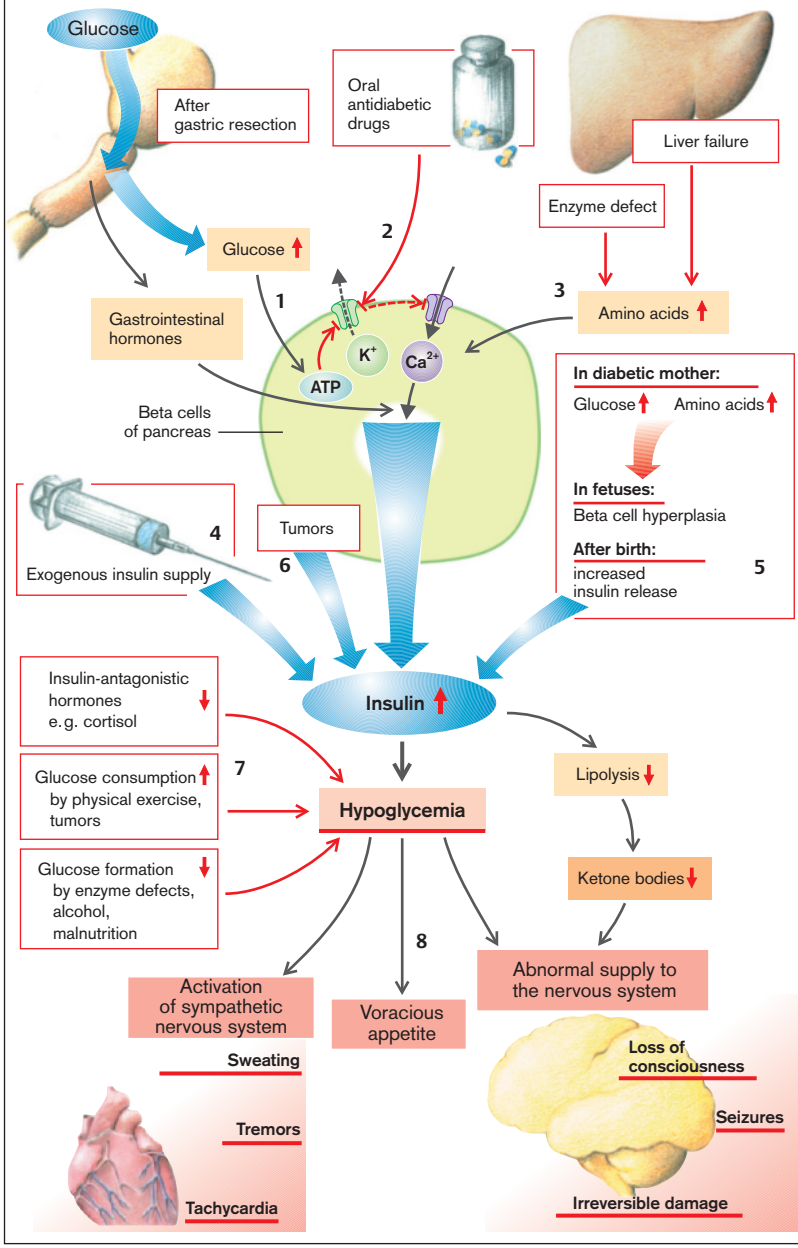
In the **dumping syndrome** after a gastric resection, sugar taken orally reaches the gut without delay, abruptly stimulates the release of gastrointestinal hormones, and is quickly absorbed. The gastrointestinal hormones and the steeply rising glucose concentration lead to an excessive release of insulin, so that hypoglycemia occurs after an interval of one to two hours (→ p. 160).

In rare cases an excess of insulin is caused by an **insulin-producing tumor** (→ **A6**).

Relative insulin excess can also occur with normal insulin release if the release and/or the action of the **insulin-antagonistic hormones** (glucocorticoids, epinephrine, glucagon, somatotropin) is impaired. This is especially so if the glucose reserves are low and gluconeogenesis from amino acids is limited, as in liver failure, renal insufficiency, after starvation or alcoholism, but also on increased glucose utilization, as during heavy work, sepsis, or in tumors (→ **A7**).

The most important **effect** of absolute or relative insulin excess is **hypoglycemia**, which causes a voracious appetite and leads to massive sympathetic nervous stimulation with tachycardia, sweating, and tremors (→ **A8**). The impaired energy supply of the nervous system, which requires glucose, can result in seizures and loss of consciousness. Ultimately, the brain may be irreversibly damaged. Repeated periods of hyperglycemia blunt the reaction of the autonomic nerve system leading to delayed response and more profound hypoglycemia (hypoglycemia unawareness).

A. Hyperinsulinism



Histamine, Bradykinin, and Serotonin

Histamine (→ **A 1**) is formed by the tissue mast cells and basophils. Its **release** is stimulated by *antigen–antibody* (*IgE*) *complexes* (type 1 allergy; → p. 52, 56), *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 (H_2 receptor) 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_2 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 (→ p. 156 ff.). Histamine is largely responsible for the symptoms of type 1 allergy, such as a fall in blood pressure, skin edema (urticaria), rhinitis, and conjunctivitis.

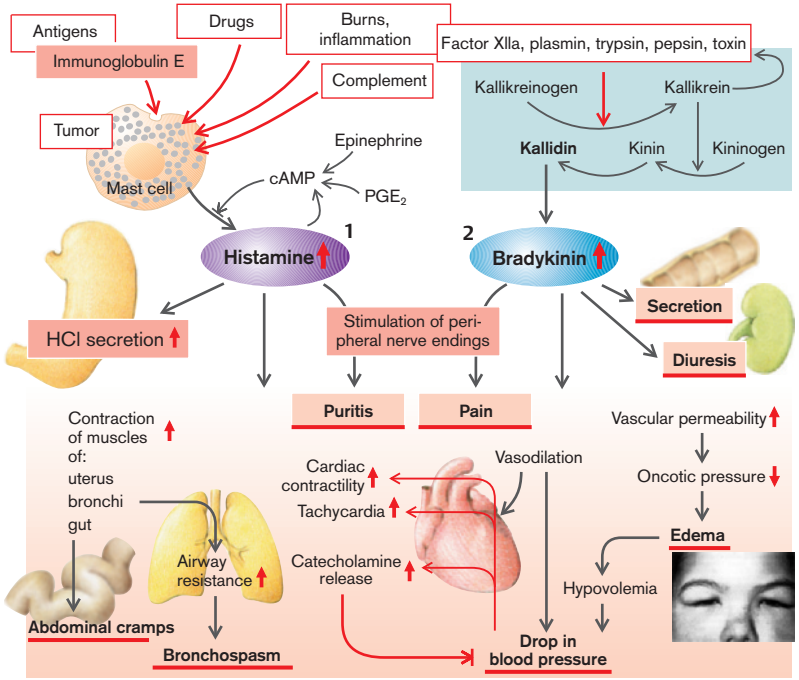
Bradykinin. The enzyme **kallikrein** is required for bradykinin synthesis (→ **A 2**). It is formed from kallikreinogen in *inflammations, burns, tissue damage* (especially pancreatitis; → p. 172), and on activation of *blood coagulation* (factor XIIa) as well as under the influence of peptidases and some toxins. Kallikrein promotes its own activation via stimulation of factor XIIa (→ p. 64). 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.

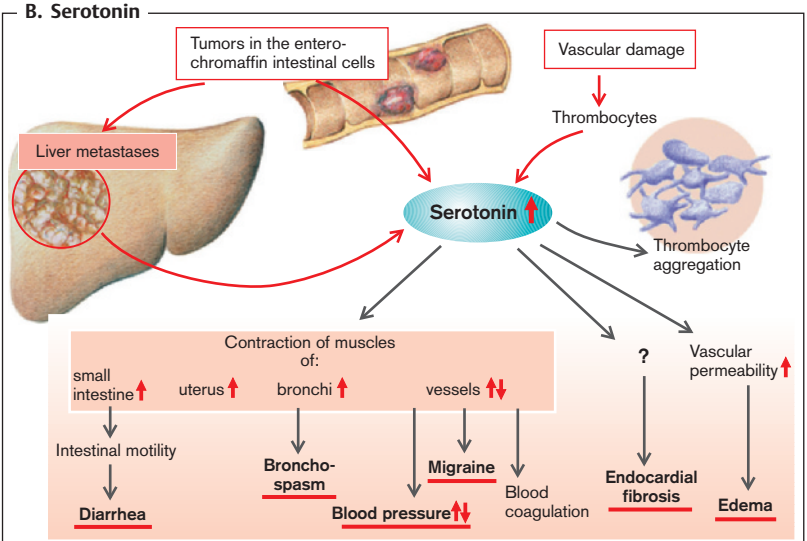
Serotonin. In addition to being stored in the central nervous system (→ p. 372), serotonin (→ **B**) is formed in the enterochromaffin cells of the gut, in thrombocytes, proximal tubular cells, and the bronchi. Its **release** is increased especially in *tumors* of the enterochromaffin cells (carcinoid).

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. Serotonin further contributes to the liver injury in viral hepatitis. 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



B. Serotonin



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* A_2 (→ **A1**). This enzyme is activated by cell swelling and by an increase of intracellular Ca^{2+} concentration. It is stimulated by a number of mediators, such as histamine, serotonin, bradykinin, and norepinephrine (via α-receptors). Phospholipase A_2 is inhibited by glucocorticoids (via lipocortin) and epinephrine (via β-receptors).

Arachidonic acid can be transformed by **lipoxygenase** to leukotrienes and by **cyclo-oxygenase** (COX) to prostaglandin G [PGG_2]. PGG_2 (via *PGH*$_2$) may be converted to thromboxan A_2 (TXA_2) and the prostaglandins $F_{2\alpha}$ ($PGF_{2\alpha}$), E_2 (PGE_2), and I_2 (PGI_2) (→ **A3**). There are two cyclo-oxygenase isoforms (COX1 and COX2). Both are inhibited by non-steroidal anti-inflammatory drugs (NSAIDs) (e.g., acetylsalicylic acid). COX2 may further be inhibited specifically. Inflammations and tissue damage cause activation of both cyclo-oxygenase and lipoxygenase, and thus increase the formation of eicosanoids.

The **leukotrienes** (→ **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.

TXA_2 is formed largely in thrombocytes and is essential for blood clotting. An excess of TXA_2 favors the formation of **thrombi**. Administration of small doses of acetylsalicylic acid can thus reduce the risk of myocardial infarction because of its effect of reducing thrombocyte aggregation.

$PGF_{2\alpha}$ stimulates the release of a series of hormones and the *contraction of the smooth muscles* of blood vessels, gut, bronchi, and uterus.

PGE_2 inhibits the release of hormones and lipolysis and stimulates the contraction of smooth muscles in 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. PGE_2 increases the *glomerular filtration rate*. It raises vascular permeability and thus promotes the development of **edemas**.

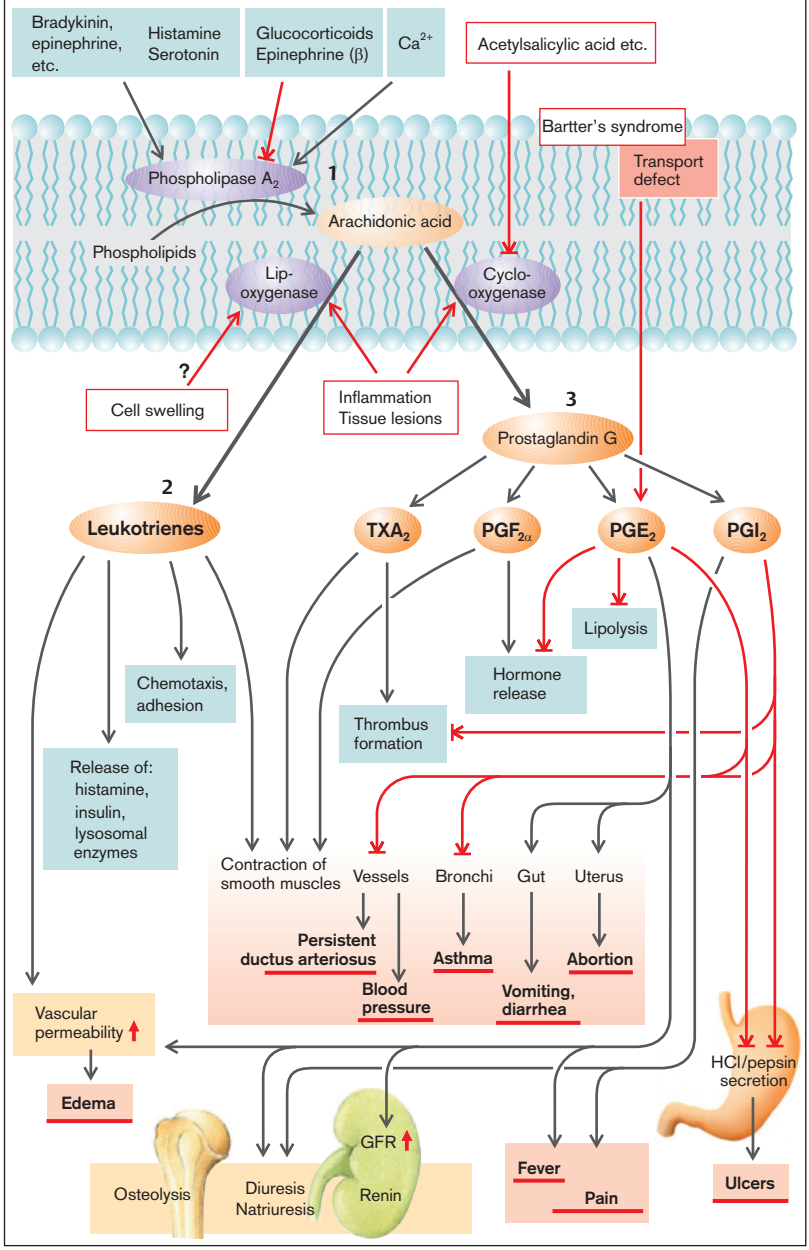
PGE_2 and **PGI_2** aid in the demineralization of the bones (**osteolysis**). They stimulate the renal formation of renin and, by inhibiting the tubular reabsorption of Na^+ and water, they produce natriuresis and diuresis. They raise the target level of temperature regulation (**fever**) and cause **pain**. The effects of the prostaglandins contribute to a large extent to the **symptoms of infection**.

PGE_2 has an essential, protective role in the stomach by inhibiting the secretion of HCl and pepsin while promoting the secretion of HCO_3^- and mucus, which has a protective effect. It also causes **vascular dilation**. A reduction in PGE_2 formation by cyclo-oxygenase inhibitors favors the development of **gastric ulcers**.

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.

PGE_2 is also of great importance in **Bartter's syndrome**, which is due to mutations of the Na^+-K^+-2 Cl^- cotransporter, the luminal K^+ channels, or the basolateral Cl^- channels (→ p. 106) in the loop of Henle. An excessive local formation of PGE_2 is the consequence of the resulting transport defect. The inhibitory action of 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 life-threatening renal salt loss of the affected children may thus be blunted by cyclo-oxygenase inhibitors.

A. Eicosanoids



Overview

The nervous system with its approx. $2 \cdot 10^{10}$ neurons 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 thereby 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 adequate 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.), as well as electrolyte abnormalities. Other possible causes include drugs, toxins (e.g., heavy metals, alcohol), radiation, inflammation, and infection (parasites, bacteria, viruses, prions, autoimmune diseases).

The functions of the effectors in the periphery (sensory receptors, muscles, and organs innervated by the autonomic nervous system; → **A1**), peripheral nerve conduction (→ **A2**), spinal cord function (→ **A3**), and/or the supraspinal nervous system (→ **A4**) can be impaired as a **consequence** of nervous system disorders.

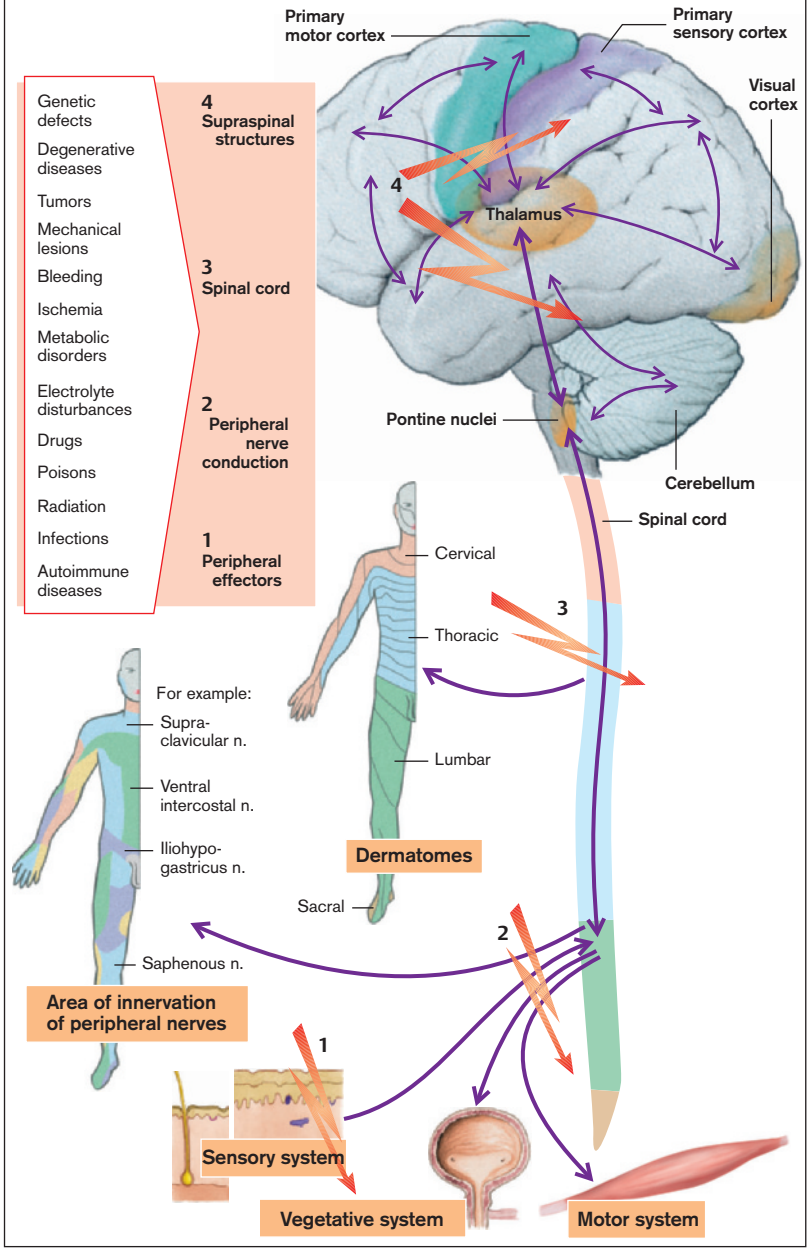
Damage to the peripheral effectors (→ **A1**) leads to disturbance of the particular function, which may be localized (e.g., individual muscles) or generalized (e.g., the entire musculature). Such damage can result in overactivity (e.g., involuntary muscle cramps or inadequate activity of sensory receptors 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** (→ **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 (→ **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 (→ **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 and motor cortical areas, which, however, comprise only some 10% of the cortex). 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)



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 Ca^{2+} channels. Ca^{2+} 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.

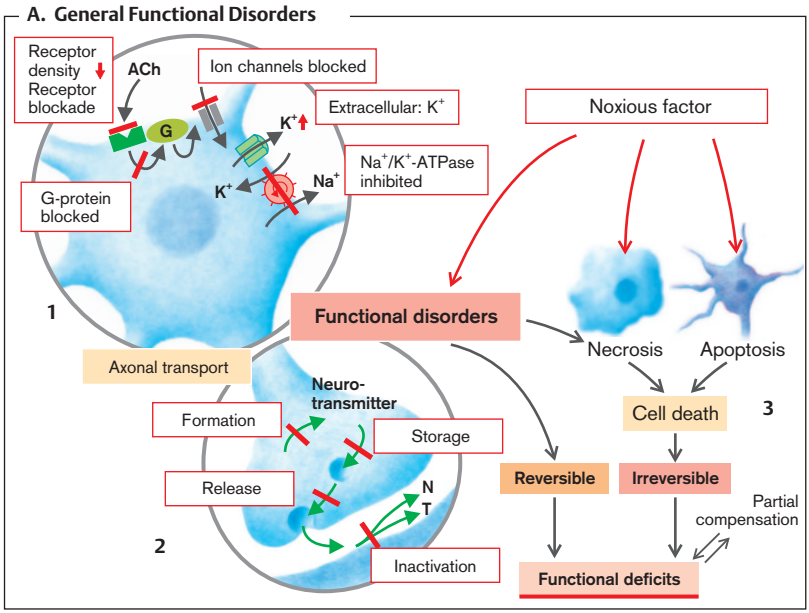
Abnormalities can interfere with each element of this cascade (→ **A**). For example, receptor density can be reduced by down-regulation. Also, certain mechanisms of intracellular transmission can be blocked. An example is the blocking of G proteins by, among others, pertussis toxin (→ **A 1**). Ionic channels can be blocked by drugs, or their activity changed by Ca^{2+}, Mg^{2+}, 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 (→ **A 2**) can be impaired, for example, by genetic defects or drugs. **Functional abnormalities** can be reversible once the damage is no longer effective.

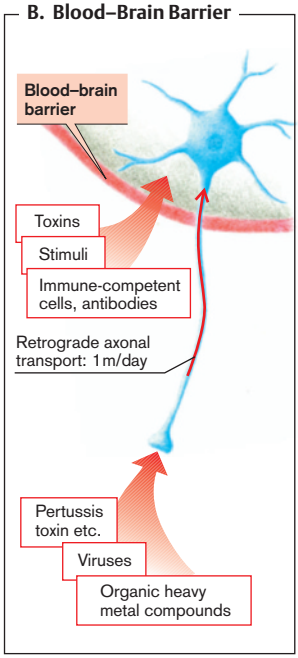
Lesions may also lead to **irreversible destruction of neurons**. Thereby neurons could die by direct damage (necrosis, e.g., due to energy deficiency or mechanical destruction), or by apoptosis (→ **A 3** and p. 14). Apoptosis plays a major role in neurodegenerative disease (e.g., Alzheimer's disease, Huntington chorea, amyotrophic lateral sclerosis, infantile spinal muscle dystrophy), and contributes to cell death during ischemia. Neuronal apoptosis is fostered by a wide variety of disorders including lack of NO synthase (NOS), of poly-ADP-ribose polymerase (PARP), or of superoxide dismutases (SOD). In the adult brain, the replacement of dead neurons is hardly possible (in the hippocampus and olfactory bulb). Neuronal death thus leads to mostly irreversible loss of function even if other neurons can partly take over the function of the dead cell.

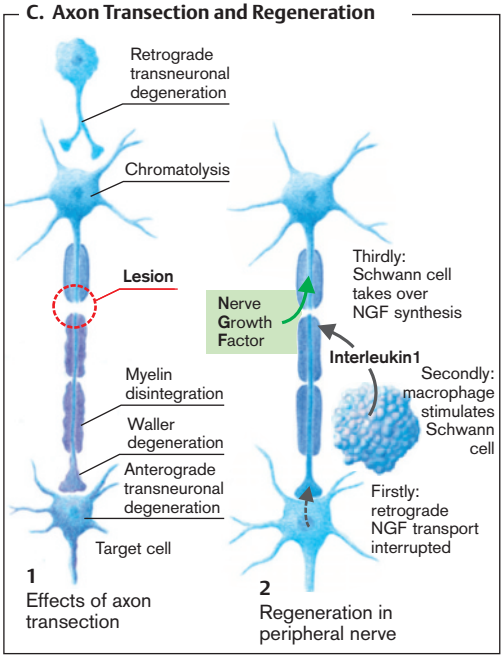
Deleterious substances must pass the **blood–brain barrier** if they are to reach the neurons of the central nervous system (CNS) (→ **B**). An intact blood–brain barrier impedes the passage of most substances and prevents pathogens and immunocompetent cells entering (→ p. 378). However, some toxins (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. 378). 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. The axonal regeneration is inhibited by extracellular macromolecules, such as chondroitin sulfate, oligodendrocytic myelin glycoprotein (OMGP), myelin-associated protein (MAG), and Nogo. 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 (→ **C 2**). 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 (→ **C 1**), 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**).







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 saltatory 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 increases the membrane resistance (R_m) and decreases the capacity (C_m) of the membrane (→ **A**, left).

The **resistance** of the internodal axonal membrane is very high because of the low density of ionic channels. Furthermore, the perimembranous space is insulated by a layer of fat from the free extracellular space. The low internodal **capacitance** 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.

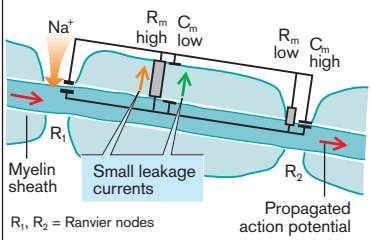
Demyelination (→ **A**, right) can be caused by degenerative, toxic, or inflammatory damage, or by a deficiency of vitamins B_6 or B_{12}. If this happens, R_m will be reduced and C_m raised in the internodal segment. As a result, more current will be required to change the polarity of the internodal segment (green arrow) and, through opening up the ionic channels, large losses of current may occur (orange arrow).

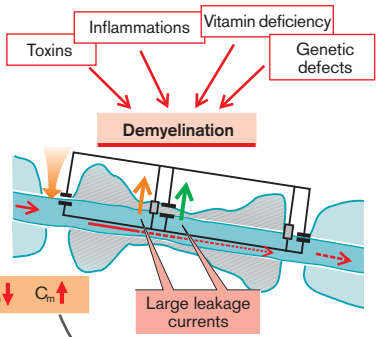
If, after the losses in the internodal segment, the current generated at R_1 is not adequate to depolarize R_2 to the threshold level, excitation is interrupted, even though the axon is completely intact. High frequency of action potentials and low temperature favor interruption of conduction because of decreasing sensitivity of the node R_2 (→ **A 1**). 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 following nodes (→ **A 2**). 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 been damaged or is under mechanical pressure (→ **A 3**); excitation can jump across two neighboring damaged nerve fibers (ephaptic transmission; → **A 4**), or conduction may run retrogradely (→ **A 5**).

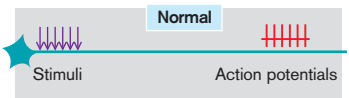
Genetic defects affecting myelin-sheath proteins (e.g., myelin protein zero [P_0, MPZ], peripheral myelin protein 22 [PMP 22]), regulators of myelin synthesis (EGR2), myelin degradation (SIMPLE), or gap junctions in the Schwann cells (connexin 32) lead to hereditary peripheral neuropathies (**Charcot–Marie–Tooth syndrome**, Déjérine–Sottas syndrome, congenital hypomyelinization, hereditary neuropathy with pressure palsy).

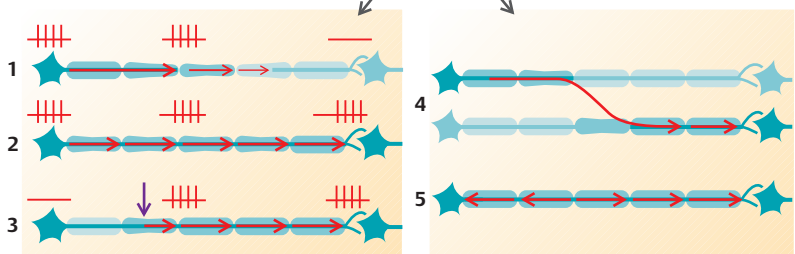
The most important demyelinating disease is **multiple sclerosis** (→ **B**). It is more common in women than men, familial aggregation sometimes occurs, and it has a higher incidence among carriers of certain gene variants (e.g., MHC [HLA = human leukocyte antigen], interleukin 2 receptor, interleukin 7 receptor). It is an **autoimmune disease** that may be triggered by a viral infection and is characterized by demyelinating inflammatory foci (→ **B 1**). In many patients autoreactive T-lymphocytes are directed against myelin basic protein and antibodies against myelin oligodendrocytic glycoprotein. 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 or completely regress when the local inflammatory process has subsided and the nerves (in the case of intact axons) have been remyelinated. The example in **B 2** illustrates that at first there is a fully reversible loss of vision due to a damaged optic nerve (→ p. 348), followed by a partly reversible sensory loss when the sensory tracts of the spinal cord are affected (→ p. 340). Finally, ataxia sets in when the cerebellum becomes involved (→ p. 338).

A. Development and Effects of Demyelination

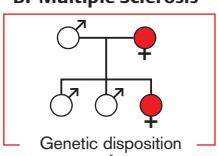








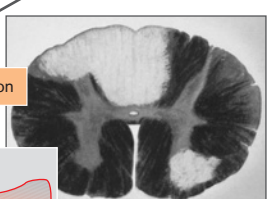
B. Multiple Sclerosis



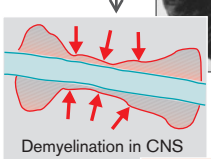
Autoimmune disease, possibly caused by viruses ?

MHC
IL-2 rec.
IL-7 rec.

Inflammation



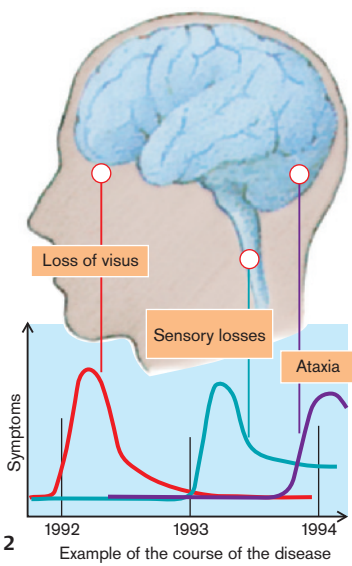
Demyelinating foci in spinal cord (after Netter)



Multiple sclerosis

periodically recurrent neuronal losses

1



2 Example of the course of the disease

Disorders of Neuromuscular Transmission

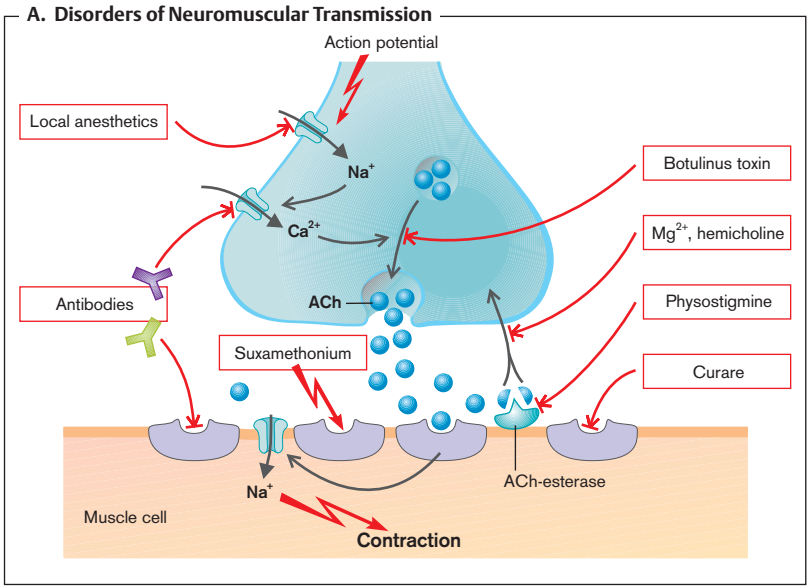
Neuromuscular transmission is a sequence of events (→ **A**) that can be interrupted at various levels. The action potential is carried along by activation of the *Na^+ channels* to the nerve ending, where it depolarizes the cell membrane and thus opens the voltage-gated *Ca^{2+} channels*. The Ca^{2+} ions that enter the nerve ending trigger 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.

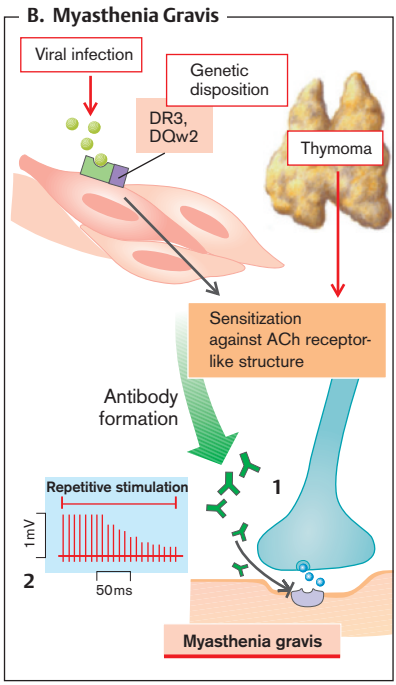
Abnormalities can affect any element of this process. *Local anesthetics*, for example, inhibit the voltage-gated **Na^+ channels** of the neuron and thus interrupt nerve transmission to the end-plate. The **Ca^{2+} channels** can be blocked by *antibodies* (see below). *Botulinus toxin* inactivates 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.

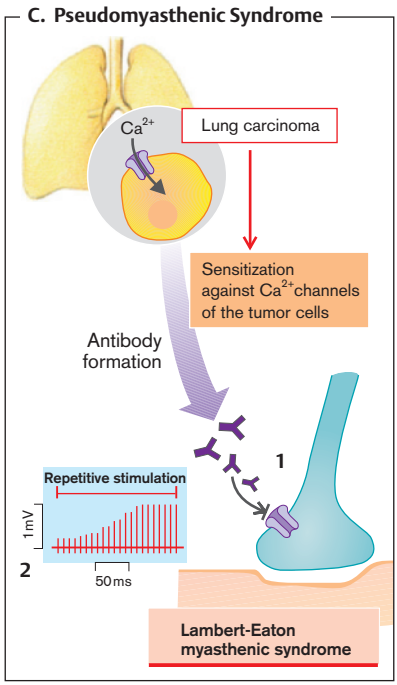
Succinylcholine (suxamethonium chloride) leads to **continuous stimulation of the receptors**, continuous depolarization of the postsynaptic membrane, and thus to an inactivation of the postsynaptic Na^+ channels. In this way it can, like curare, block neuromuscular transmission. In low concentrations, 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 because 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 triggered by viral infection, which presumably upregulates MHC and thus renders the antigen visible to the immune system (→ p. 308). 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) or HLA (= human leukocyte antigen, → p. 50). In rare cases, myasthenia is caused by genetic defects of channels, ACh receptor or acetylcholinesterase. 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 **pseudomyasthenic 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**).







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, these cells are destroyed. *Amyotrophic lateral sclerosis* (ALS) is caused by genetic defects of the superoxide dismutase (SOD), which normally protects the neurons against oxidative stress. The SOD deficiency leads to the death of spinal α-motoneurons and supraspinal motoneurons (→ **A 1**). Other mutations affect dynactin (axonal transport), mitochondrial cytochrome *c* oxidase, and alsin (regulation of endosomal transport). The death of α-motoneurons in the X-chromosomally inherited Kennedy's syndrome is due to a defective androgen receptor.

Damage to or death of **axons** may, among other causes, be due to autoimmune diseases, a deficiency of vitamin B_1 or B_{12}, diabetes mellitus, poisoning (e.g., lead, alcohol), or genetic defects (e.g., Charcot–Marie–Tooth syndrome; → p. 324) (→ **A 2**).

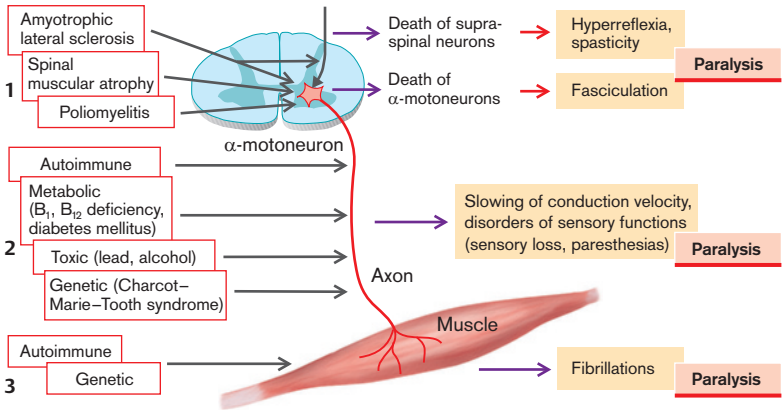
The **skeletal muscles** (→ **A 3**) can also be affected by autoimmune diseases (e.g., dermatomyositis). In addition, genetic defects may involve skeletal muscles, for example, in myotonia or dystrophy (see below).

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. 326), 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. 324). 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.

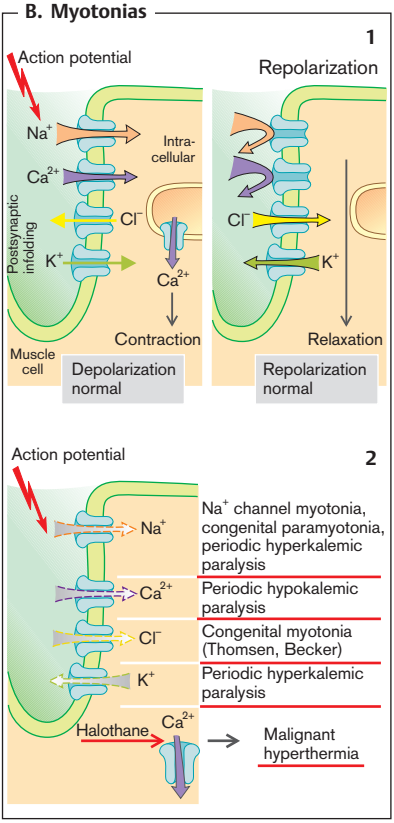
Genetic ionic channel defects (→ **B**) are the cause of a group of functional muscle diseases. Normally (→ **B 1**) depolarization of the muscle cell membrane is triggered on excitation by a voltage-gated Na^+ channel that causes the opening of a voltage-gated Ca^{2+} channel (→ p. 326) and a Ca^{2+} channel of the sarcoplasmic reticulum. As a result, intracellular Ca^{2+} 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 Ca^{2+} channels so that the intracellular Ca^{2+} 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*; → **B 2**). Cold further slows Na^+ channel inactivation such that cramps occur, particularly in paramyotonia when the muscle gets cold. Another 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 Ca^{2+} channel also leads to *hypokalemic periodic paralysis*. Defects in the Cl^- channels result in myotonia. The channels are composed of several subunits. If insertion of the mutated subunit disrupts the function of the complete channel complex, the mutation leads to dominant inheritance (*congenital myotonia, Thomsen's disease*). If the subunit is itself nonfunctional but does not disturb the function of intact subunits, the mutation leads to recessive inheritance (*Becker's myotonia*). In certain defects of sarcoplasmic Ca^{2+} channels (ryanodin receptor) the volatile halogenated anesthetics may bring about potential-independent activation of these channels with an increase in intracellular Ca^{2+}. The resulting

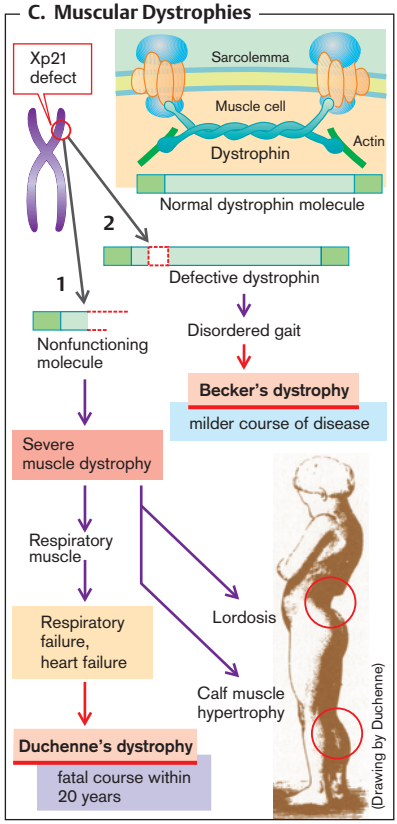
A. Diseases of the Motor Unit



B. Myotonias



C. Muscular Dystrophies



massively increased energy metabolism causes hyperthermia (*malignant hyperthermia*; → p. 26).

In Duchenne's or Becker's **degenerative muscular dystrophy** (→ **C**; → p. 328) dystrophin, an element of the cytoskeleton, is defective. The responsible gene is on 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 (→ **C1**). 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. Involvement of cardiac muscle cells may lead to cardiomyopathy. In *Becker's dystrophy* the dystrophin is also defective, but its function is less impaired and the disease therefore less severe (→ **C2**; → p. 328).

Muscle dystrophies may be caused by defects in further muscle proteins including myotilin, lamin, caveolin, calpain, dysferlin, sarcoglycan, telethonin, and titin. Moreover, myopathies may result from defects of metabolism (e.g., glycogenoses), endocrine disorders (e.g., hyperthyroidism) or further autoimmune diseases (e.g., polymyositis, dermatomyositis).

Diagnosis of Motor Unit Diseases

A primary myopathy can be distinguished from a neurogenic myopathy by **electromyography** (→ **D**).

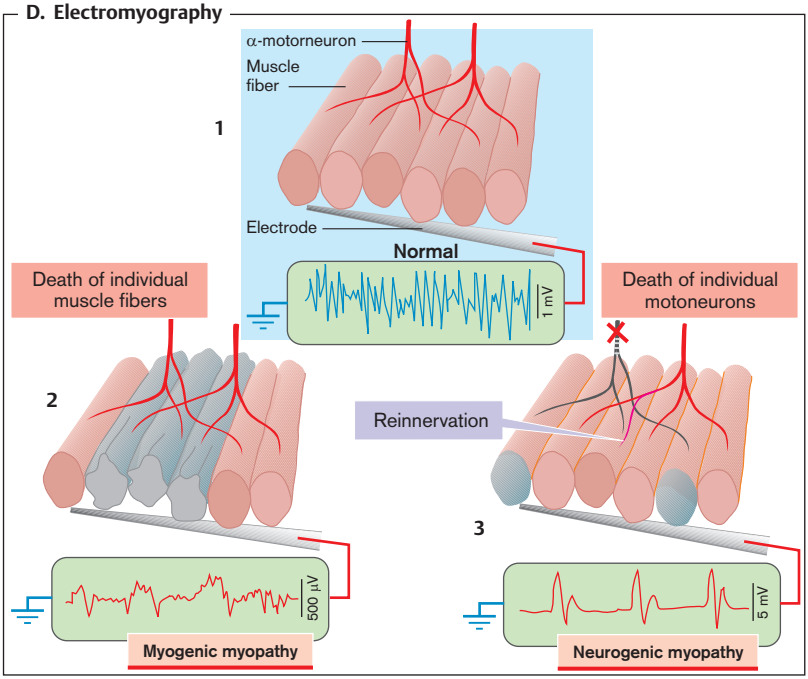
This is carried out by putting a needle into the muscle and measuring the potential difference from an indifferent electrode on the surface of the skin. As the tip of the intramuscular electrode is largely extracellular, only a fraction of the potential difference across the cell membrane is measured. 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.

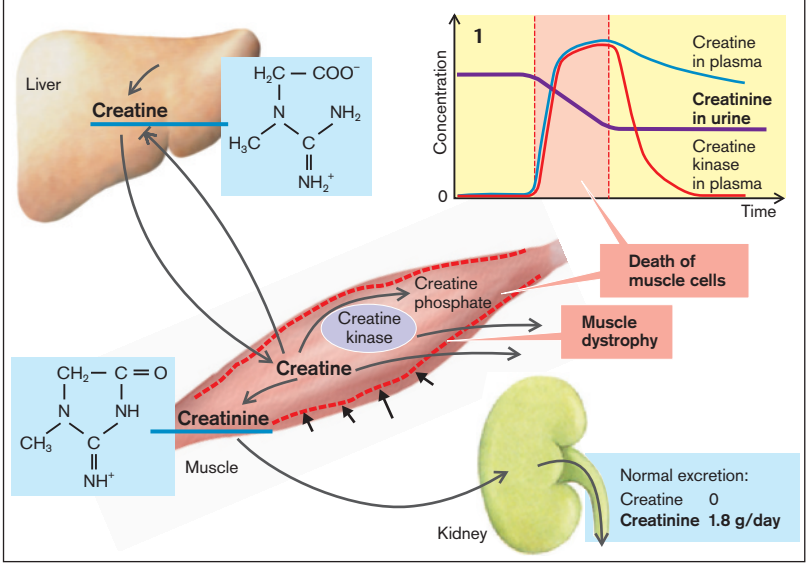
Normally those muscle fibers in a muscle that are innervated by one α-motoneuron do not lie next to each other, but are distributed over a larger cross-sectional area (→ **D1**). If muscle fibers are destroyed (**myogenic myopathy**; → **D2**), the number of muscle fibers near the electrode decreases. 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 exits the muscle cell across 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 strictly parallel the reduction in muscle mass.

D. Electromyography



E. Creatine Metabolism



Lesions of the Descending Motor Tracts

Spinal α-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 medullar 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 α-motoneurons (→ **A3a**). The antigravity muscles are also affected, less so than the other muscles though, by the reduced supraspinal activation of the α-motoneurons. In spinal shock the muscles are flaccid and no reflexes are elicited (areflexia).

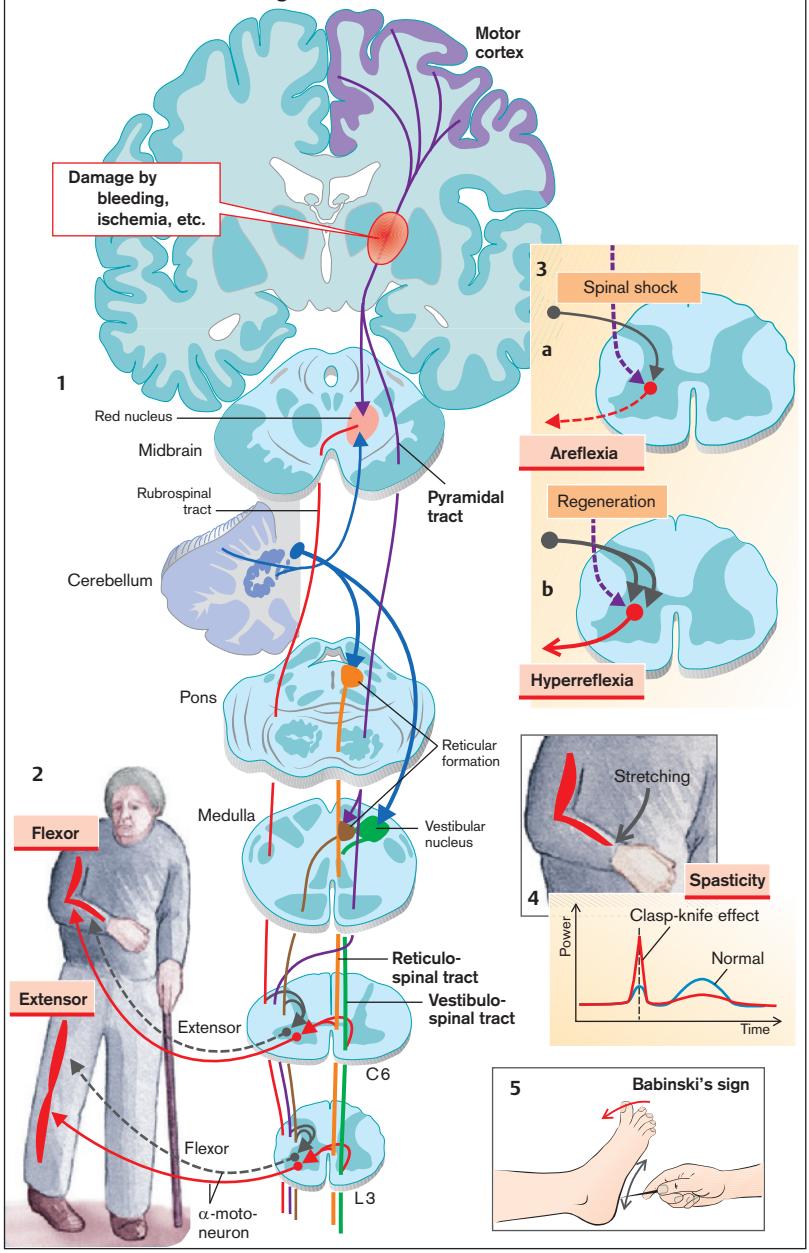
However, partial "denervation" of the α- and γ-motoneurons as well as of interneurons leads to a gradual increase in sensitivity of these neurons. In addition, the endings of supraspinal neurons that are out of action are replaced by synapses with the spinal cord neurons (→ **A3b**). As a consequence, the reflexes gradually gain a stronger influence on the activity of the α-motoneurons, and **hyperreflexia** occurs.

Another consequence is **spasticity.** After loss of function of the descending tracts, the activity of the α-motoneurons comes under the increasing influence of the muscle spindles and Golgi tendon organs (→ **A4**). Stretching the muscle spindles stimulates the α-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. 272]), 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 α-motoneurons. In **lesions of the vestibular nucleus** abnormalities of balance with vertigo, nystagmus, and nausea predominate (→ p. 352).

A. Lesions of the Descending Tracts



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

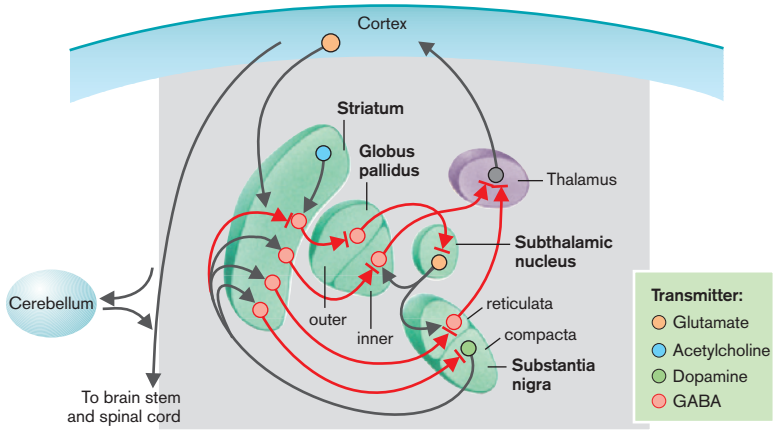
Parkinson's disease is a disease of the substantia nigra (p.c.) which via dopaminergic tracts influences GABAergic cells in the corpus striatum. **Causes** include genetic defects of α-synuclein, parkin or of the ubiquitin-carboxyterminal hydroxylase. Those and a variety of further genetic defects lead to *hereditary disposition* that in middle to old age leads to degeneration of dopaminergic neurons in the substantia nigra (→ **B 1**). 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 (→ **B 1**). This leads 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. In addition, 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).

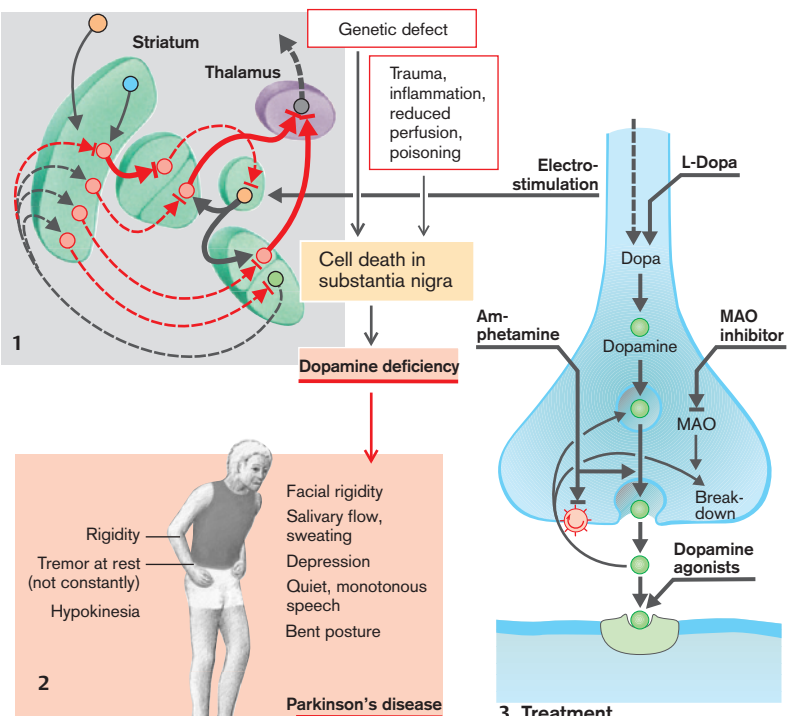
Inhibition of the thalamus **suppresses voluntary movement** (→ **B 2**). Patients have difficulty initiating movement or can do so only as a reaction to external stimuli (**hypokinesia**). Muscle tone is greatly increased (**rigor**). In addition, **resting tremor** (4–8 per second) is common, with alternating movements especially of the hands and fingers (a movement similar to that used when counting money). The combination of rigor and tremor leads to the cogwheel phenomenon. Hypokinesia typically forces the patient to adopt a moderately bent posture with slightly angled arms and legs. It also leads to a rather rigid facial expression, micrographia, and soft, monotone, and indistinct speech (hypophonia). Further disturbances include anosmia, increased salivation, excessive sweating, obstipation, urinary urgency, pain, sleeping disorders, anxiety, 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 (→ **B 3**) 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). The dopamine breakdown can be delayed by inhibitors of monoaminooxidase (*MAO inhibitor*) or of catechol-*O*-methyltransferase (COMT). Moreover, the effect of dopamine can be imitated by dopamine-like drugs. ▶

A. Basal Ganglia



B. Parkinson's Disease



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.

Apoptotic death of the nigrostriatal neurons could be counteracted by antioxidative drugs and growth factors. *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. A particularly effective approach is the inhibition of the subthalamic nucleus by continuous current via implanted electrodes.

Parkinsonism is observed **in further neuronal diseases**, such as postencephalitic Parkinson's syndrome, multiple systems atrophies (MSA), progressive supranuclear palsy (SPP), and corticobasal degeneration (BD). In those diseases α-synuclein (MSA) and tau (PSP and CBED) play a role. In postencephalitic Parkinson's syndrome, but not the other disorders, L-dopa is therapeutically effective.

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 disease is caused by mutations in huntingtin, which lead to enhanced excitotoxic action of the excitatory neurotransmitter glutamate, which stimulates neurons by activating calcium-permeable ionic channels. The cell is damaged by excessive entry of Ca^{2+}. With progression, the disease affects in addition neurons outside the striatum with the appearance of additional symptoms (depression, dementia).

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 are 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.

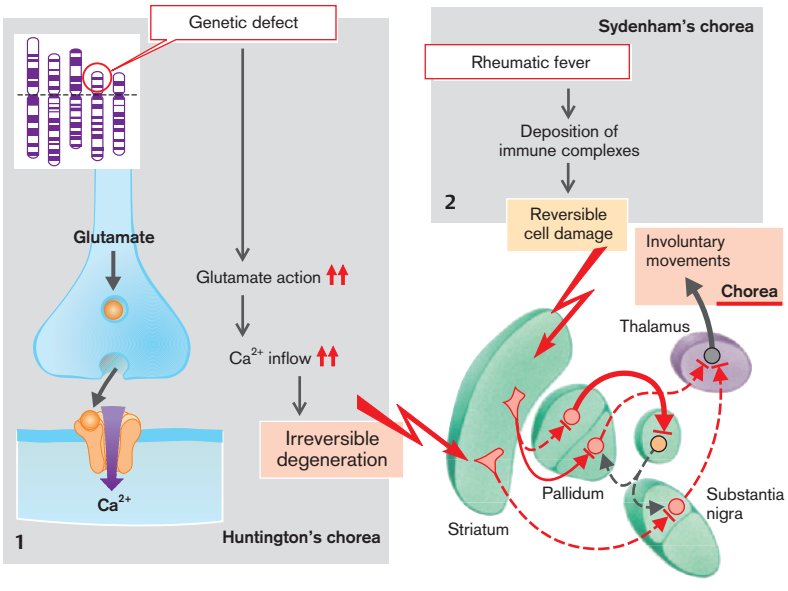
Hemiballism. After destruction of the subthalamic nucleus (by ischemia or tumor) sudden flinging movements occur. They are thought to be due to decreased stimulation of inhibitory GABAergic neurons in the internal part of the pallidum and substantia nigra (p.r.). It leads to disinhibition of neurons 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. 374). 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 the 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.

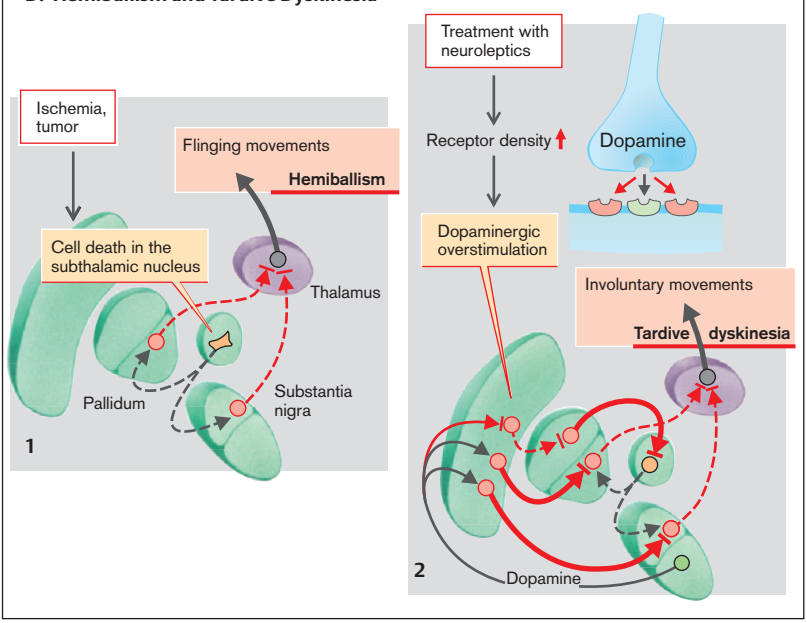
Lesions of the striatum and pallidum additionally lead to **athetosis**, a hyperkinesia marked by excruciatingly slow, screw-like movements.

Lesions in pallidum and thalamus cause **dystonia**, simultaneous lasting contractions of agonists and antagonists leading to twisting and repetitive movements, such as involuntary closure of eyes (blepharospasm) or twisting of the neck (torticollis). Dystonia is present during attempted voluntary movements, is frequently aggravated by stress and fatigue, and may be attenuated by specific sensory inputs.

C. Chorea



D. Hemiballism and Tardive Dyskinesia



Lesions of the Cerebellum

Lesions of the cerebellum may be caused by poisoning (especially by alcohol, but also DDT, piperazine, 5-fluorouracil, lithium, or diphenylhydantoin), heat stroke, hypothyroidism, malabsorption, genetic defects (e.g., K^+ channels [KCNA1], Ca^{2+} channels [CACNA1], protein phosphatase A_2, hexosaminidase, glutamate dehydrogenase, pyruvate dehydrogenase, α-oxidation, DNA repair, transport of neutral amino acids, mitochondrial proteins, ataxins [partially Ca^{2+}-regulating proteins]), further degenerative processes, inflammation (e.g., multiple sclerosis [→ p. 324], viruses, prions), as well as cerebellar and extracerebellar tumors (paraneoplasia; → p. 18). In hereditary Friedreich's ataxia (mutation of the mitochondrial protein frataxin), cerebellar function is indirectly affected, for example, by degeneration of the spinocerebellar tracts. In ataxia teleangiectasia (mutation of ATM, a protein involved in cell cycle control), the ataxia is paralleled by enhanced risk to develop tumors. 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 (→ **A6**). From here spinal motoneurons are activated via the pyramidal tract (violet). Lesions in the hemispheres or in structures connected with them thus impair initiation planning and learning of movements.

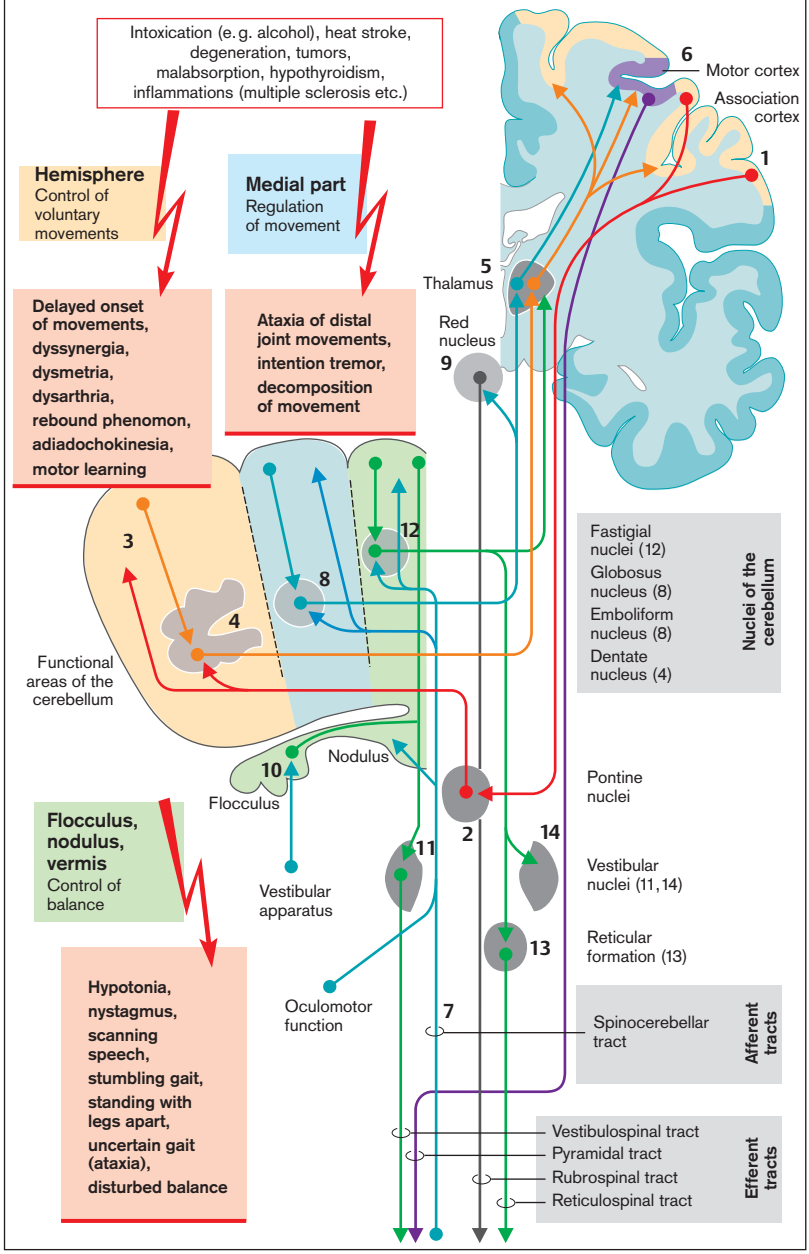
The **intermediate part** (spinocerebellum, light blue) is mainly responsible for the *control of movement*. Via spinocerebellar afferents (blue) (→ **A7**) it receives information about the state of the motor apparatus. Its neurons project to the red nucleus (→ **A9**) and thalamus via the nuclei emboliformis 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**). The flocculus, nodulus, and vermis further receive direct afferent signals via spinocerebellar fibers (→ **A7**) and 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 reticular 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.

Cerebellar **lesions** delay 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. 352) 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



Abnormalities of the Sensory System

Specialized receptors (sensors) of the *skin* are stimulated by vertical pressure (Merkel), touch (mainly Meissner bodies), lateral 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 (CO_2, H^+, glucose, osmolarity). Pain stimuli are perceived by nociceptors (free nerve endings) in the skin, motor apparatus, internal organs, and vessels (→ p. 342).

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 **spinocerebellar 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–Sequard'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. 332).

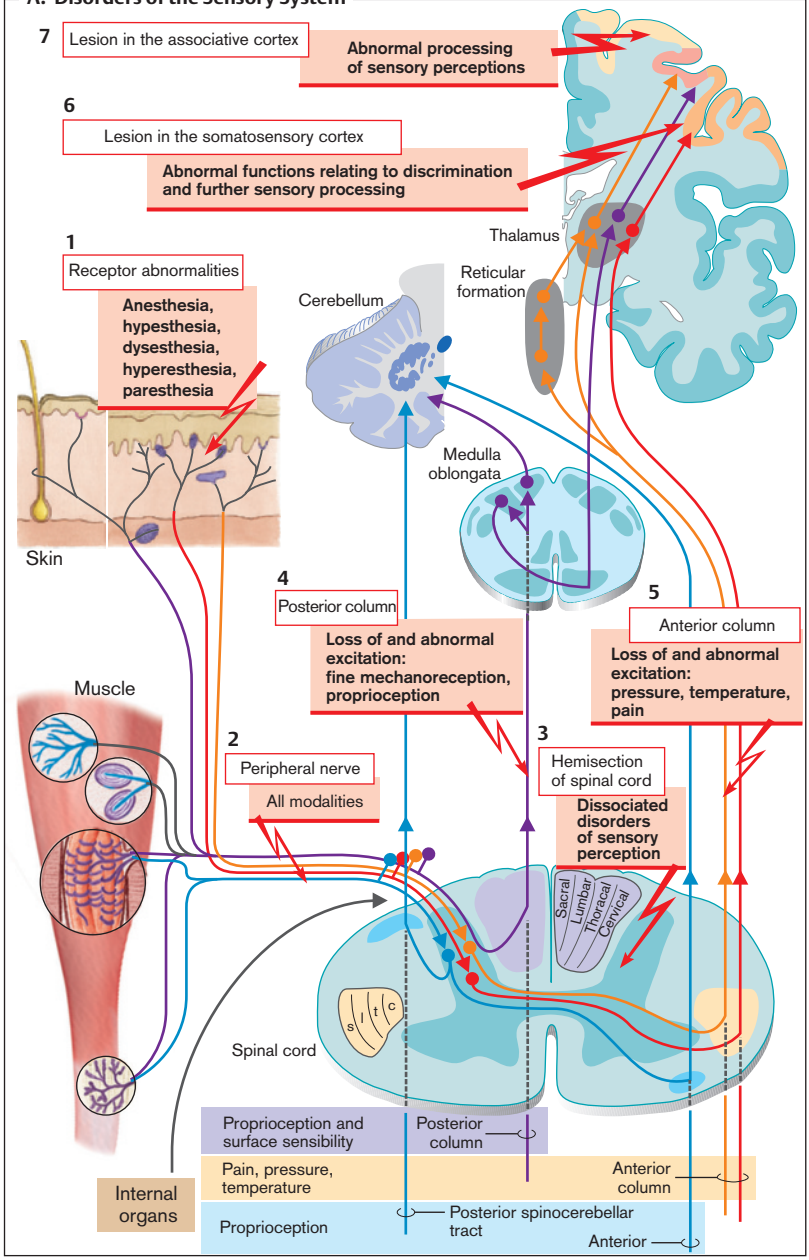
An interruption in the **dorsal column** (→ **A4**) stops adequate vibratory sensation and diminishes the ability to precisely define mechanical stimuli in space and time, and accurately to determine their intensity. Proprioception is also affected, which means that it is mainly information from the 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 senses 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 the inability to identify the exact spot where a sensation is felt (topagnosis). 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



Pain

Pain stimuli in the skin and the viscera by high-intensity, non-noxious stimuli (distension, temperature) as well as by **tissue lesions** active nociceptors by opening of specific ion channels (e.g., TRPV1 [transient receptor potential], ASIC [acid sensing ion channel]). Necrotic cells release K^+ and intracellular proteins. K^+ 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. 316 ff.). *Leukotrienes, prostaglandin E_2, bradykinin, cytokines, neurotrophins,* 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. 316). If there is vascular occlusion, **ischemia** occurs and the resulting extracellular accumulation of K^+ and H^+ further activates the sensitized nociceptors. *Histamine, bradykinin,* and *prostaglandin E_2* 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). A genetic cause of migraine is a mutation in the gene encoding the L-type voltage gated Ca^{2+} channel CACNL1.

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).

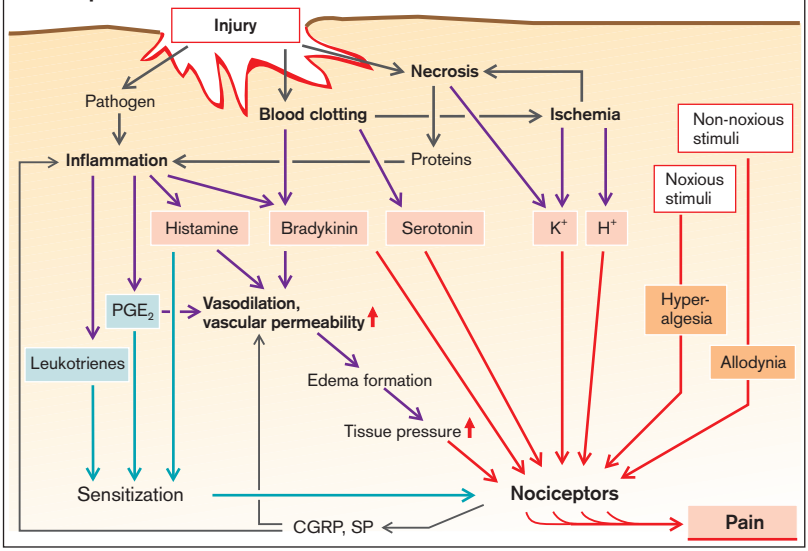
Projected pain is produced by stimulation of a nerve (e.g., of the ulnar nerve in the ulnar sulcus; → **B2**). The perception of pain is projected to the innervation area of the nerve. A special form of projected pain is *phantom pain* of an amputated limb. In *neuralgia* continued abnormal stimulation of a nerve or posterior root results in chronic pain in the area of innervation.

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 and consequences 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 employing norepinephrine, serotonin, and especially endorphines. Lesions of the thalamus, for example, can produce pain through an absence of these inhibitions (*thalamus syndrome*).

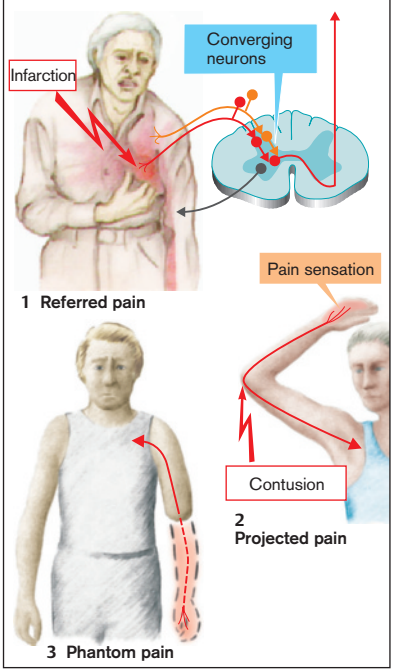
To **counteract pain,** the activation of pain receptors can be inhibited, for example, by cooling of the damaged area and by *prostaglandin synthesis inhibitors* (→ **C1**). The *transmission of pain* can be inhibited by cooling and by Na^+ channel blockers (local anesthetics; → **C2**). Transmission in the thalamus can be inhibited by anesthesia and alcohol (→ **C5**). Pain transmission may be interrupted by surgical nerve transection (→ **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 treatment.

Pain may be absent due to pharmacological treatment or the very rare congenital condition of **congenital analgesia** (e.g., mutations of the Na^+ channel SCN9A). If the cause of the pain is not removed, the consequences can be life-threatening. Variants of certain genes relevant for pain sensation and transmission may lead to genetic hypalgesia (e.g., opioid receptor OPRM1, catechol-*O*-methyltransferase COMT, melatonin 1 receptor MC1R and TRPV1).

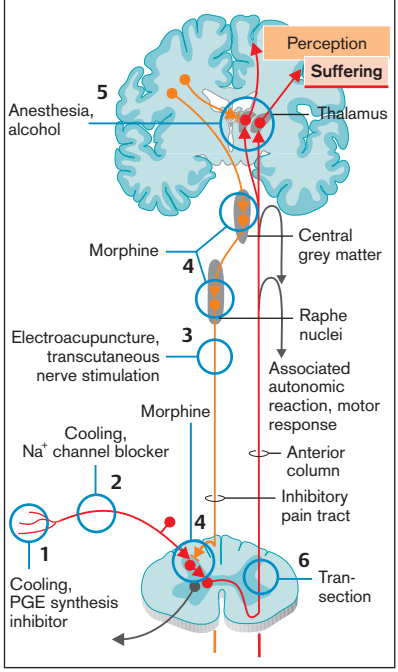
A. Peripheral Mechanisms of Pain



B. Referred Pain



C. Pain Relief



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**.

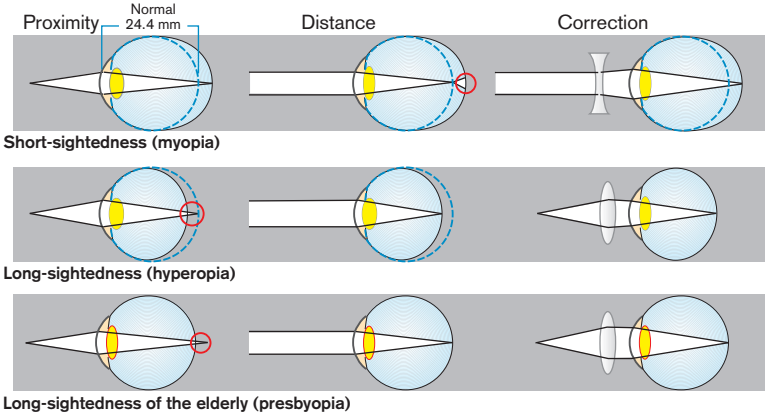
Astigmatism (→ **B**). The surface of the eye is not perfectly spherical. In *regular astigmatism* the curvature's radiuses in the horizontal and vertical axes are different; and an upright square is imaged as a rectangle. This abnormality can be corrected by means of a cylindrical lens. A minor form (< 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).

Glaucoma. 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.

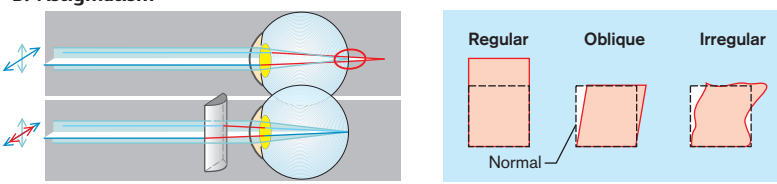
The high intraocular pressure gradually but irreversibly damages the optic nerve, leading to visual field defects that start around (Mariotte's) blind spot and in the nasal periphery (→ **C 2**). Attempts at treating the defects involve lowering the intraocular pressure by narrowing the pupil (parasympathetic drugs) and reducing aqueous production. Aqueous humor secretion, like the reabsorption of HCO_3^- in the kidney's proximal tubules (→ p. 104 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 endproducts [AGE]) (→ **C 3**). Similar products also accumulate with age. In diabetes mellitus there is also an accumulation of sorbitol in the lens (→ p. 312). Irregular hydration and a change in connective tissue proteins bring about clouding or opacification of the lens (**cataract**; → **C 3**).

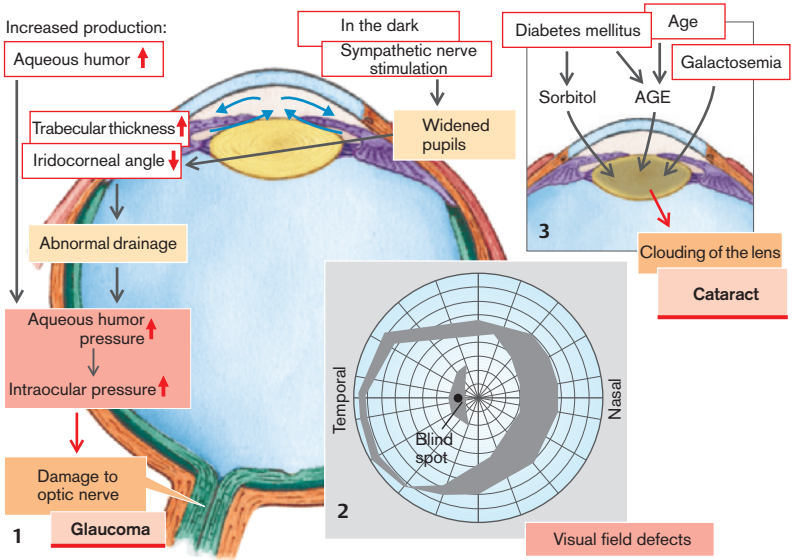
A. Refraction Abnormalities



B. Astigmatism



C. Glaucoma and Cataract



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 phagocytozed. The photoreceptors transmit their excitation via bipolar cells (Bps) to the ganglion cells (Gs). Amacrine cells (Ams) and horizontal cells (Hcs) form cross-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. 312), swell up, and thus narrow the vessels. Additionally, the vessel walls are thickened by glycation (AGE; → p. 312). This results in ischemia of the tissues, formation of angiotensin II, which in turn stimulates the synthesis of the vascular endothelial growth factor VEGF, a strong angiogenetic factor. Consequences include angiogenesis, increase in vascular permeability, formation of new vessels, and hemorrhages. This bleeding opacifies the vitreal body, the ischemia destroys the retina and may ultimately lead to blindness.

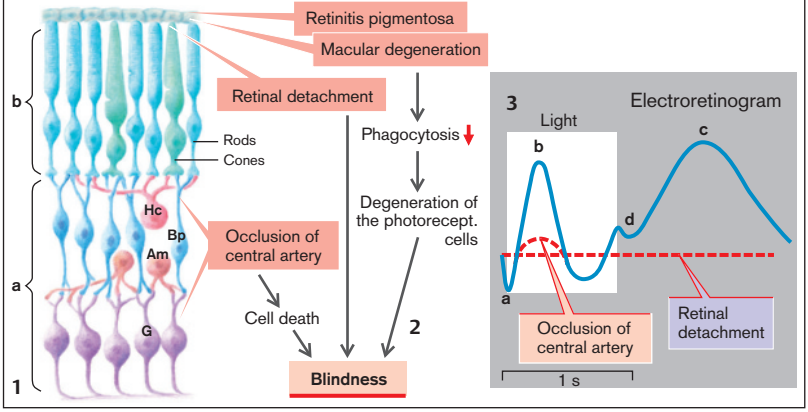
Night blindness. The visual pigment consists of 11-cis-retinol, a metabolite of vitamin A and a protein that is different in the rods and the three types of cones (→ **C 1**). In vitamin A deficiency the formation of visual pigment in rods and cones is impaired, resulting in reduced light perception 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 the parafoveally located rods (**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



B. Diabetic Retinopathy

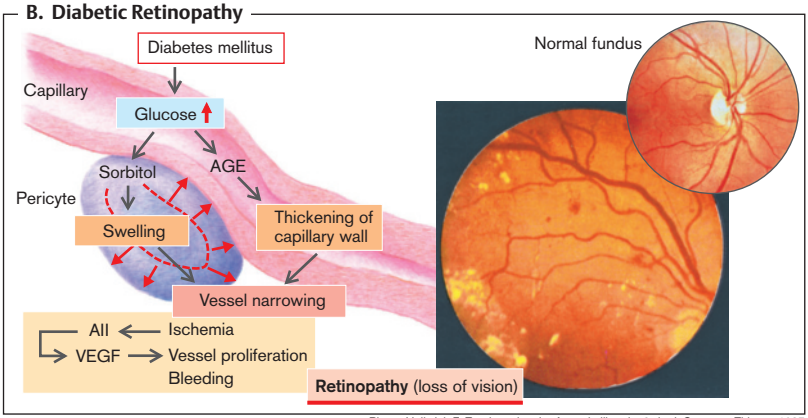
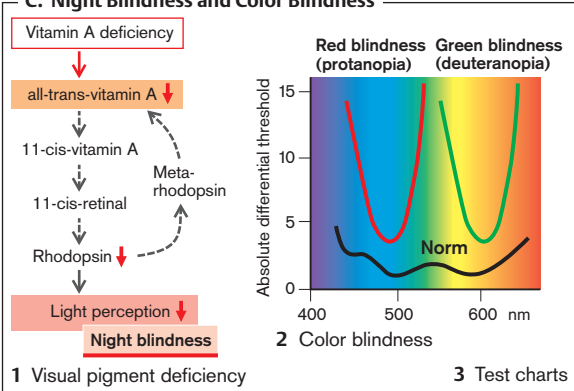


Photo: Hollwich F. Taschenatlas der Augenheilkunde. 3rd ed. Stuttgart: Thieme; 1987

C. Night Blindness and Color Blindness



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 synapting 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 pretectal 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 a lesion is in the region of the pretectal 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 **blind sight** 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.

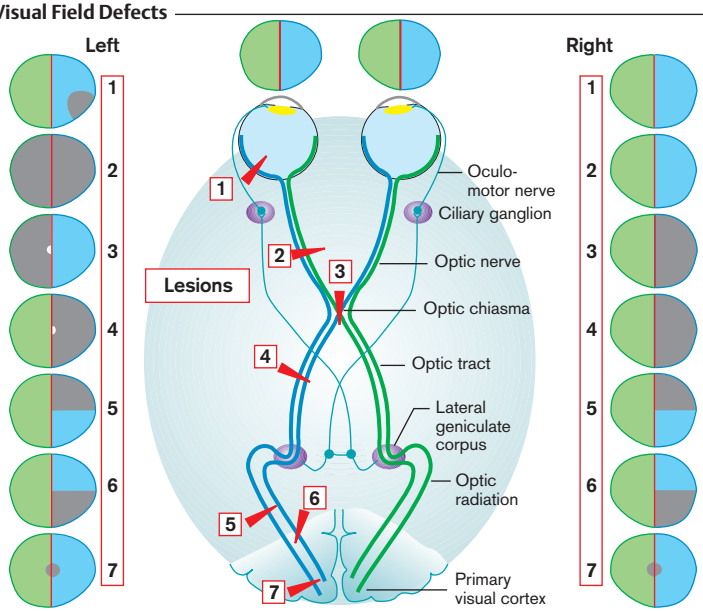
If there are lesions in the *occipitotemporal association fields*, neither objects (**object agnosia**), faces and facial expressions (**prosopagnosia**), nor colors (**achromatopsia**) can be recognized.

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**).

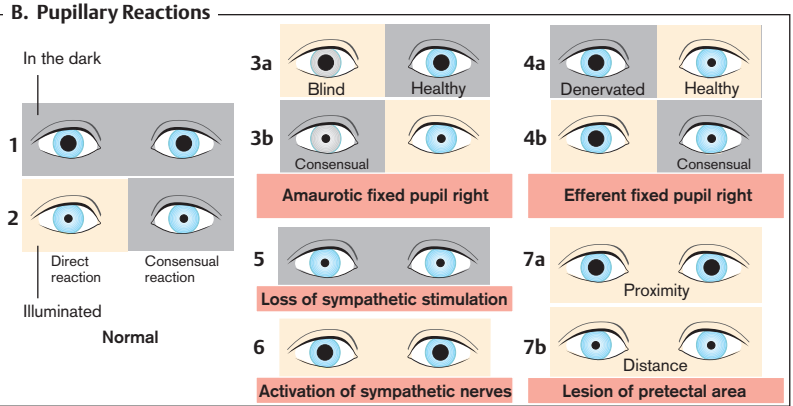
With lesions in the visual association fields, faulty spatial and three-dimensional perception also often occurs, objects being perceived as distorted (*dysmorphopsia, metamorphopsia*), as too small (*micropsia*), or too large (*macropsia*). Other lesions cause simultanagnosia or *asynthesia* (inability to combine different properties of one object).

If the connection from the visual cortex to area 39 is interrupted (→ p. 366), the patient is no longer able to read (*alexia*).

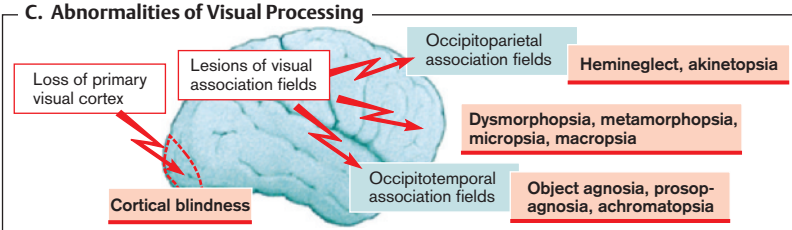
A. Visual Field Defects



B. Pupillary Reactions



C. Abnormalities of Visual Processing



Hearing Impairment

Sound waves are transmitted from the eardrum (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 a Na^+-K^+-$2Cl^-$ cotransporter (NKCC1), the Na^+/K^+-ATPase, and a Cl^- channel composed of the subunit barttin and either ClC-Kb or ClCKa in the antiluminal membrane, as well as by a luminal K^+ channel (KCNE1/KCNQ1) in the apical cell membrane (→ **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 glutamate from the inner hair cells. By contracting, the outer hair cells increase the local dislocation of the basilar membrane and thus augment the stimulation of the hair cells. K^+ released from the hair cells recirculates through several cells back to the epithelial cells of the stria vascularis, involving K^+ channels (KCNMA1, KCNQ4, KCNJ10), KCl cotransporter (KCC4) and connexins (e.g., 26). A H^+-ATPase and the Cl^-/HCO_3^- exchangers pendrin and AE1 accomplish a slight acidification of the endolymph.

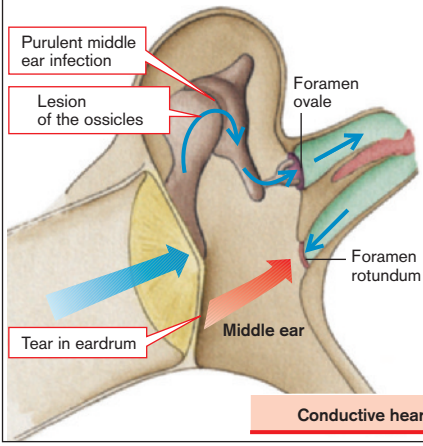
Causes of deafness. A tear in the eardrum, a lesion in the ossicles, or immobilization of the conduction apparatus, for example, caused by a purulent middle ear infection, dampen transmission to the fenestra vestibuli. If there is a hole in the drum, the fenestra cochleae is no longer protected, resulting in **middle ear hearing loss**. While conduction through the air is impaired, bone conduction remains normal (→ **A**).

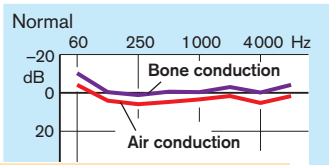
The **hair cells** can be damaged by *sound stress* (too loud for too long) and *ischemia*. Several drugs are accumulated by the stria vascularis in the endolymph (e.g., aminoglykosides, cisplatin) and are thus particularly toxic to the inner ear. Loop diuretics may cause (transient) deafness by inhibition of the Na^+-K^+-$2Cl^-$ cotransport. Hearing loss further results from genetic defects of structural proteins (e.g., MYO7A, MYO15, TECTA, DIAPH1), transcription factors (e.g., POU3F4, POU4F3) and transport molecules (e.g., KCNQ4, KCNMA1, KCNJ, KCNE1, KCNQ1, connexin 26,30,31, barttin, ClC^-Kb + ClC-Ka, KCC4, NKCC1, Pendrin, H^+-ATPase). Defective barttin leads simultaneously to renal NaCl loss (Bartter's syndrome, → p. 106), a defective KCNE1/KCNQ1 to delayed repolarization of the heart (long QT; *Jervell–Lange–Nielson's syndrome*), and a defective pendrin to hypothyroidism (Pendred's syndrome). The **inner ear hearing loss** 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 cortex.

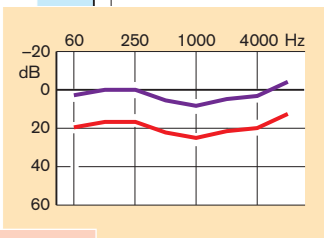
Stiffening of the basilar membrane disturbs the micromechanics and thus probably contributes to **hearing loss in the elderly** (→ **B1**).

Abnormal absorption of endolymph can also cause deafness. The endolymph space becomes evaginated, distorting the relationship between hair cells and tectorial membrane (**endolymph edema**; → **B6**). Increased permeability between the endolymph and perilymph spaces may be responsible for **Menière's disease**, which is characterized by attacks of deafness and vertigo (→ **B7**).

A. Conductive Hearing Loss

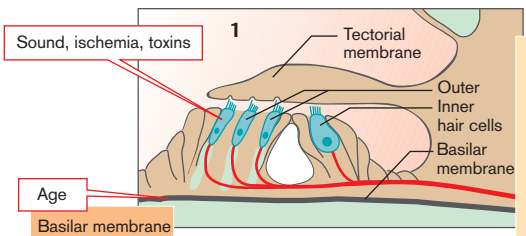


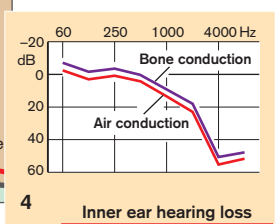


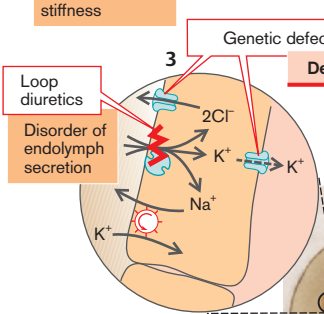


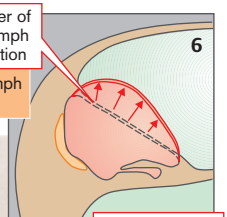
Conductive hearing loss

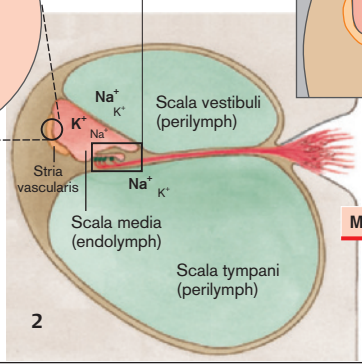
B. Inner Ear Hearing Loss

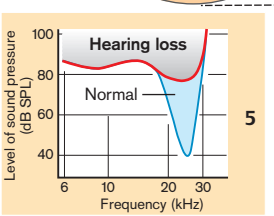












7
Increased permeability
Deafness
Vertigo
Menière's disease

Vestibular System, Nystagmus

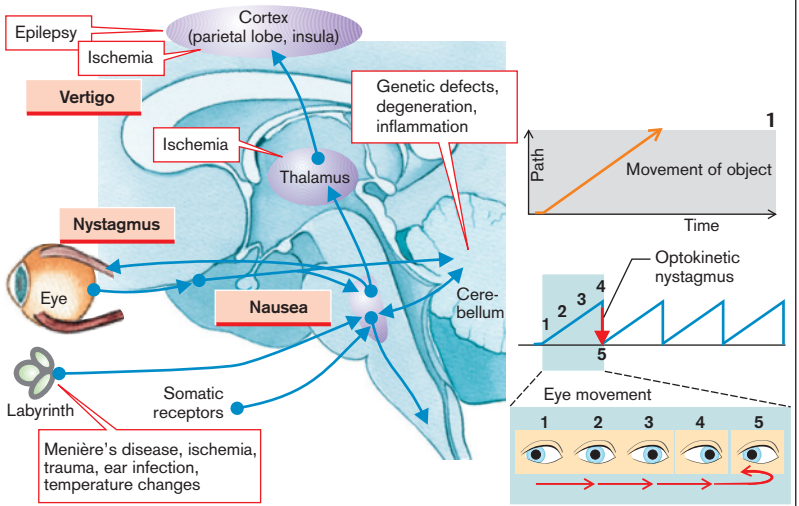
In order to maintain positional equilibrium the organism requires information about the movement of the endolymph in the semicircular canals, the position of the statoliths in the inner ear (in relation to gravity), the position and tension of the body's musculature as well as the retinal image in relation 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 (→ **A 1**). 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. 350]), the *cerebellum* (intoxication, genetic defects, degenerative disease, inflammation [→ p. 338]), the *thalamus* (ischemia), and the *cerebral cortex* (ischemia, epilepsy [→ p. 360]). 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, Taste

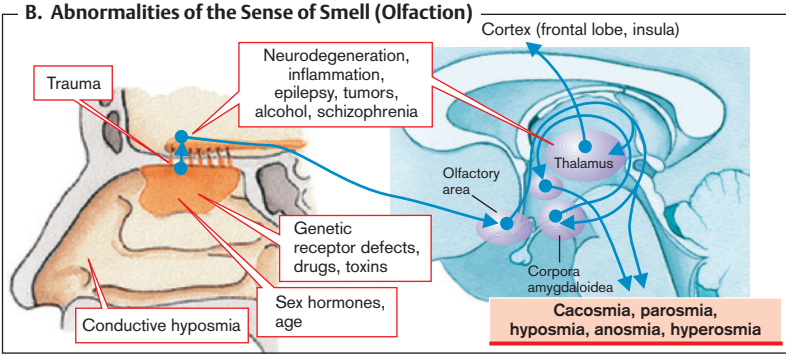
Olfaction: Sensory cells in the olfactory mucosa express some 250 distinct G-protein-coupled olfactory receptors, which transmit different qualities of odor, namely flowery, ethereal, musky, camphoric, foul, sweaty, and stinging. Their axons pass through openings in the cribriform plate to the olfactory bulb (→ **B**). From there the information reaches the olfactory cortex via the olfactory tract and is then transmitted to the hypothalamus, the amygdaloidal 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. Genetic defects may compromise the function of the olfactory receptors or sensory cells, which can further be affected by some drugs (e.g., cocaine, morphine), toxins (e.g., cement dust, lead, cadmium, cyanide, chlorine compounds), viral infections, tumors, and radiation. The *axons* of the sensory cells can be torn by fracture in the region of the cribriform plate. The *central processing* of olfactory sensations is impaired by viral infections, trauma, toxins (alcohol, smoking), malnutrition, inflammation, tumors, hypothyroidism and neurodegenerative disease (Alzheimer's disease [→ p. 370], Parkinson's disease [→ p. 334 ff.], Huntington chorea), epilepsy (→ p. 360) and schizophrenia (→ p. 374). This results in reduced (**hyposmia**) or absent (**anosmia**) sense of smell, or increased (**hyperosmia**), inadequate (**parosmia**), or unpleasant (**cacosmia**) olfactory sensation.

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; those with an aldosterone deficiency cannot sense salty. 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 (**hypogeusia** or **ageusia**, respectively). The sense of taste may also be increased (**hypergeusia**), inadequate (**parageusia**), or unpleasant (**dysgeusia**).

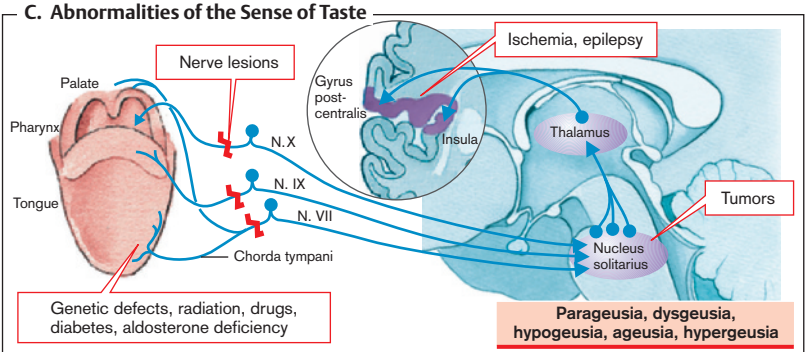
A. Disturbance of Balance, Nystagmus



B. Abnormalities of the Sense of Smell (Olfaction)



C. Abnormalities of the Sense of Taste



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 in the adrenal medulla (**pheochromocytoma**) can release epinephrine. Lastly, some *drugs* can trigger sympathetic nerve activity. During *pain* (→ p. 342), activation of sympathetic nerves may produce autonomic side effects.

Activation of the sympathetic nervous system (→ **A**) will, via β_1-receptors, increase the cardiac contractility (*inotropism*), heart rate (*chronotropism*), conduction velocity of the action potential (*dromotropism*), excitability of the heart (*bathmotropism*), and velocity of relaxation (*lusitropism*). *Blood vessels* in the skin, lung, kidney, gut, and sex organs are constricted via α_1-receptors, while those in the heart, muscle, and liver (arteria hepatica) are dilated by β_2-receptors. The circulatory effects of the sympathetic nerves are to raise the blood pressure, the skin becomes pale through vasoconstriction.

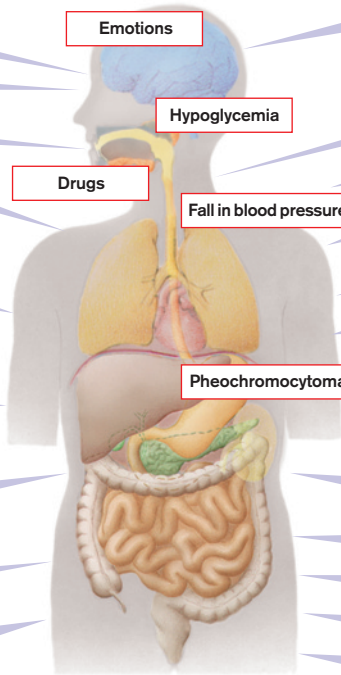
The sympathetic nerves stimulate *sweat* (cholinergic) and *salivary* (β) *secretion*, hair becomes erect (arrectores pilorum muscle [α_1]), eyelids are raised (levator palpebrae muscle [α_1]), and the pupils dilated (dilator pupillae muscle [α_1]). In addition, bronchial and uterine musculature is dilated (β_2), 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 (β_2), *lipolysis* (β_2) as well as the release of 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). The autonomic nerve system is frequently affected by diabetes mellitus, amyloidosis, alcoholism, porphyria, or autoimmune disease (Guillain–Barré syndrome and autoimmune autonomic neuropathy). The autonomic system may further be involved in several genetic diseases of the nerve system (e.g., multiple system atrophy, Parkinson's disease, Shy Drager syndrome [autonomic failure with striatonigral degeneration]). 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 susceptible individuals. 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 (♂), vasocongestion (♀), and tear, salivary, bronchial, and gastrointestinal secretions are inhibited. If there is an anticholinergic action, sweat secretion is also inhibited.

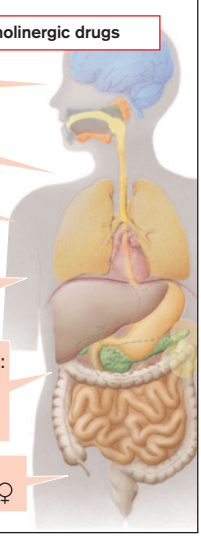
Section of the spinal cord (→ **C**) causes the loss of autonomic nervous system regulation. At first spinal shock occurs (→ p. 332). Below the level of the lesion in the spinal cord the cutaneous blood vessels are dilated and autonomic functions, for example, defecation and **micturition**, are lost. 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



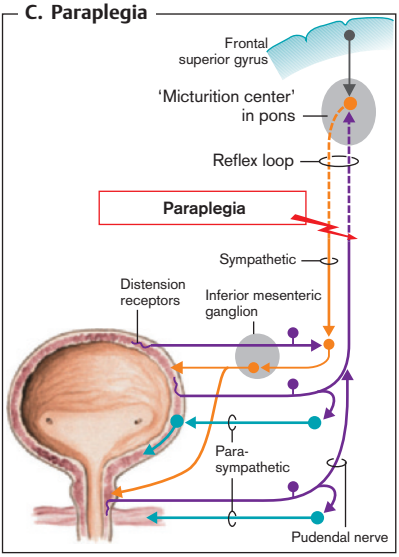
- Eye opening
- Pupil dilation ↑
- Salivary secretion ↑
- Bronchial dilation
- Heart: Contractility ↑, Rate ↑, Stroke volume ↑, Conduction velocity ↑
- Vasodilation: Heart, liver, muscles
- Leukocyte mobilization, thrombocyte aggregation
- Ejaculation
- Vasoconstriction: Skin, lung, kidney, gut, sex organs
- Emotions
- Hypoglycemia
- Drugs
- Fall in blood pressure
- Pheochromocytoma
- Hair becomes erect
- Skin pallor
- Blood pressure ↑
- Glycogenolysis (liver, muscle) ↑
- Lipolysis ↑
- Sweat secretion ↑
- Endocrine etc.: Glucagon ↑, Corticotropin (ACTH) ↑, Somatotropin ↑, Renin ↑, Insulin, histamine ↓
- Uterus contraction ↓
- Intestinal motility ↓
- Muscle tremor
- Sphincter contraction ↑

B. Loss of Parasympathetic Stimulation



- Anticholinergic drugs
- Pupil dilation
- Inhibition of sweating
- Tachycardia
- Decreased motility: Bronchi, gut, bladder (but not sphincters)
- Decreased secretion: Tears, saliva, bronchi, gastrointestinal
- 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 (→ **A 1**).

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 supraoptic and paraventricular 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. 30). 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.

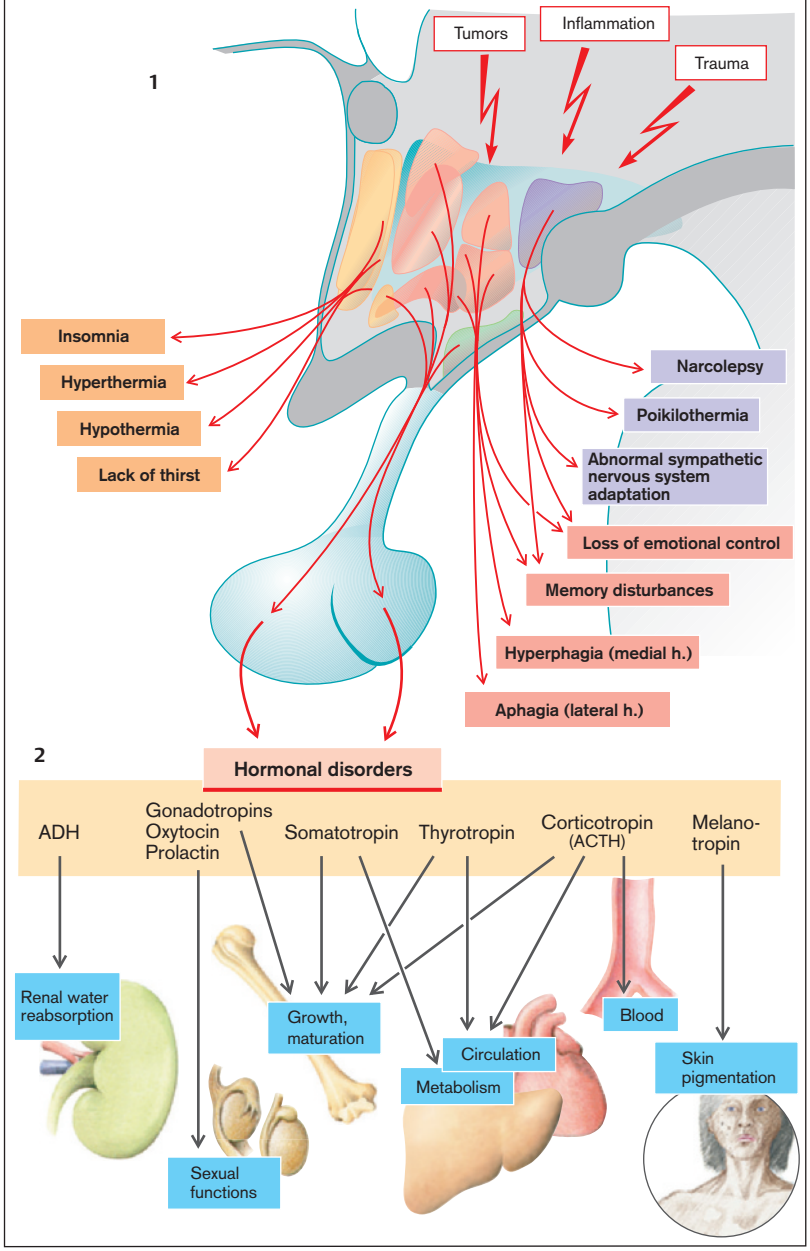
Abnormal release of hypophyseal hormones occurs with lesions in different parts of the hypothalamus. As a result, the peripheral functions regulated by the hormones are affected (→ **A 2**). When ADH is not released *diabetes insipidus* develops in which the kidney can no longer produce concentrated urine and may excrete as much as 20 l of urine daily (→ p. 282).

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. 294 ff.).

Longitudinal growth is promoted by the sex hormones, somatotropin (→ p. 284 ff.), and the TSH-regulated thyroid hormones (→ p. 302 ff.). A reduced concentration of these hormones delays growth, reduced release of the sex hormones retarding the fusion of the epiphyseal plates which may eventually cause gigantism, despite the slower growth. Corticotrophin inhibits longitudinal growth via the action of cortisol.

The main hormones that affect **metabolism** are somatotropin, thyroid hormones, and the ACTH-regulated adrenocortical hormones (→ p. 290 ff.). 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 neutrophils, while decreasing the number of lymphocytes and eosinophils. They thus affect immune defenses (→ p. 290 ff.).

A. Hypothalamic Lesions



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 appropriate leads. The EEG can provide valuable clues to neuronal functions and as a result has gained great clinical importance. Like the electrocardiogram ([ECG] → p. 198), 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 **postsynaptic potentials at dendrites of the pyramidal cells** (→ **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, Na^+ enters the cell and thus leaves behind a local negative extracellular potential (→ **A1**). The depolarization promotes an efflux of 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 (→ **A1**; to simplify matters the 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 (→ **A1**). Conversely, activation of specific *thalamocortical fibers* are more likely to lead to positive potentials at the surface (→ **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 usually not strong enough to be registered at the surface of the scalp (→ **A3**).

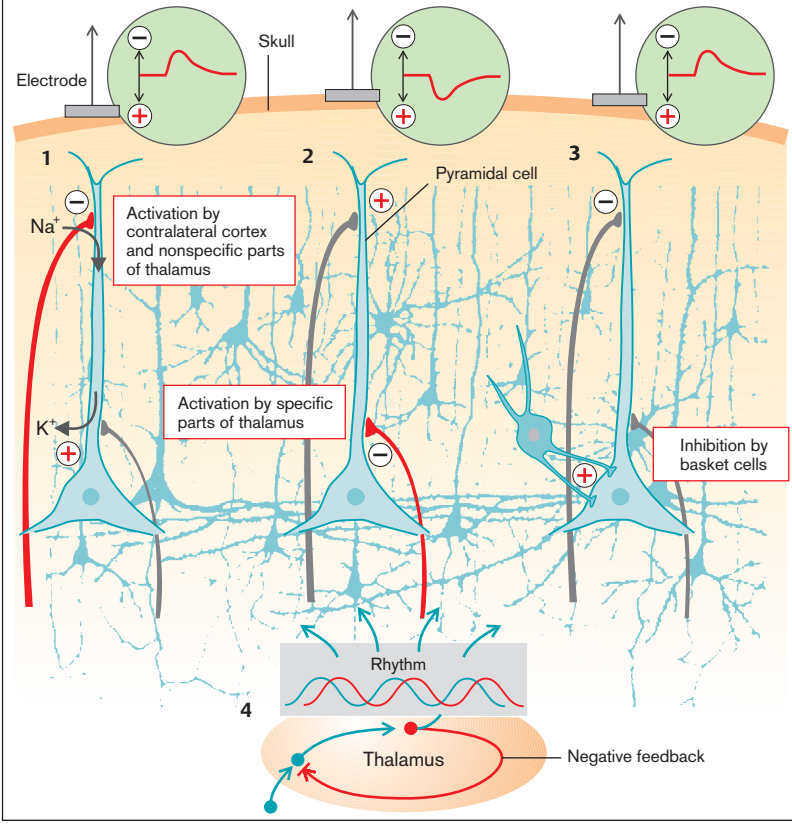
The neurons in the thalamus that excite the cortical pyramidal cells undergo a rhythmical activity due to negative feedback (→ **A4**). This rhythm is transmitted by the thalamocortical tracts to the pyramidal cells, with one thalamic neuron simultaneously exciting several pyramidal cells. Because of 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 (→ **B1**). In adults who are awake with their eyes open it is predominantly β-waves (14 – 30 Hz) that are registered. With their eyes closed the somewhat slower α-waves (8 – 3 Hz) dominate. Yet slower waves such as the Θ-waves (4 – 7 Hz) and the δ-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 (→ p. 362). Some diseases of the brain can result in *slowing* (sleeping-drug overdose, dementia, schizophrenia) or *acceleration* (alcoholism, manic-depressive illness) of the recorded frequency.

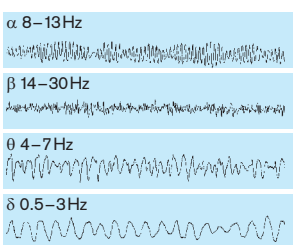
The EEG is of particular importance when diagnosing **epilepsy**, which is characterized by massive synchronized excitation of cortical neurons (→ p. 360). It causes "spike" activity ("seizure spikes"; → **B2**) or "spike and wave" complexes (→ **B3**).

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.

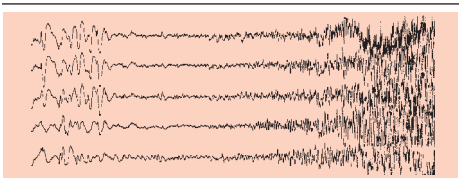
A. Genesis of the EEG



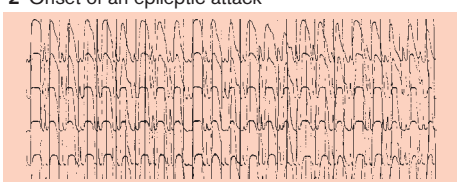
B. Wave Frequency Pattern of EEG



1 Normal EEG frequencies



2 Onset of an epileptic attack



3 Rhythmic spike-wave complexes in absences

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 (e.g., paresthesia, lightening, hallucinations, vertigo), autonomic (e.g., salivation, sweating, vasodilation, piloerection), or complex cognitive or emotional (e.g., anxiety, déjà vu, micropsy) functions (→ **A**).

The epileptic seizures can occur locally (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 does not necessarily lose consciousness unless the seizures spread to the other side of the body (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 Ca^{2+} channels (→ **A 1**). The entering Ca^{2+} opens Na^+ channels and thus causes massive depolarization, which is terminated by activation of GABA receptors and opening of the Ca^{2+}-activated K^+ and Cl^- channels. Moreover, the propagation of Ca^{2+} waves via gap junctions of glial cells contributes to epilepsy. An epileptic seizure occurs when a sufficient number of neurons has been excited. Causes or factors which favor epilepsy are, for example, genetic defects (e.g., K^+ channels [KCNQ2, KCNQ3], Na^+ channels [SCN1A, SCN2A, SCN1B], T-type Ca^{2+} channels, Cl^- channels [CLCN2], hyperpolarization- and nucleotide-regulated channels [HCN], GABA receptors [GABRA1, GABRG2], cholinergic receptors [CHRNA4, CHRNB2] and signaling molecules [phosphatase Laforin EPM2A, protease inhibitor cystatin CSTB, microtubuli-binding double cortin, leucine rich, glioma inactivated gene *LGI1*]), malformation of the brain, trauma to the brain (glial scars), tumor, bleeding, or abscesses, poisoning (e.g., alcohol), infections, inflammation, fever (particularly children), cell swelling or (less likely) shrinkage, hypoglycemia, hypomagnesemia, hypocalcemia, uremia, liver insufficiency, 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 trigger seizures. The incidence of epileptic seizures may increase or decrease in pregnancy.

Neuronal excitation or the spread of excitation to neighboring neurons is promoted by a number of **cellular mechanisms**:

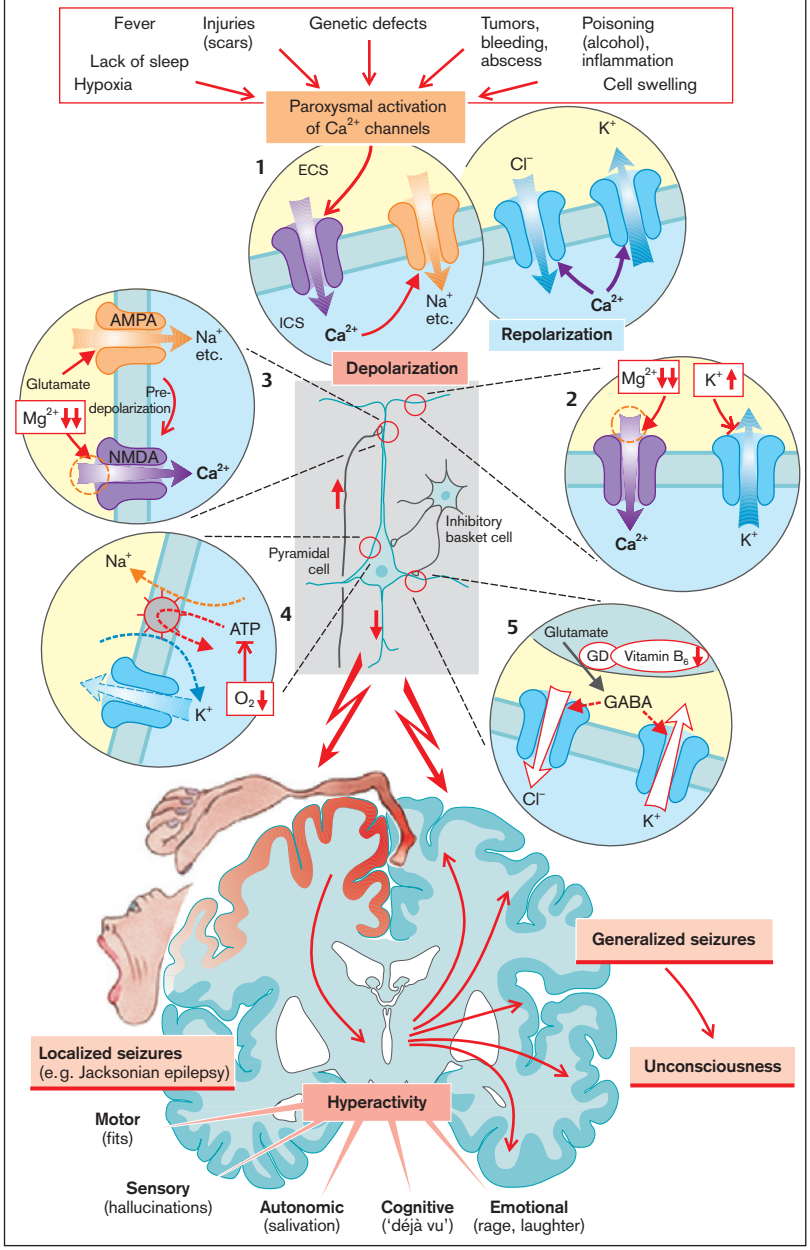
The dendrites of the pyramidal cells contain voltage-gated **Ca^{2+} channels** that open on depolarization and thus increase depolarization. In *lesions* of neurons more of these Ca^{2+} channels are expressed. They are inhibited by **Mg^{2+}**, while *hypomagnesemia* promotes the activity of these channels (→ **A 2**). An increased extracellular *concentration of K^+* reduces K^+ efflux through the K^+ channels, leading to depolarization and activation of Ca^{2+} channels.

The dendrites of pyramidal cells are also depolarized by **glutamate** from excitatory synapses (→ **A 3**). Glutamate acts on a cation channel that is impermeable to Ca^{2+} (AMPA channel) and one that is permeable to Ca^{2+} (NMDA channel). The NMDA channel is normally blocked by Mg^{2+}. However, the depolarization that is triggered by activation of the AMPA channel abolishes the Mg^{2+} block (co-operation of the two channels). *Mg^{2+} 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** (→ **A 4**). A *lack of available energy* (e.g., due to O_2 deficiency or hypoglycemia) impairs Na^+/K^+-ATPase and thus promotes depolarization of the cell.

Normally depolarizations are reduced by inhibitory neurons that may activate K^+ and/or Cl^- channels via **GABA** (→ **A 5**). GABA is formed by glutamate decarboxylase (GD), an enzyme that needs pyridoxine (vitamin B_6) as co-factor. *Vitamin B_6 deficiency* or a reduced affinity of the enzyme for vitamin B_6 (genetic defect) favors the occurrence of epilepsy. *Hyperpolarization of thalamic neurons* may sensitize T-type Ca^{2+} channels, thereby promoting the onset of absences.

A. Epilepsy



Sleep Disorders

Normal sleep requires the interplay of several cerebral structures, among them serotoninergic neurons in the raphe nucleus, cholinergic neurons in the pons, and GABAergic and galaninergic neurons in the ventrolateral preoptic nucleus. A lesion 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 the central rhythm generator, the **suprachiasmatic nucleus** (**SCN**) the transcription factors Clock and Cycle stimulate the expression of period and cryptochrome. The two proteins combine with tau to form a complex, which inhibits the expression of period and cryptochrome. The negative feedback triggers the rhythm. Exposure of the retina to light leads to activation of glutamate receptors with subsequent stimulation of the expression of period and cryptochrome. In this way the rhythm is adapted to the dark/light cycle. A mutation of period-2 shortens the rhythm and leads to early onset of sleep and arousal (advanced sleep phase syndrome). Destruction of the NSC 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. Degeneration of the anterior and dorsomedial thalamic nuclei is followed by complete insomnia. Desynchronization between subcortical activity and cortical sleep may be the cause of **sleepwalking** (somnambulism). A decreased hypothalamic formation of the peptide hypocretin (orexin) results in narcolepsy, a disorder with involuntary falling asleep and loss of muscle tone in the daytime.

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 "**sleep pressure**" (NREM sleep pressure or slow wave sleep [SWS]; → **C 1**) is generated, which declines during sleep. 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.

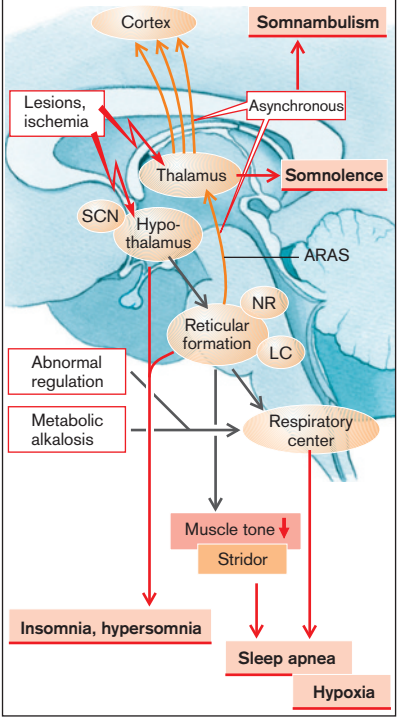
Following a change of time zone (**jet lag**; → **C 2**) or **shift work**, the circadian rhythm at first continues to oscillate in the original phase. When the day is shortened, it is impossible to go to sleep at the local time because of the low net sleep pressure. When the day gets longer, the sleep pressure is increased by the longer waking period and falling asleep at the local time is no problem. The circadian rhythm, however, causes early awakening.

Falling asleep is also disturbed by **delayed sleep phase insomnia** (→ **C 3**), caused by a too long inflexible circadian rhythm. 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.

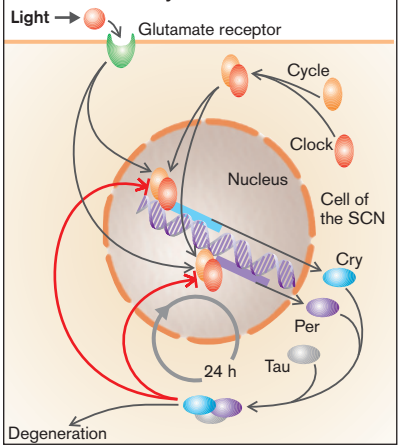
Depression (→ **C 4**) possibly reduces through a lack of serotonin (→ p. 372) the net sleep pressure (red line) and thus causes difficulty in falling asleep. The sleep pressure can be increased by sleep deprivation the next day, and thus normal sleep can be achieved.

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.

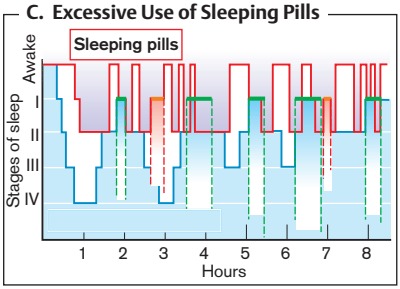
A. Disorders of Sleep Regulation



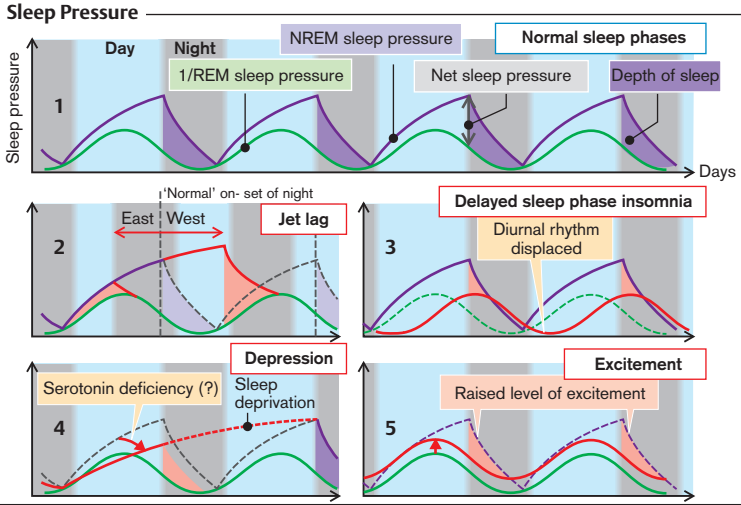
B. Circadian Rhythm



C. Excessive Use of Sleeping Pills



D. Sleep Pressure



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. 368). 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**).

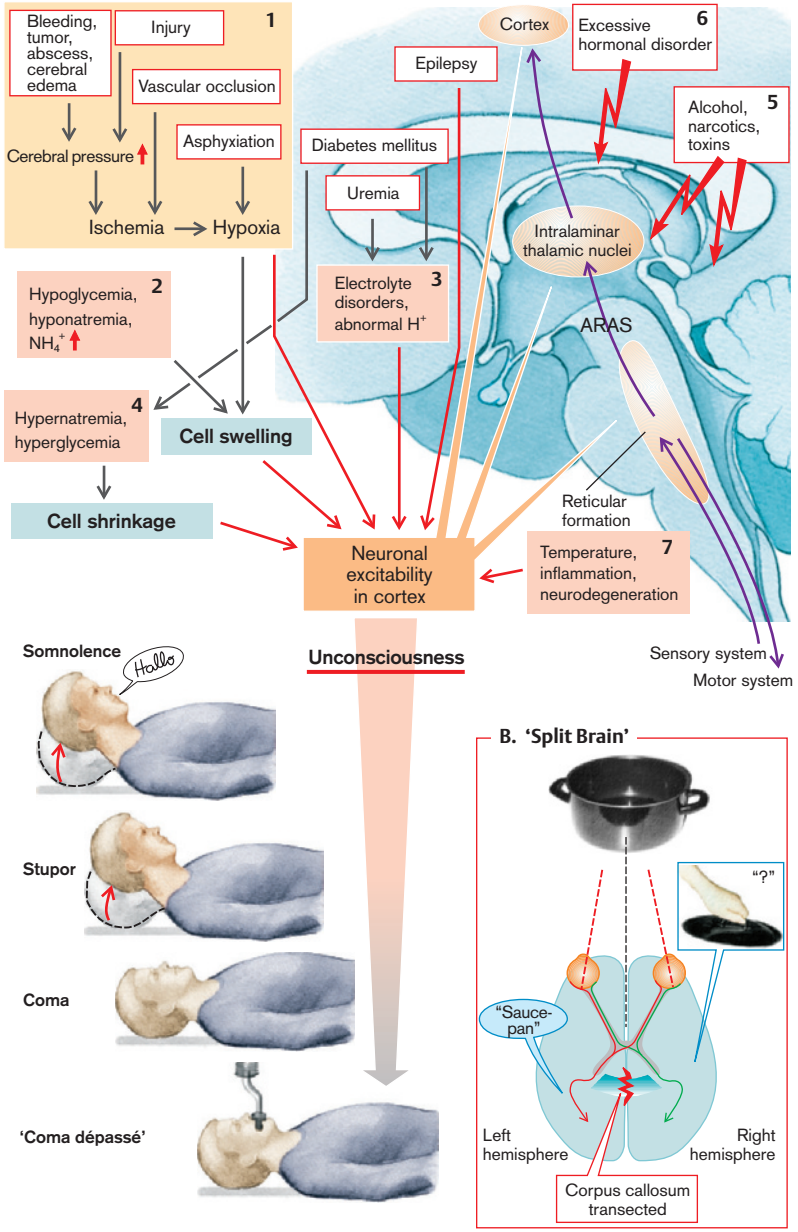
Damage to large areas of the cortex and/or breakdown of the ARAS brings about **loss of consciousness**. In addition, there may be primary causes influencing neuronal excitability in the above-mentioned neuronal structures. Ischemia (e.g., atherosclerotic vascular occlusion) or hypoxia (e.g., suffocation) (→ **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 (NH_4^+) also act via this mechanism. The rise in NH_4^+ in hepatic encephalopathy (→ p. 188) 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. 360), hyperosmolarity (hypernatremia, hyperglycemia; → **A3**) as well as by disorders of electrolyte (Ca^{2+}, Mg^{2+}, HPO_4^{2-}) 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) and heavy metals. Extreme excess or lack of hormones (e.g., T_3, T_4, parathyroid hormone, adrenocorticoid hormones, pheochromocytoma) as well as massive neuronal excitation, for example, caused by pain or psychogenic disease (schizophrenia), can similarly lead to loss of consciousness (→ **A6**). Lastly, neuronal excitability can also be so severely impaired by hypothermia, inflammatory (e.g., meningitis) or mechanical damage, and neurodegenerative disease with resulting 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



B. 'Split Brain'

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 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 premotor 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.

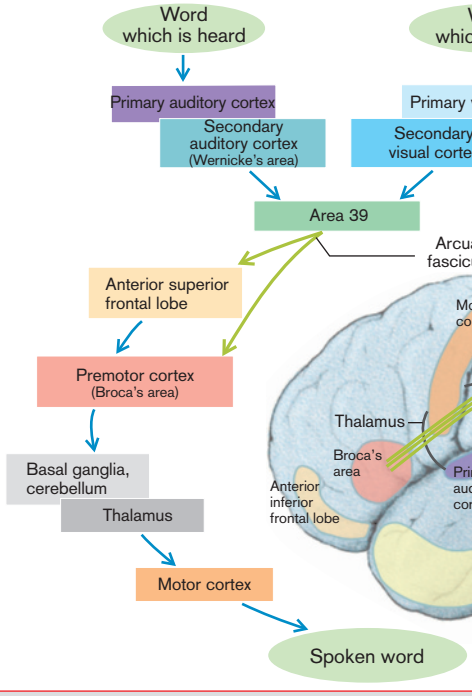
Anomic aphasia is the result of a lesion in the temporal lobe in the region of the medial and inferior gyri. Patients' speech is largely normal but it is difficult for them to find the right word for certain objects. In **achromatic aphasia** (lesion at the left inferior temporal lobe close to temporal-occipital 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



Type	Spontaneous speech	Repetition of words	Language comprehension	Finding words
Broca's aphasia	abnormal	abnormal	normal	impaired
Wernicke's aphasia	fluent (at times logorrhea, paraphasia, neologisms)	abnormal	impaired	impaired
Conduction aphasia	fluent, but paraphasic	markedly impaired	normal	abnormal, paraphasic
Global aphasia	abnormal	abnormal	abnormal	abnormal
Anomic aphasia	fluent	normal, but anomic	normal	impaired
Achromatic aphasia	fluent	normal, but anomic	normal	impaired
Motor transcortical aphasia	abnormal	normal	normal	abnormal
Sensory transcortical aphasia	fluent	fluent	abnormal	abnormal
Subcortical aphasia	fluent	normal	abnormal (transient)	abnormal (transient)

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* (→ **A 3**) does not require conscious activation for storage and recall. It is required, e.g. for learning to play the piano.

To form **declarative memory** (→ **A 1**) 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 (→ **A 2**). Such rehearsal is not an essential precondition for the formation of long-term memory, however. The most important hippocampal transmitter is **glutamate** (NMDA receptors). Memory consolidation is supported by **epinephrine** and **acetylcholine** (nicotinic receptors). Survival of the neurons involved is maintained by neurotrophines. Eventually, memory consolidation requires an altered influence of the involved synapses.

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. 370), trauma, ischemia, alcohol, carbon monoxide, and inflammation. In addition, memory formation can be temporarily stopped by electric shock.

Lesions in the hippocampus or its connections result in **anterograde amnesia** (→ **A 2**). 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.

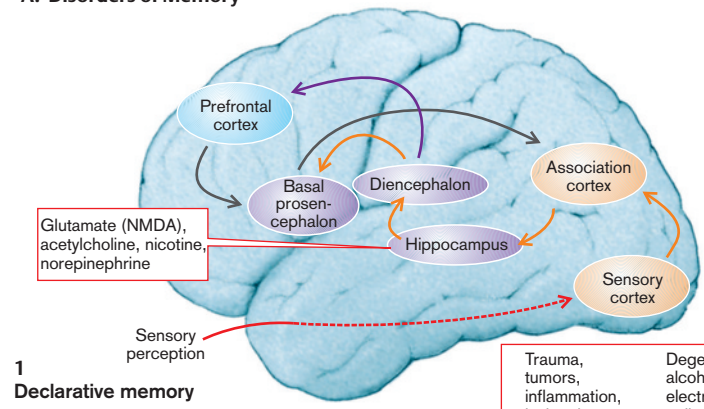
Retrograde amnesia (→ **A 2**), i.e., the loss of already stored information, occurs in disorders in the relevant associative cortical fields. Depending on the extent and localization of the disorder, the loss can be reversible or irreversible. In the former case the patient will lose items of memory, but they can be retrieved. In irreversible loss the particular items are permanently lost.

A lesion of the dorsomedial thalamic nucleus results in loss of episodic memory. 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.

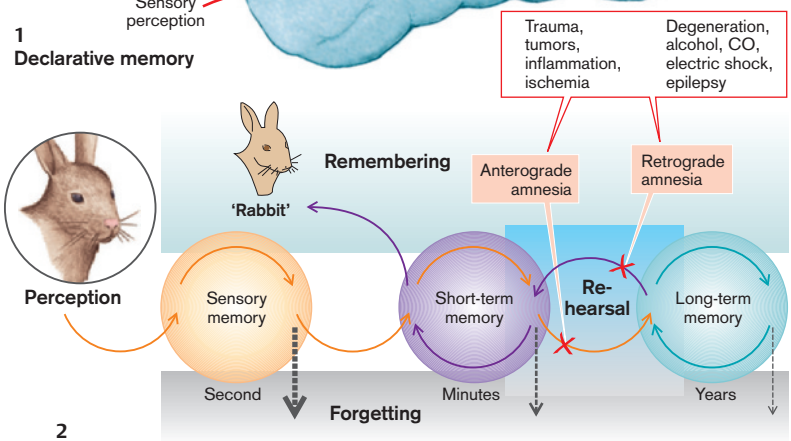
The **procedural** (**implicit**) **memory** (→ **A 3**) is not impaired in lesions of the hippocampus. It allows imprinting, learning of skills, sensitization, habituation, and conditioning. Depending on the task, cerebellum, basal ganglia, amygdala and cortical areas are involved. Both the cerebellum 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 are important in conditioning **anxiety reactions**. They receive their information from the cortex and thalamus and influence 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**).

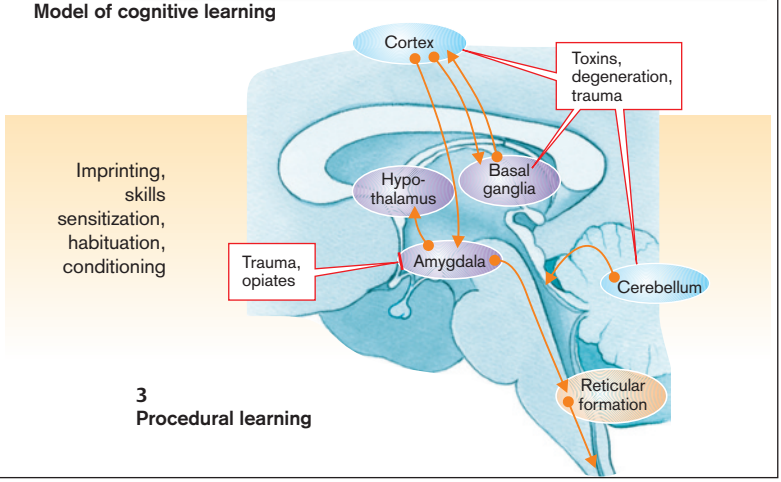
A. Disorders of Memory



1
Declarative memory



2
Model of cognitive learning



3
Procedural learning

Alzheimer's Disease, Dementia

The occurrence of Alzheimer's disease, the most common cause of (senile) dementia (about 70%), is favored by a **genetic disposition**. In some patients, on chromosome 21 a genetic defect of the protein **β-amyloid precursor** is found that can be broken down to amyloid peptides of 42 amino acids. These can bunch themselves together into protein fibrils 7–10 nm long (→ **A1**). Together with ApoE4, proteoglycans and α_1-antichymotrypsin these amyloid fibrils can then form aggregates, 10 µm to several hundred µm in diameter (**senile plaques**), which are frequently found in the brain of patients with Alzheimer's disease (→ **A2**). In addition, these plaques contain distorted dendrites and axons with abnormal intracellular neurofibrils. Phosphorylation of the ApoE-binding cytoskeletal protein tau by the glycogen synthase kinase (GSK) 3 stimulates the formation of neurofibrills. GSK3 and thus neuronal cell death is inhibited by neurotrophins (NGF, BDNF), which signal through PKB/Akt (→ p. 10). Another disease with deposition of amyloids is Down's syndrome (trisomy 21), which is similarly associated with dementia. Causes include the enhanced formation of β-amyloid precursor. A number of further genetic defects (e.g., ApoE, presenilin 1 and 2) and the influence of external factors may result in the formation and deposition of amyloid. Presumably toxins may enter the brain via olfactory nerves and trigger the disease.

β-amyloid peptides can react with receptors at the cell surface, such as the **receptor for advanced glycation end products** (**RAGE**), and a **scavenger receptor** (**RA**). In the following oxygen radicals are formed, which may increase the neuronal intracellular concentration of Ca^{2+} (→ **A3**), possibly via depolarization of the cell membrane and activation of NMDA receptors. The O_2 radicals and Ca^{2+} 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.

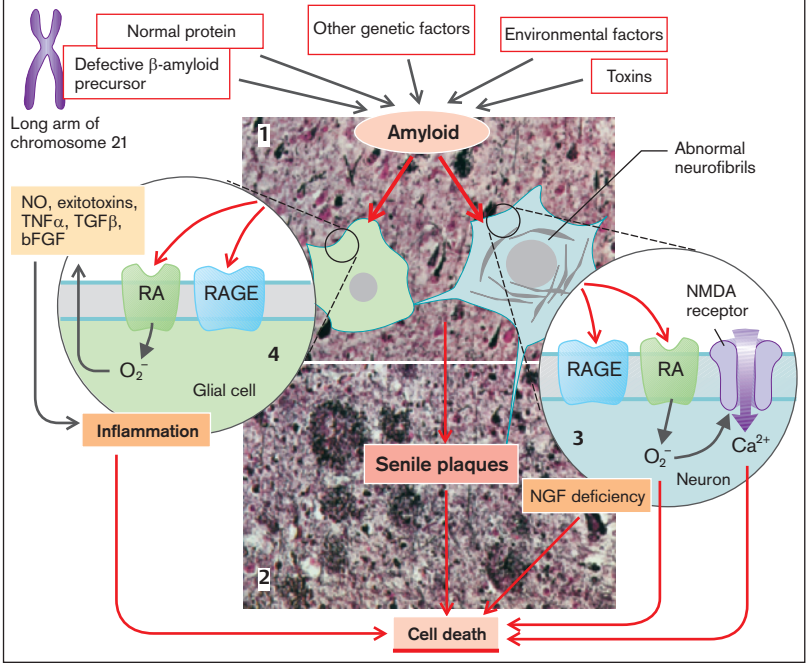
Cholinergic neurons in the basal nucleus of Meynert, in the **hippocampus** (especially CA1, the subiculum) and in the entorhinal cortex (→ **B1**) are particularly affected by cell death, but neurons also die in other cerebral areas, such as the frontal lobes, anterior temporal lobes, parietal lobes, 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] corticoliberin).

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. 368) 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.

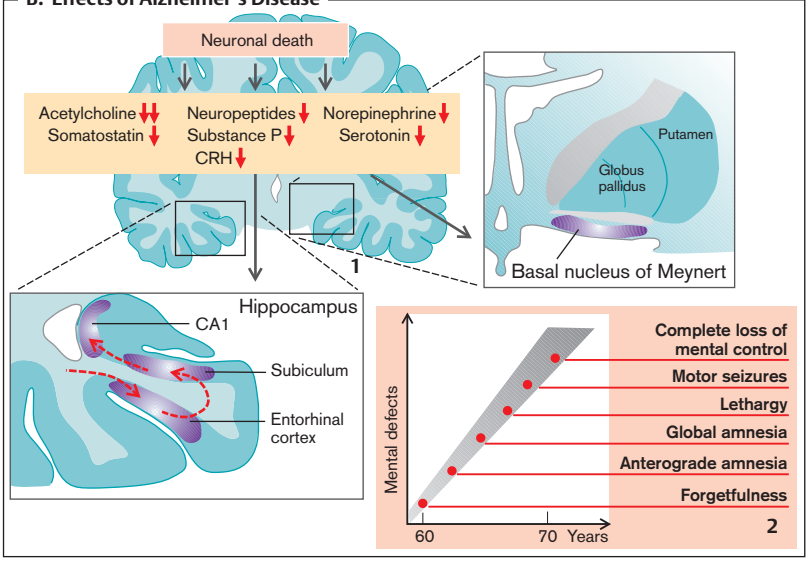
Further diseases resulting in dementia include recurrent periods of ischemia (vascular dementia, → p. 382), alcoholism (→ p. 368), Parkinson's disease (→ p. 334), Huntington's chorea (→ p. 336), frontotemporal dementia (aggregations of mutated tau), dementia with Lewy bodies (aggregation of α-synuclein), CADASIL (*cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy* caused by mutations of notch3), vitamin B_1 deficiency (Wernicke's encephalopathy), schizophrenia (→ p. 374), and infections with viruses (e.g., HIV), bacteria (e.g., syphilis) or prions (Creutzfeldt–Jakob disease).

A. Causes of Alzheimer's Disease



Photos: Doerr W. et al.. Atlas der pathologischen Anatomie. Stuttgart: Thieme; 1975.

B. Effects of Alzheimer's Disease



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*). Pathophysiologically, depression is thought to be connected with decreased (relative or absolute) availability of serotonin and/or norepinephrine in the brain.

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 (→ **B 1**) favors development of depression: (1) in genetic gene variants of the serotonin transporter (5-HTT); (2) by *inhibiting synthesis* from tryptophan (e.g., chlorophenylalanine); (3) by *inhibiting uptake* in presynaptic stores (e.g., reserpine); (4) 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** (→ **B 2**):

◆ *Availability of tryptophan* can be increased by administering glucose, promoting insulin release. 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. The presynaptic reuptake of serotonin and epinephrine can be inhibited by serotonin-epinephrine reuptake inhibitors (SNRI), which increase their synaptic concentration.

◆ Tricyclic antidepressants (e.g., imipramine, fluoxetine) similarly inhibit the *re-uptake* of serotonin in presynaptic stores, exert in addition antihistaminergic and anticholinergic effects, and thus have significantly more side effects.

◆ MAO-A inhibitors (see above) raise the availability of serotonin by *inhibiting its breakdown*.

◆ Exposure to light *inhibits the conversion of serotonin to melatonin*. Depression is particularly frequent in northern countries with short dark days during winter. Conversely, depression can sometimes be succesfully treated by exposure to bright light (phototherapy).

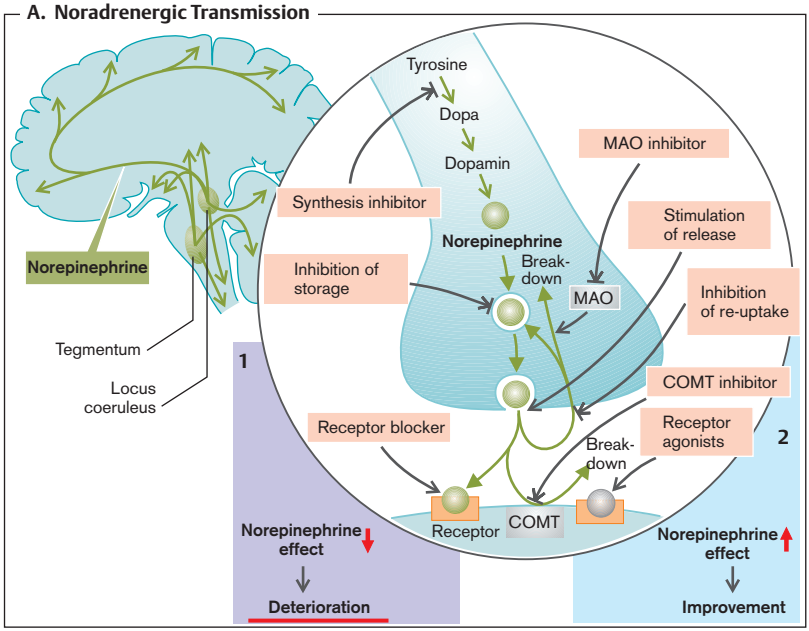
◆ Agonists (e.g., lysergic acid diethylamide [LSD]) can directly *stimulate serotonin receptors*.

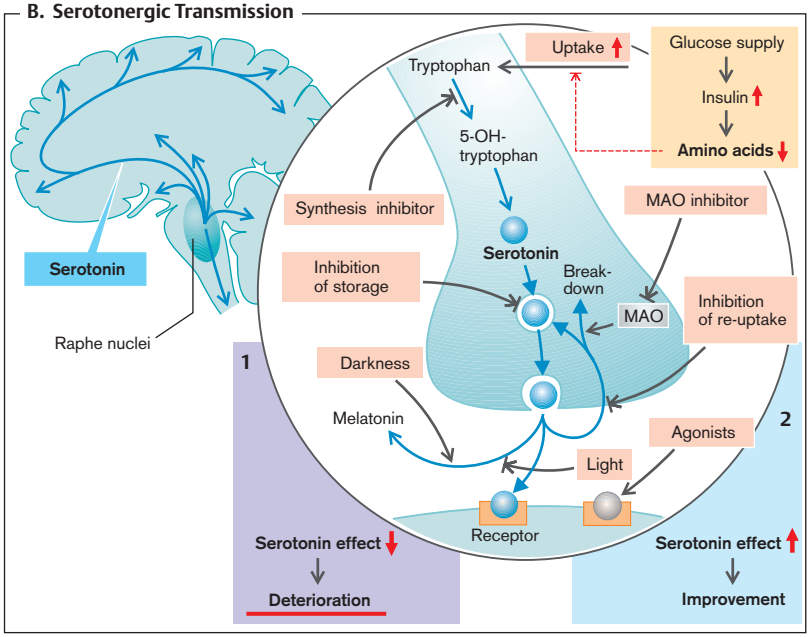
Norepinephrine is formed in neurons of the locus ceruleus and the tegmentum (→ **A**). Axons from the tegmentum predominantly connect with the hypothalamus, anterior pituitary, brain stem, and spinal cord. Fibers from the locus ceruleus project to the spinal cord, hypothalamus, thalamus, limbic system, and cortex.

The release and action of norepinephrine at the nerve endings may be reduced in depressive patients by a decreased number of noradrenergic neurons in the locus ceruleus. It can further be **reduced** by a number of substances, leading to depression (→ **A 1**): 1. The *synthesis of norepinephrine* from tyrosine via DOPA can be reduced by enzyme inhibitors (e.g., methyltyrosine). 2. The *uptake of norepinephrine in presynaptic stores* can be inhibited (e.g., by reserpine). 3. Norepinephrine can be *displaced at the postsynaptic receptors* (e.g., phenoxybenzamine, phentolamine).

The synaptic norepinephrine concentration and action can, however, be **increased,** an effect that is in part utilized in the drug treatment of depression (→ **A 2**). 1. 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. 2. Inhibitory substances of catechol-ortho-methyl-transferase ([COMT] e.g., tropolone) delay the *breakdown of norepinephrine*. 3. Amphetamines increase synaptic concentrations of norepinephrine, dopamine, and serotonin by inhibiting transport. 4. Desipramine inhibits *re-uptake*, and thus similarly increases the synaptic norepinephrine concentration.

The mania in bipolar disorders is fostered by activation of the glycogen synthase kinase 3 (GSK3). The enzyme is inhibited by lithium, which is therapeutically used in bipolar disorders. The brain-derived neurotrophic factor (BDNF) inhibits GSK3 via PKB/Akt (→ p. 6). The BDNF expression is stimulated by CREB, the cerebral concentration of which is decreased in depression. Depression or bipolar disorders may further by paralleled by decreased efficacy of thyrotropin-releasing hormone (TRH), excess of corticotropin-releasing hormone (CRH) and cortisol, as well as excessive release of inflammatory mediators.





Schizophrenia

Schizophrenia is a disease with an increased familial incidence. It is characterized by delusions, hallucinations, disorders of self, and formal disorders of thought (*positive symptoms*). Lack of affect and of motivation also frequently occur (*negative symptoms*). In some patients the positive symptoms predominate, in others the negative ones.

In schizophrenia there is **reduced blood flow and glucose uptake especially in the prefrontal cortex**. In addition, abnormal migration of neurons during brain development is of pathophysiological significance (→ **A 2**). The disease may be paralleled by atrophy of cortex, amygdala, hippocampus, prefrontal cortex, and thalamus.

Particularly 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 (→ **A 1**). The glutamatergic transmission is presumably regulated by dysbindin, which is genetically defective in some patients with schizophrenia. In patients with schizophrenia, a genetically caused overactivity of the serine degrading D-aminoxidase (DAAO) leads to lack of serine, a co-agonist of glutamate receptors. Symptoms of schizophrenia can be triggered by pharmacological inhibition of glutamate receptors and ameliorated by activators of glutamate receptors. 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**, which may suppress glutamatergic transmission: excessive availability of dopamine or dopamine agonists can produce symptoms of schizophrenia, and inhibitors of D_2 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 (→ **A 1**), and a reduction of D_1 and D_2 receptors correlates with negative symptoms of schizophrenia, such as lack of affect. It is possible that the reduction in dopamine receptors is the result of an increased dopamine release and in itself has no pathogenetic effect. The dopamine release is stimulated by neuregulin (NRG-1), which is genetically defective in some patients with schizophrenia.

Dopamine serves as a transmitter in several pathways (→ **A 2**):

- 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. 282 ff.).
- It controls motor activity in the *nigrostriatal system* (→ p. 334 ff.).

Release and action of dopamine are increased by several substances that **promote the development of schizophrenia** (→ **A 3**, 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.

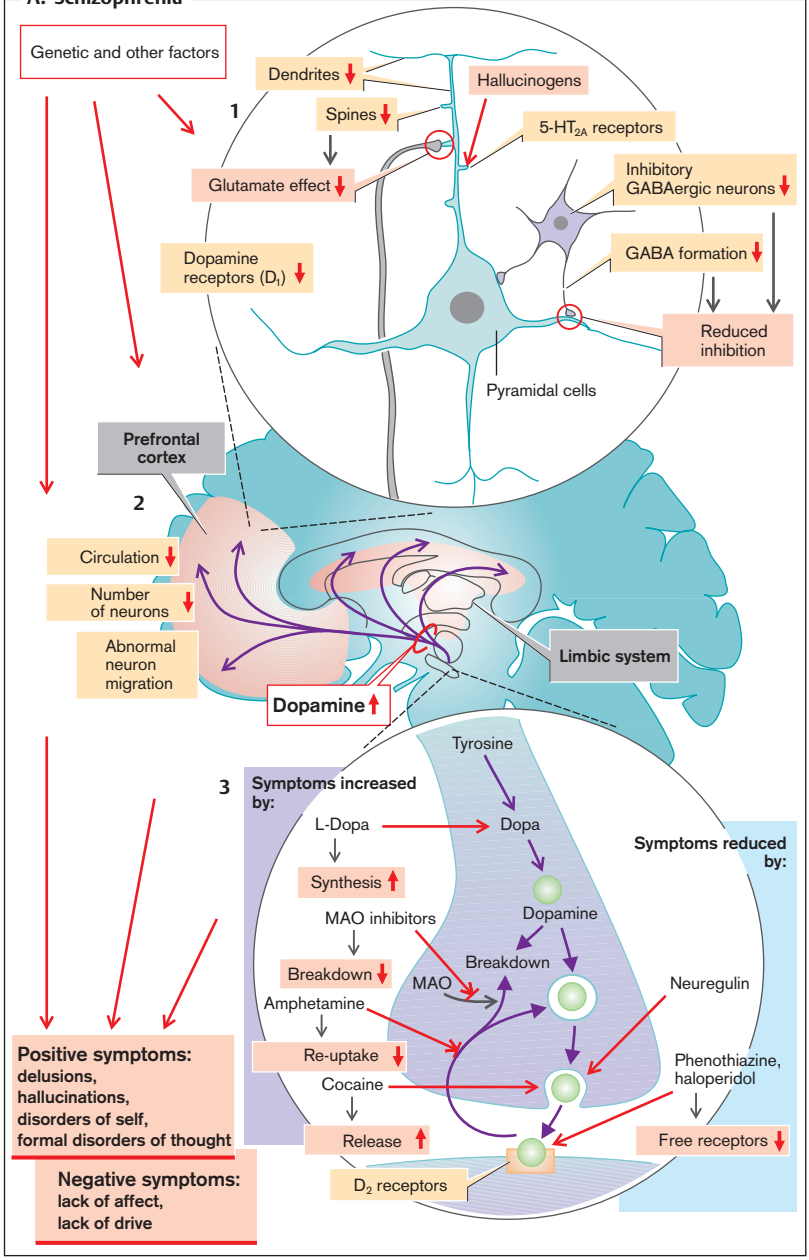
Conversely, antidopaminergic substances can **improve schizophrenia** (→ **A 3**, right):

- Some substances (e.g., phenothiazines, haloperidol) *displace dopamine from receptors* and thus have an antidopaminergic action.

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. 336). 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 (→ **A 1**).

A. Schizophrenia



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.

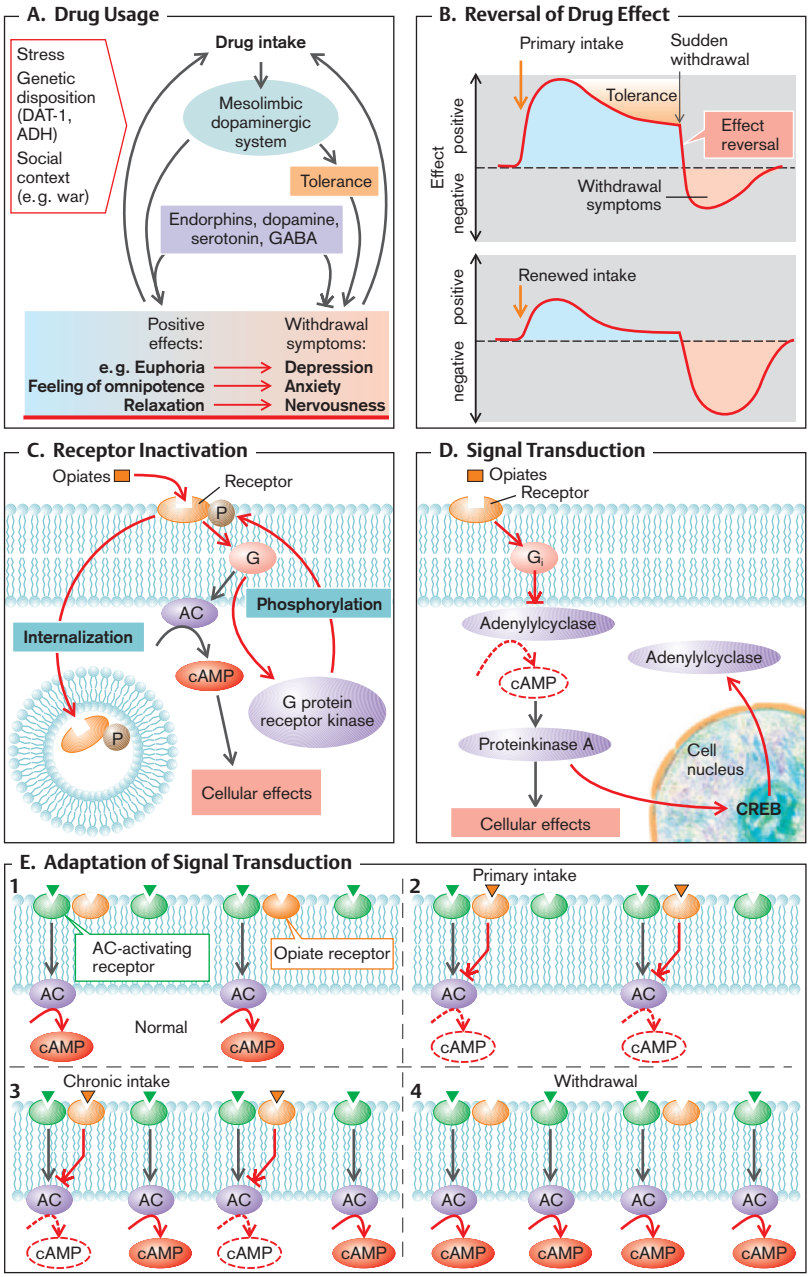
It is not only the supply of the particular drug that is important in the **development of addiction**, as only some of those who take a drug become dependent. Of great significance for the development of addictive behavior is a **genetic disposition** (→ **A**). It has been shown that in those dependent 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, particularly in nucleus accumbens (→ **A**; see also p. 374) 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 adenylylcyclase (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 adenylylcyclase 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.



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 (→ **A 1**) into the third ventricle and from there into the fourth ventricle via the aqueduct (→ **A 2**). It then circulates via the foramina of Luschka and Magendi (→ **A 3**) into the subarachnoid space and the arachnoid villi of the sinuses of the dura mater (Pacchionian bodies) and from there into the venous sinuses (→ **A 4**).

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*) (→ **A 5**). Once the bony sutures have fused, an excess of CSF causes an increased CSF pressure (→ p. 380).

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 Ca^{2+} 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).

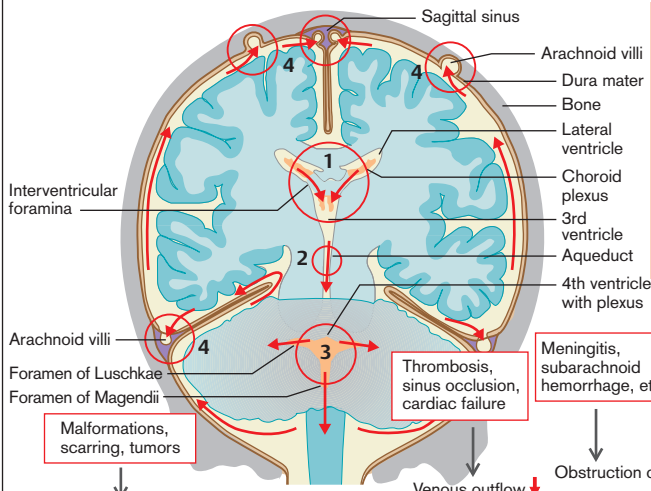
The **glucose concentration in CSF** is decreased by tumors, acute bacterial infections, tuberculosis, fungal infections of the brain as well as defective glucose transport in rare cases.

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.

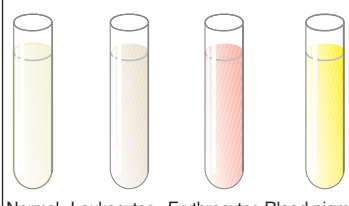
The blood–brain barrier is not yet closed in newborns. As a result, in hyperbilirubinemia of the newborn bilirubin can reach the brain and damage nuclei ("Kerne") in the brain stem (hence **kernicterus**). Damage to the basal ganglia may, for example, cause hyperkinesias (→ p. 336).

The peripheral nerve system is not protected by a blood–brain barrier. Particularly the spinal roots (Guillain–Barré syndrome) and neuromuscular junctions (myasthenia, myasthenic syndrome) are frequent targets of autoimmune disease.

A. Cerebrospinal Fluid (CSF) Flow

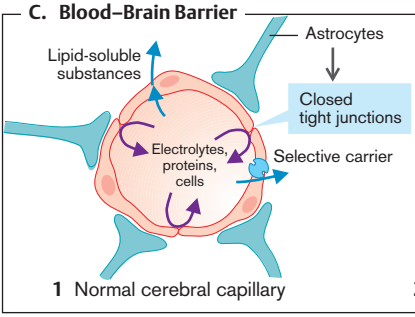


B. CSF Composition



		Serum normal	CSF normal	Abnormal CSF
	Proteins g/L	70	0.2	↑ Infections, CSF obstruction
	Glucose	5	3	↓ Tumors, infection
mmol/L	Na^+	145	150	
mmol/L	K^+	4	3	
mmol/L	Ca^{2+}	2.5	1	↑ Infections, CSF obstruction
mmol/L	Mg^{2+}	0.8	1	
	Osm	295	295	
	pH	7.4	7.33	

C. Blood–Brain Barrier



Cerebrospinal Fluid Pressure, Cerebral Edema

After 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. 12).

Reduction of extracellular osmolarity can also cause cell swelling, for example, in hypotonic hyperhydration (→ p. 132).

Treatment of prolonged hypernatriemia demands caution. The glial cells and neurons compensate for the extracellular hyperosmolarity by intracellular accumulation of osmolytes (e.g., inositol), a process that takes days. If the hypernatremia is corrected too quickly, the osmolytes 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).

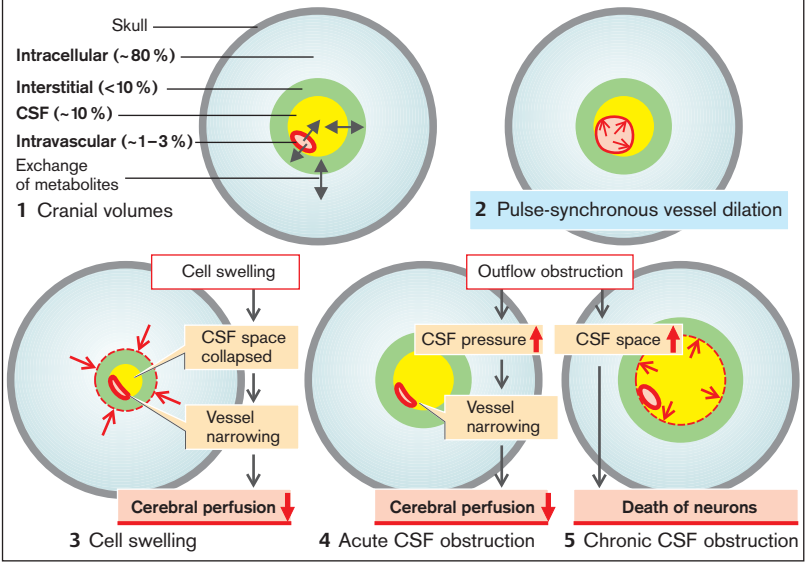
Water can also accumulate in the interstitial space when the blood–brain barrier is intact but the osmolarity of the interstitial space is higher than that of blood, for example, if there is a rapid fall in the concentration of blood sugar (during treatment of diabetes mellitus), of urea (dialysis), 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. 378). 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 (→ **A5**).

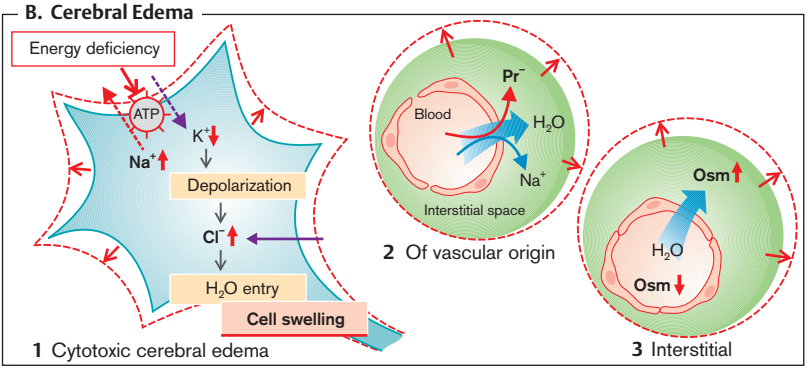
Tumors and **bleeding** (→ **A3**) take up intracranial volume at the expense of other compartments, especially the CSF space.

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. 382).

A. Volume Changes of Brain Compartments



B. Cerebral Edema



C. Effects of Increased Intracranial Pressure

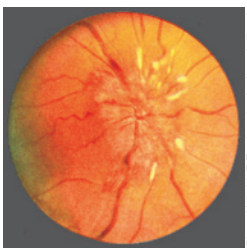
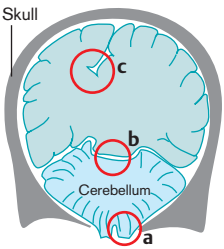


Photo: Hollwich F. Taschenatlas der Augenheilkunde. 3rd ed. Stuttgart: Thieme; 1987

1 Papilledema

Headache
Nausea
Vomiting
Coma
Bradycardia
Hypertension
Squint
Fixed pupils

2 Additional effects



3 Herniation

Disorders of Cerebral Blood Flow, Stroke

Complete cessation of cerebral blood flow causes **loss of consciousness** within 15 – 20 seconds (→ p. 364) and **irreversible brain damage** after 3 – 10 minutes (→ **A 1**). 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, thrombosis, embolism, vasculitis). **Bleeding** (due to trauma, vascular aneurysm, hypertension; → p. 222) also causes ischemia by compressing neighboring vessels.

By inhibiting Na^+/K^+-ATPase, energy deficiency causes the cellular accumulation of Na^+ and Ca^{2+} 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. 12). It also promotes the release of glutamate, which accelerates cell death via the entry of Na^+ and Ca^{2+}. Ca^{2+} may damage the mitochondria (→ p. 12). Hyperthermia and hyperglycemia accelerate the cell damage. 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 conjugée" 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.

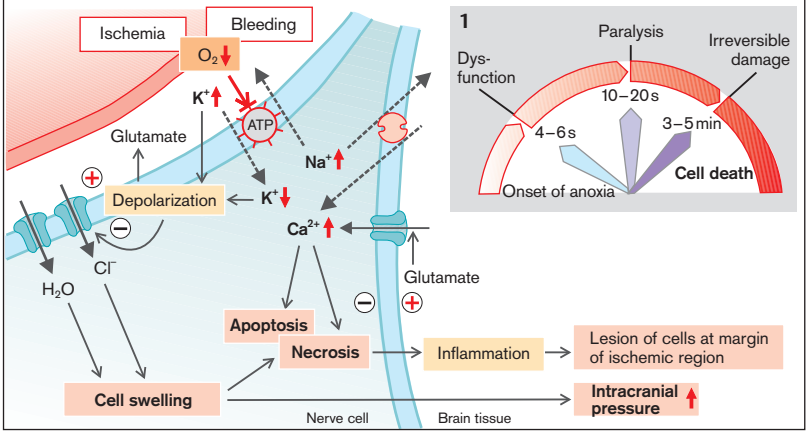
Occlusion of the **posterior cerebral artery** leads to partial *contralateral hemianopsia* (primary visual cortex) and *blindness* in bilateral occlusion. In addition, there will be *memory losses* (lower temporal lobe).

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.

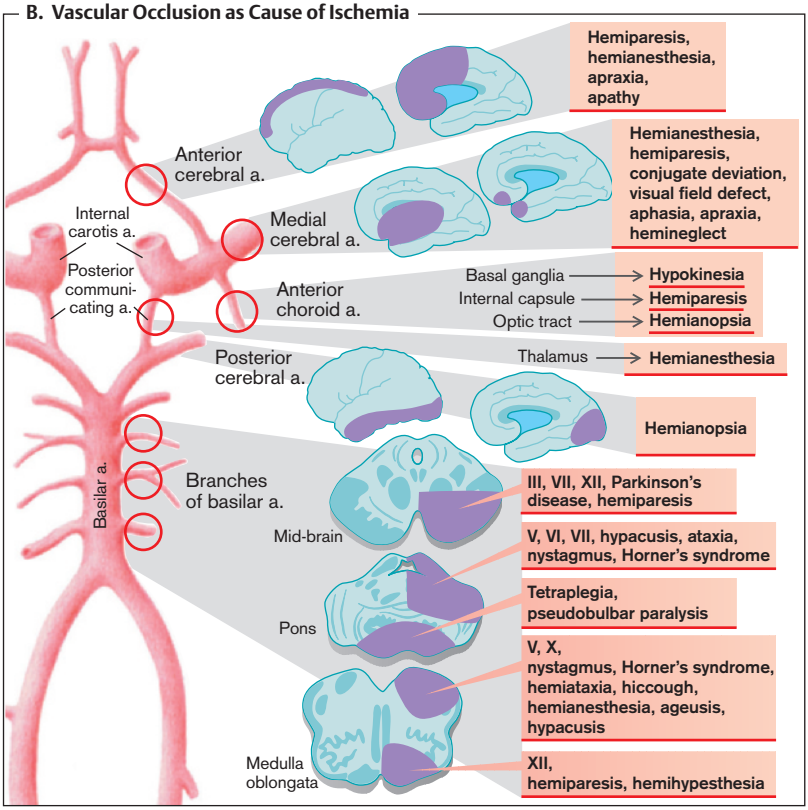
Complete occlusion of the **basilar artery** causes paralysis of all limbs (*tetraplegia*) and of the ocular muscles as well as *coma* (→ p. 364). Occlusion of the **branches of the basilar artery** can cause infarctions in the cerebellum, mesencephalon, pons, and medulla oblongata. The effects depend 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 spinothalamic tract).
- *Hypacusis* (auditory hypesthesia; cochlear nerve), *ageusis* (salivary tract nerve), *singultus* (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



B. Vascular Occlusion as Cause of Ischemia



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