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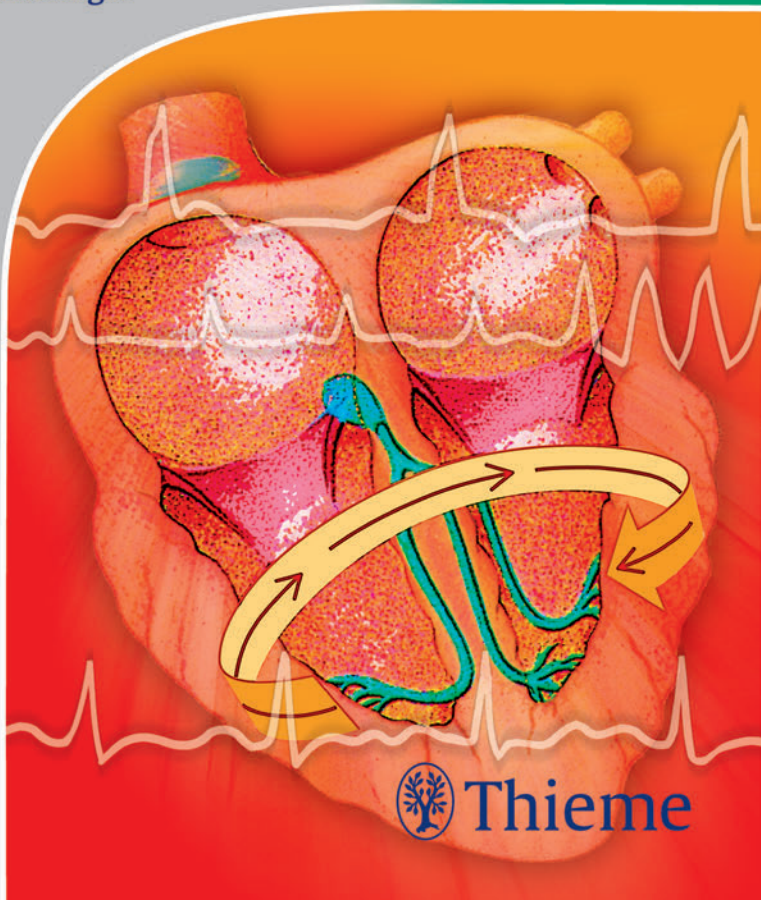
Color Atlas of Pathophysiology

Stefan Silbernagl
Florian Lang

Illustrations by
Ruediger Gay
Astried Rothenburger

basic sciences

3rd Edition



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At a Glance

Color Atlas of Pathophysiology

3rd Edition

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195 color plates by
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Thieme
Stuttgart · New York · Delhi · Rio de Janeiro

Library of Congress Cataloging-in-Publication Data
is available from the publisher

Translator: Geraldine O'Sullivan, Dublin, Ireland

Illustrator: Atelier Gay + Rothenburger,
Sternenfels, Germany

4th German edition 2013
2nd English edition 2010
1st Chinese edition 2012 (Taiwan)
3rd French edition 2015
2nd Czech edition 2012
1st Greek edition 2002
1st Indonesian edition 2007
2nd Japanese edition 2011
1st Korean edition 2013
1st Polish edition 2011
2nd Portuguese edition (in preparation)
1st Romanian edition 2011
1st Russian edition (in preparation)
1st Spanish edition 2010
2nd Turkish edition 2010

Thieme Publishers Stuttgart
Rüdigerstr. 14, 70469 Stuttgart, Germany
+49 [0]711 8931 421
customerservice@thieme.de

Thieme Publishers New York
333 Seventh Avenue, New York,
NY 10001, USA
+1-800-782-3488
customerservice@thieme.com

Thieme Publishers Delhi
A-12, Second Floor, Sector-2, Noida-201301
Uttar Pradesh, India
+91 120 45 56600
customerservice@thieme.in

Thieme Publishers Rio, Thieme Publicações Ltda.
Edifício Rodolpho de Paoli, 25° andar
Av. Nilo Peçanha, 50 – Sala 2508
Rio de Janeiro 20020–906 Brasil
+55 21 3172 2297/+55 21 3172 1896

Cover design: Thieme Publishing Group
Typesetting by Ziegler + Müller,
Kirchentellinsfurt, Germany

Printed in India by Manipal Technologies,
Karnataka

ISBN 9783131165534 5 4 3 2 1

Also available as an e-book:
eISBN 9783131490636

This book is an authorized translation of the
4th German edition published and copyrighted
2013 by Georg Thieme Verlag, Stuttgart, Germany.
Title of the German edition: Taschenatlas
Pathophysiologie

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Preface to the Third 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 growth and cell adaptation as well as disorders of signal transduction, cell death, tumor growth, and aging. It then covers a wide range of pathomechanisms affecting temperatur balance, diseases of the blood, lungs, kidneys, gastrointestinal tract, heart and circulation, metabolism including endocrinal abnormalities, 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 the pathophysiological basis of therapeutic intervention.

The book has met the interest of numerous readers and thus a third 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 third 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. Angelika Findgott, Ms. Annie Hollins, Ms. Joanne Stead, and Mr. Martin Teichmann for their exceptional skill and enthusiasm in editing and producing the 3rd edition of the *Atlas*. Ms. Katharina Völker once again 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
June 2015

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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 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.

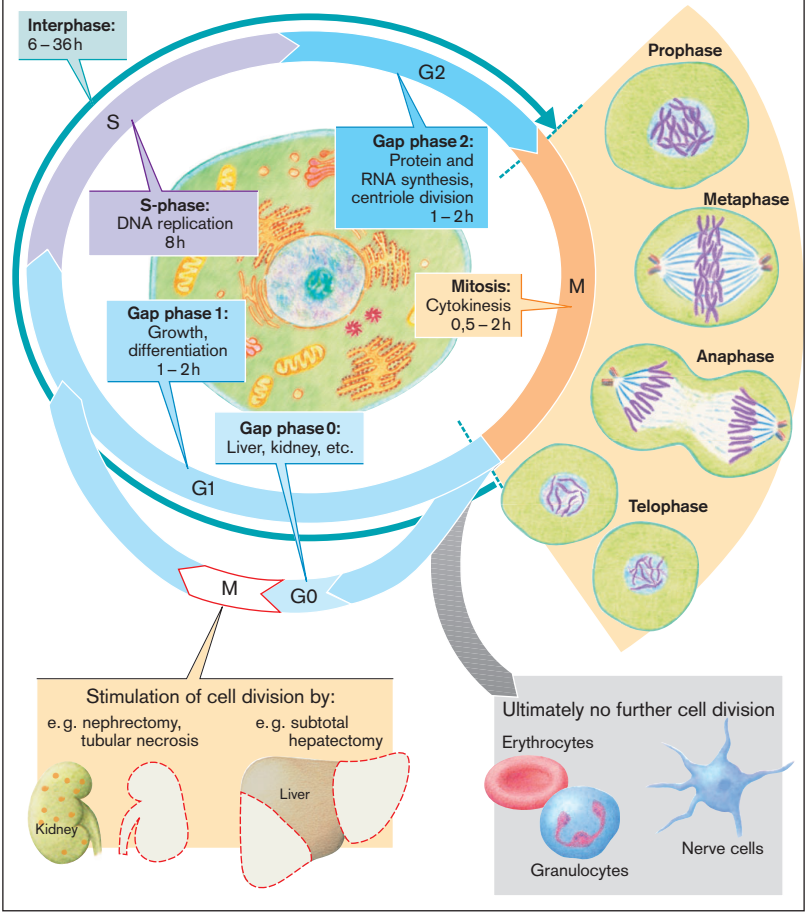
With the exception of the germ cells, whose chromosome set is halved during meiotic division (*meiosis*), most cells divide after the chromosome set has first been replicated, i.e., after **mitosis** (so-called indirect division of the nucleus) followed by division of the cell (*cytokinesis*). In this 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. 30 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*.

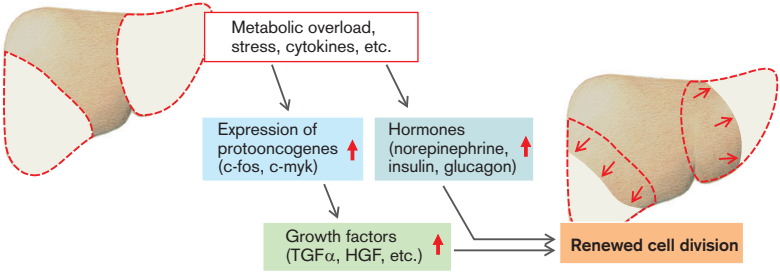
The cells of some organs and tissues do not normally proliferate (see below). Such **stable** or **resting cells** enter a resting phase, the *G_0 phase*, after mitosis. Examples of such cells are the parenchymal cells of the liver, kidneys, and pancreas as well as connective tissue and mesenchymal cells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

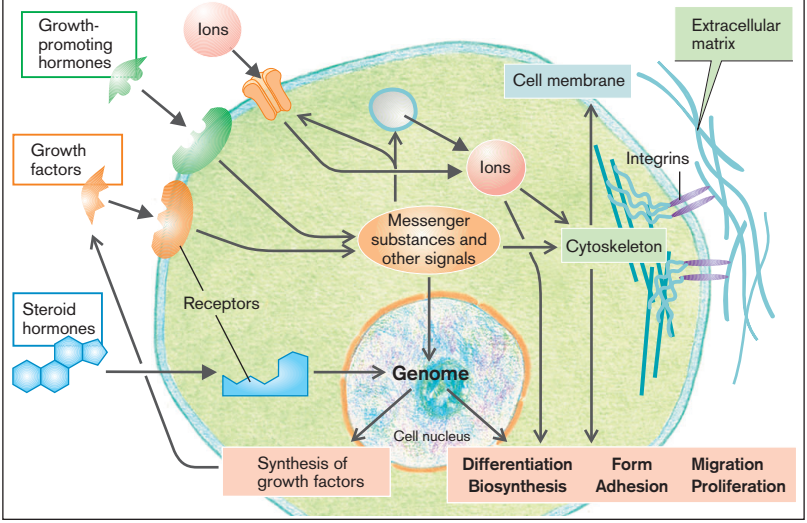
The regeneration of labile and stable cells does not necessarily mean that the original tissue structure is reconstituted. For this to happen, the **extracellular matrix** must be intact, as it serves as the guiding system for the shape, growth, migration, and differentiation of the cell (→ **C**). The 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 glycosaminoglycans. 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).

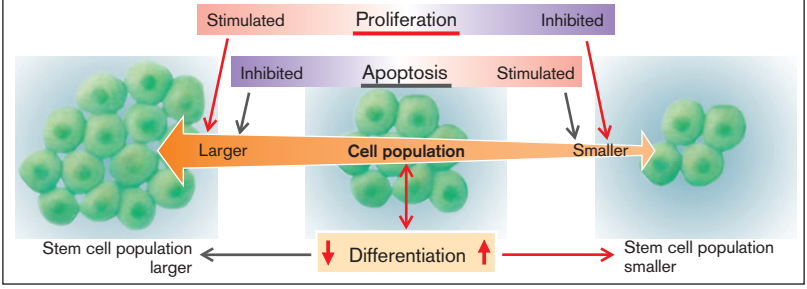
Adaptation to changed physiological or unphysiological demands can be achieved through an increase or decrease in the **number of cells** (*hyperplasia* or *aplasia*; → **D**, **E**). This can be triggered by *hormones* (e.g., development of secondary sex characteristics and growth of mammary epithelium 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 hypertensive people (→ 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. 150 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).

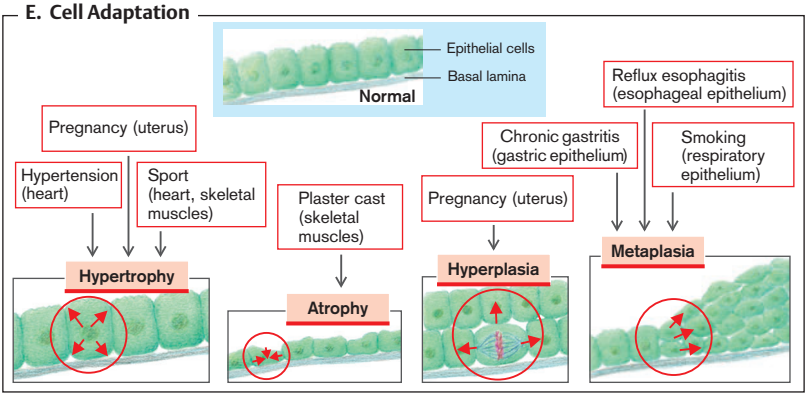
C. Regulation of Cell Proliferation, Motility and Differentiation



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., downregulation 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**) (→ **A 1**). cAMP activates *protein kinase A* (PKA), which phosphorylates and thus influences enzymes, transport molecules, and a variety of other proteins. 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, vasopressin (antidiuretic hormone [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 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 activating 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) are among the substances that act via cGMP.

Other intracellular transmitters are 1,4,5-inositol triphosphate (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 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 also acts 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, triggering 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. Janus kinases (JAK) activate the transcription factor STAT via tyrosine phosphorylation, thereby mediating the effects of interferons, growth hormones, and prolactin. Activin, anti-müllerian hormone, and the transforming growth factor TGF-β 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 the transcription factor NFAT, which, among other actions, promotes 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).

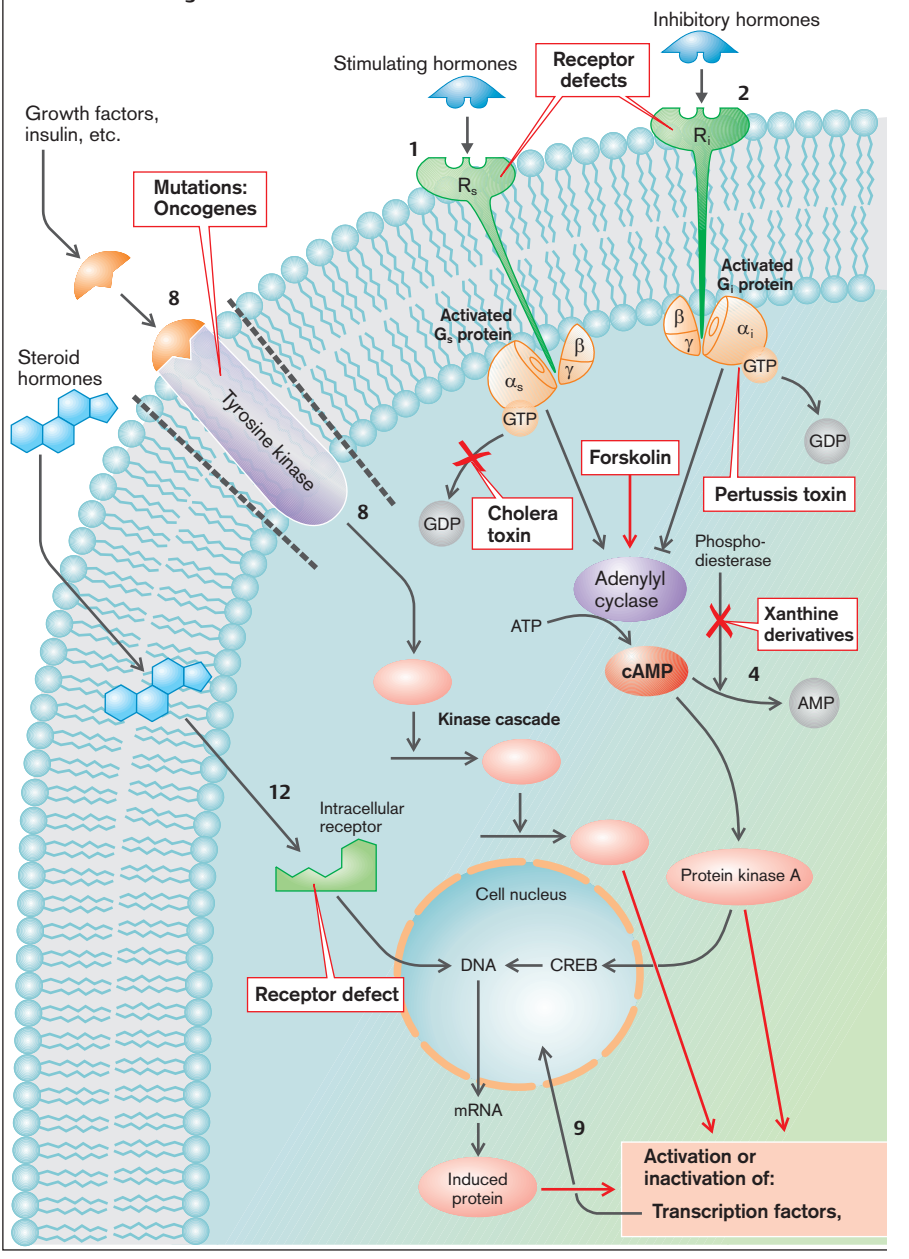
The degradation of proteins is similarly under tight regulation. **Ubiquitin ligases** attach the signal peptide ubiquitin at the respective proteins. Ubiquitinylated proteins are degraded through the proteasome pathway. Regulation of ubiquitin ligases includes phosphorylation.

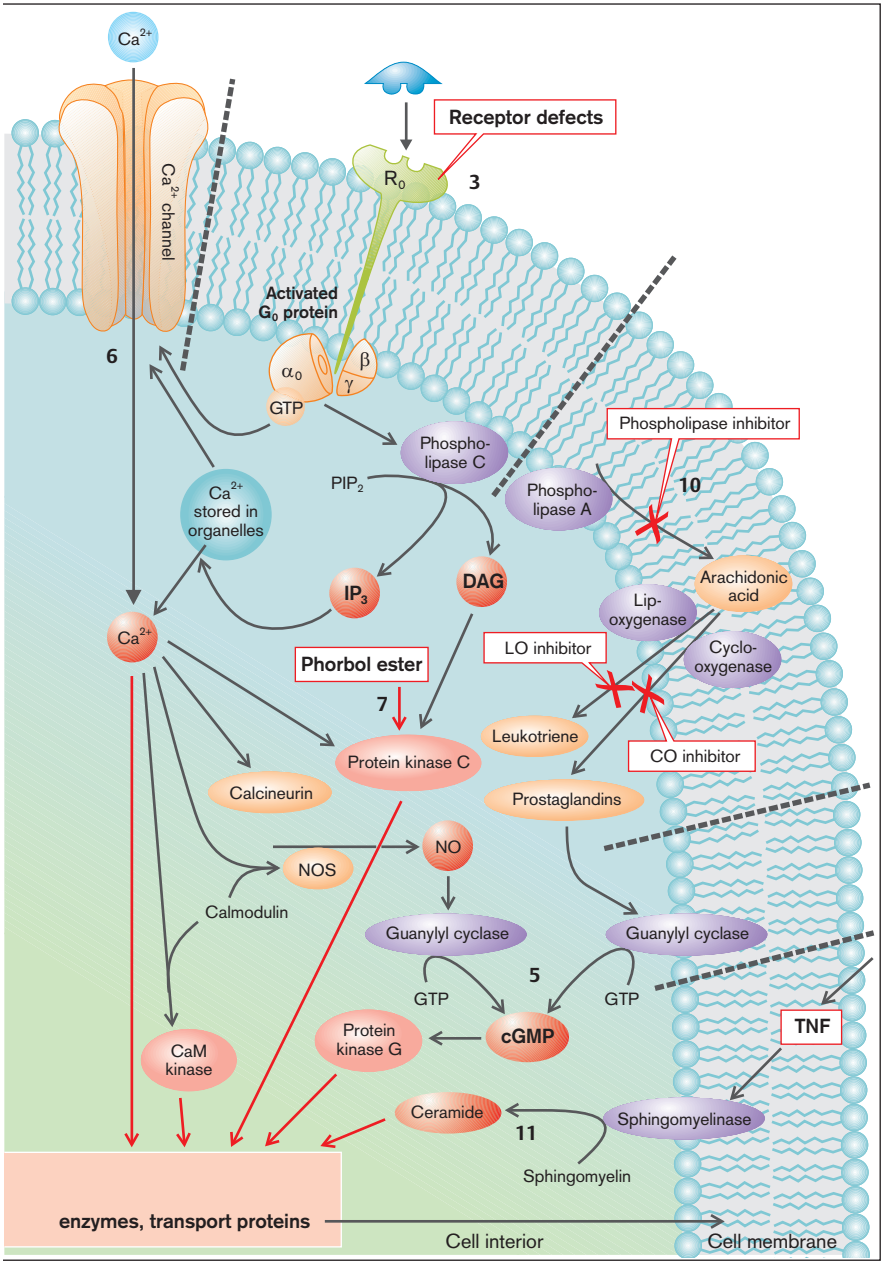
Arachidonic acid, a polyunsaturated fatty acid, can be split from membrane lipids, including DAG, by *phospholipase A* (→ **A 10**). Arachidonic acid itself has some cellular effects (e.g., on ion channels), but through the action of **cyclo-oxygenase** can also be converted to *prostaglandins* and *thromboxane*, 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. 322). **Lipoxygenase inhibitors** and **cyclooxygenase 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 cysteine-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. Hormones can also block transcription. For instance, calcitriol inhibits transcription factor NFκB (p. 10) through the vitamin D receptor (VDR).

A. Intracellular Signal Transmission and Possible Disorders




Ca2+
Ca2+ channel
Receptor defects
R0
3
Activated G0 protein
α0
β
γ
GTP
6
Phospho-lipase C
PIP2
Phospho-lipase A
Phospholipase inhibitor
10
Ca2+ stored in organelles
IP3
DAG
Arachidonic acid
Lip-oxygenase
Cyclo-oxygenase
LO inhibitor
CO inhibitor
Ca2+
Phorbol ester
7
Leukotriene
Protein kinase C
Calcineurin
Prostaglandins
NO
NOS
Calmodulin
Guanylyl cyclase
Guanylyl cyclase
5
GTP
GTP
cGMP
Protein kinase G
CaM kinase
TNF
Ceramide
11
Sphingomyelinase
Sphingomyelin
enzymes, transport proteins
Cell interior
Cell membrane

PI3-Kinase-Dependent Signal Transduction

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-triphosphate), which is anchored in the cell membrane. $PI_{3,4,5}P_3$ binds to PDK1 (phosphoinositide-dependent kinase 1) and protein kinase B (PKB/Akt). PDK1 then phosphorylates and thus activates PKB/Akt (→ **A2**). It is inhibited by calcitriol (p. 7).

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 IκB kinase (IKK) leading to its ubiquitinylation and degradation. In the absence of IκB, NFκB travels into the nucleus and stimulates gene expression. Functions stimulated by NFκB include the synthesis of extracellular matrix proteins favoring 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 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**).

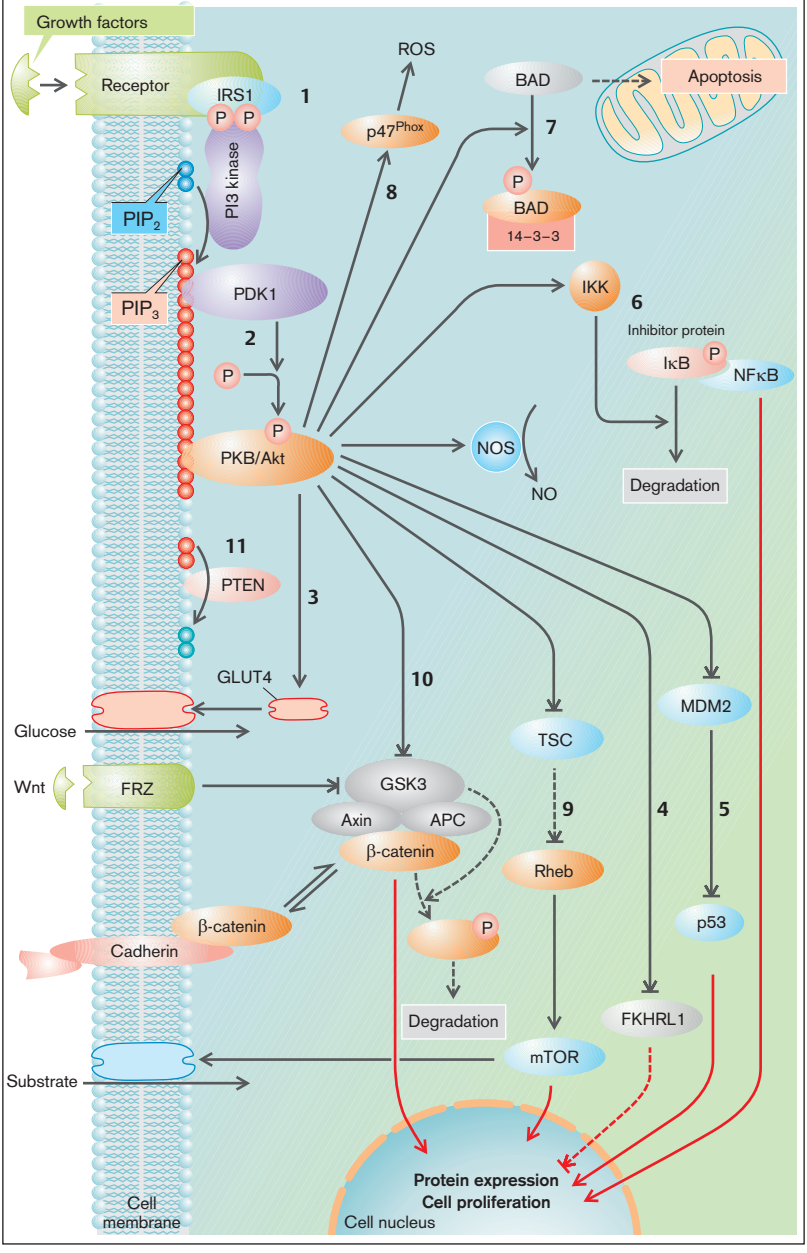
PKB/Akt phosphorylates and thereby inactivates *tuberin,* which forms a complex with hamartin (tuberin sclerosis complex, TSC). TSC inactivates the small G-protein Rheb (→ **A9**). Activated Rheb stimulates the kinase mTOR (mammalian target of rapamycin), a protein that stimulates cellular substrate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

PKB/Akt phosphorylates, and thereby inactivates, *glycogen synthase kinase 3* (GSK3α and GSK3β) (→ **A10**). The GSK3 is further inhibited by the growth factor Wnt, an effect involving the frizzled receptor and the dishevelled protein. 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 **serum- and glucocorticoid-inducible kinase** (SGK1). The expression of SGK1 is stimulated by glucocorticoids, mineralocorticoids, TGF-β, hyperglycemia, 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-dependent signaling. SGK1 promotes hypertension, obesity, development of diabetes, platelet activation, and tumor growth.

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 accomplished by the 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**). The low cytosolic Cl^- concentration osmotically counterbalances the high cytosolic concentration of organic solutes. The Na^+/K^+-ATPase uses up adenosine 5′-triphosphate (ATP) and maintenance of a constant cell volume thus requires energy.

Reduction in cytosolic 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., 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 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**).

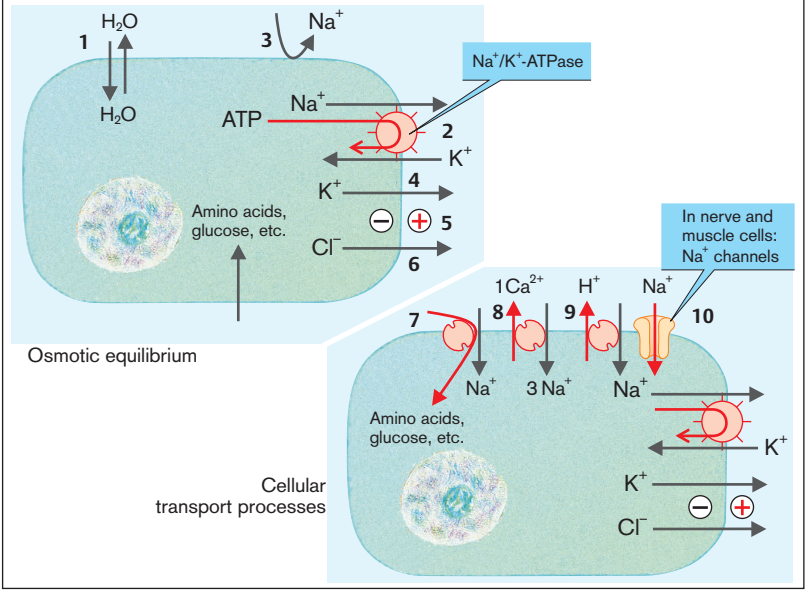
The increase in cytosolic Na^+ concentration not only leads to cell swelling, but also, via impairment of the $3Na^+/Ca^{2+}$ exchanger, to an increase in cytosolic **Ca^{2+} concentration**. Ca^{2+} produces a series of cellular effects (→ p. 6 ff.), including penetration into the mitochondria and, via inhibition of mitochondrial respiration, 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 glycolysis so that this last source of ATP dries up (→ **B**). The generation of lactate further leads to extracellular acidosis, which influences cell function through H^+-sensing receptors and channels.

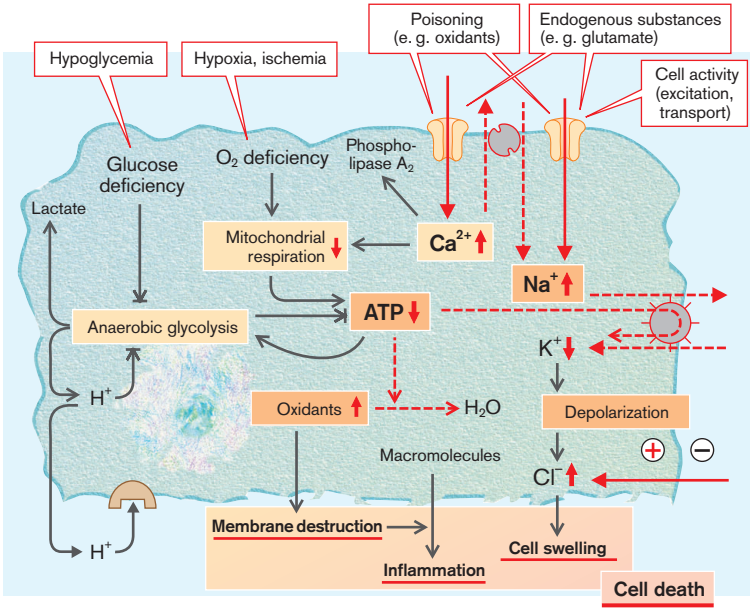
During energy deficiency, the cell is more likely to be exposed to **oxidative damage**, because the cellular protective mechanisms against oxidants (O_2 radicals) are ATP-dependent (→ **B**). Oxidative stress may destroy the cell membrane (lipid peroxidation) and **intracellular macromolecules** may be **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, and 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 **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.

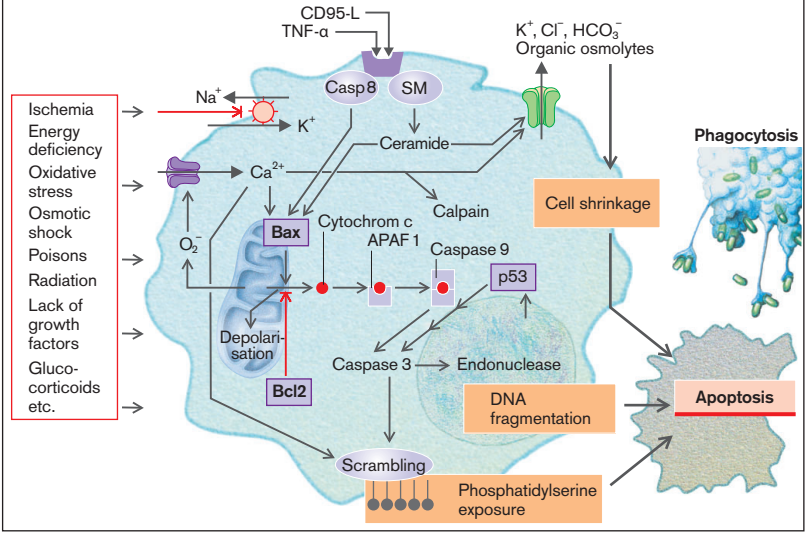
Apoptosis is mediated by a **signaling cascade** (→ **A**): the stimulation of distinct receptors (see below), excessive activation of Ca^{2+} channels, oxidative stress, or cell injury by other mechanisms leads to activation of protein-cleaving caspases and of a sphingomyelinase that releases ceramide 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 APAF-1 protein, cytochrome *c* released from the mitochondria activates 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 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).

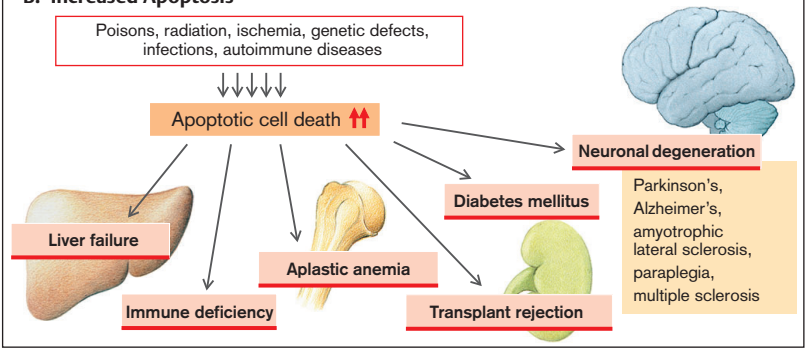
Pathologically increased apoptosis (→ **B**) may be triggered by *ischemia, toxins,* massive osmotic *cell shrinkage, radiation*, or *inflammation* (infections, autoimmune disease). The apoptosis may result in the inappropriate death of functionally essential cells, leading to organ insufficiency (→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

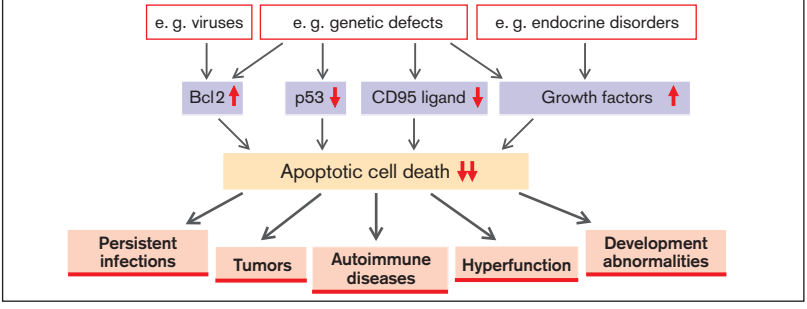
A. Triggering and Development of Apoptosis



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 hamartin (→ p. 10). 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 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)

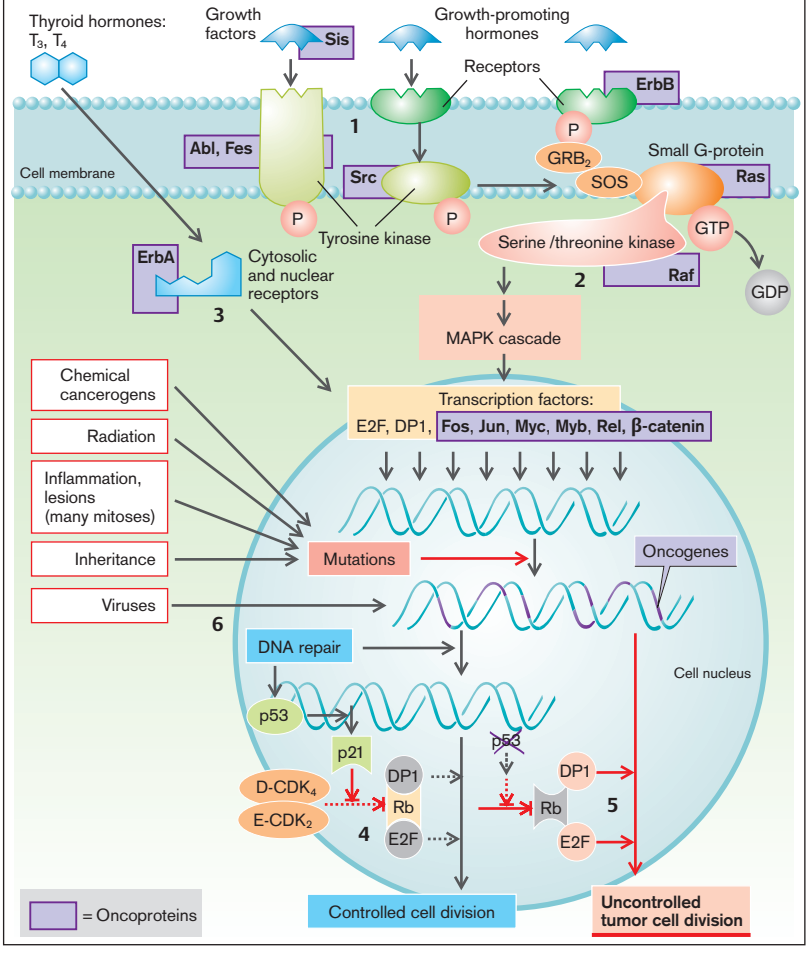
As an example, inactivation of **Ras** is accelerated by a GTPase-activating protein (GAP) (→ **B**). Mutations of Ras may cancel its sensitivity to GAP, and Ras remains active.

Tumors may result from **defective proliferation-inhibiting proteins**. Thus, a loss of Rb (retinoblastoma) or p53 (Li-Fraumeni 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) increase tumor incidence.

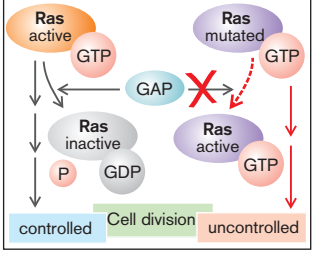
Mutations (→ **A**, left) can be **triggered by** chemical *carcinogens* or *radiation*, whereby *disorders of DNA repair* favor the occurrence of mutations. Cells are especially sensitive to mutations during mitosis, i.e., proliferating tissues (e.g., *inflammations* and *tissue lesions*) are more frequently 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**).

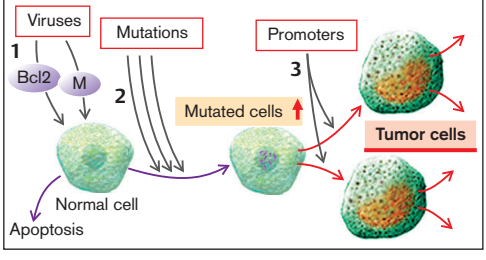
A. Mechanisms of Tumor Genesis



B. Ras Malfunction



C. Development of Tumor Cells



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. 364). 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. 384). 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 the 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 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**).

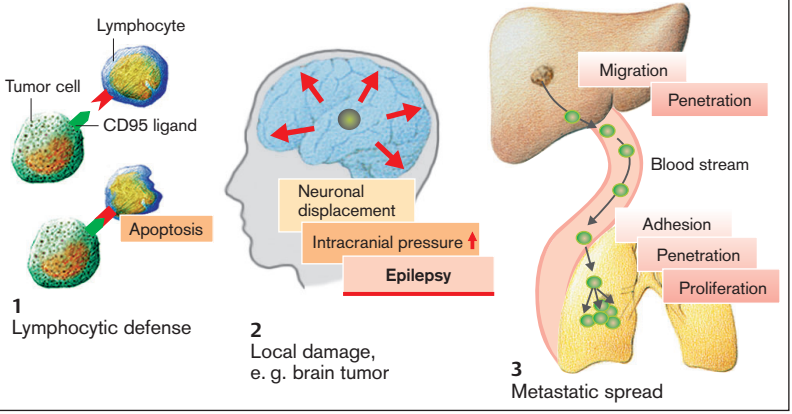
The **energy requirement** of the tumor cells is frequently met by *anaerobic glycolysis,* even if the O_2 supply is adequate, although the energy yield per mol glucose is only 5% of the oxidative glucose breakdown. The result is *hypoglycemia* and *acidosis* (→ **B**). The hypoglycemia stimulates the 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. 40 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. 330).

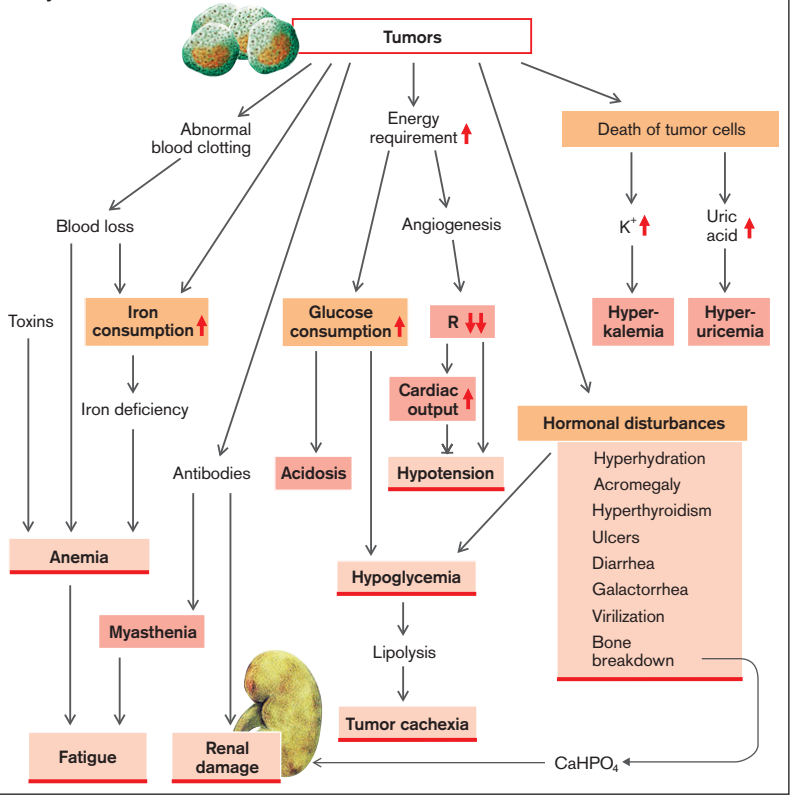
Even small tumors of endocrine tissues and dedifferentiated tumors of non-endocrine tissues (in particular small-cell bronchial carcinoma) frequently cause massive **hormonal abnormalities** (→ **B**). The increased release of hormones can result in numerous abnormalities (→ chap. 9), for example, raised 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), chorionic gonadotropin (testicular carcinoma and 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. 272).

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



B. Systemic 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.

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 in the past, 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 the variability in life-span is *not genetically determined*.

As one gets older, a **reduction of bodily functions** (→ **C**) occurs, 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, protection by vaccination is compromised and susceptibility to infectious disease, tumor growth, and autoimmune disease is enhanced. Morbidity and mortality increase accordingly.

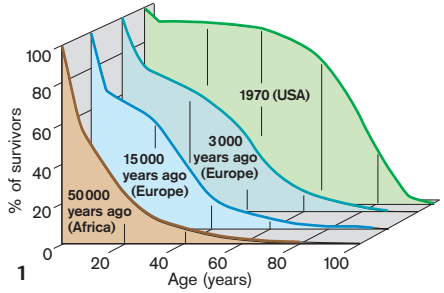
A Swedish study on the **immune-risk profile** (IRP) of 80- and 90-year-old individuals revealed increased numbers of $CD8^+$ T-cells (CMV-specific), decreased numbers of $CD4^+$ T-cells and $CD19^+$ B-cells as well as lack of CD28, the costimulator of T-cell activation. An increased IRP was associated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

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 nucleoprotein complex capping the chromosomes. In somatic cells the telomere is shortened with ▶

A. Life Expectancy



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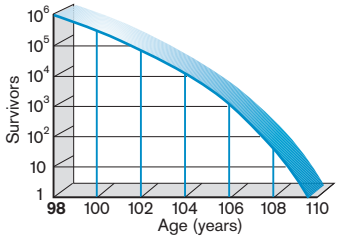
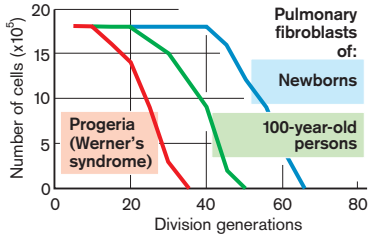
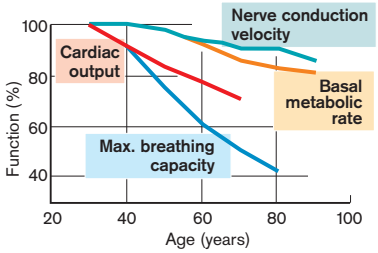


2 Life expectancy of 98-year-old persons

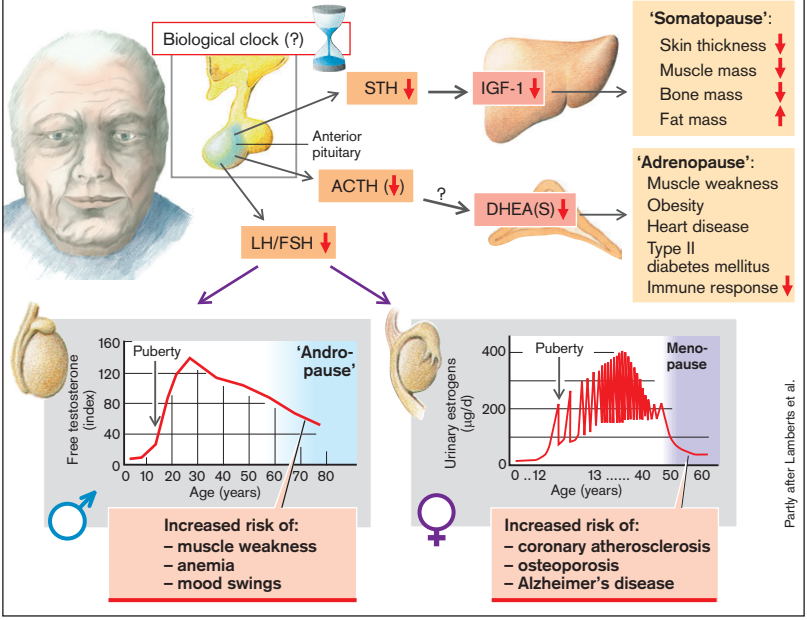
B. Dividing Capacity of Cultured Cells



C. Age-dependent Bodily Functions



D. Endocrinology of Aging



Partly after Lamberts et al.

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.

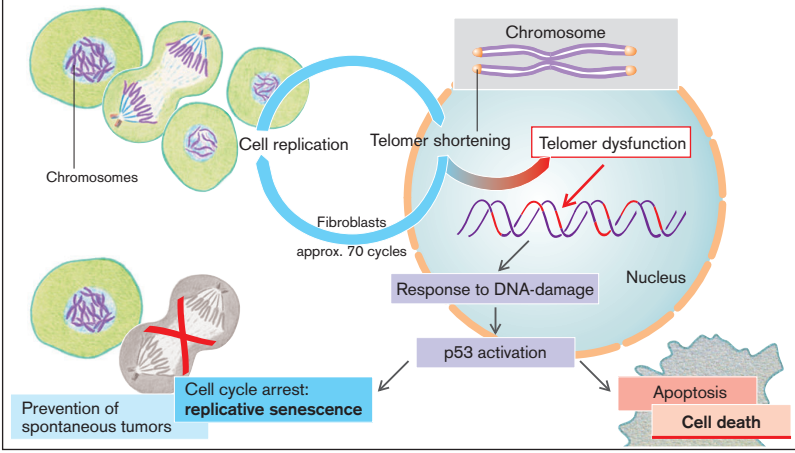
For instance, the (very rare) mutation of the *LMNA* gene on chromosome 1 leads to defects of the protein laminin A (progerin), which is expressed in the nuclear envelope. The resulting impairment of cell division leads to *progeria type I* (Hutchinson–Gilford progeria syndrome, HGPS), characterized by premature aging of skin, bone, and the vascular system from the first year of life. The children hardly reach adulthood. 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 (*Werner syndrome = 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 increased and the activity of enzymes serving antioxidant defense is decreased in the elderly.

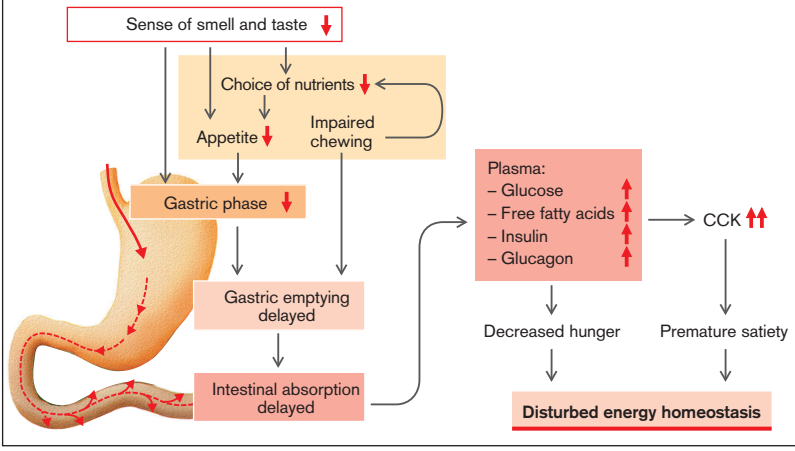
The **regulation of aging at the molecular level** is poorly understood. Aging and life-span are under the profound influence of *KLOTHO*, a single-pass transmembrane spanning protein. Excessive expression of KLOTHO leads to a substantial increase, deletion of KLOTHO to a profound shortening of life-span. 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 enormously increased production of calcitriol, with hyperphosphatemia and hypercalcemia, leading to massive tissue calcification and 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-calorie diet** increases the life-span of both humans and animals. The effect may be due to a decrease in fasting plasma glucose concentrations and plasma-cholesterol levels, enhanced insulin sensitivity, decreased visceral fat tissue, and decreased release of adipokines from that tissue (→ p. 268). All of these parameters are known risk factors for coronary heart disease. As a low-calorie 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 life-span without individuals having to refrain from their preferred eating habits. The positive effects of a low-calorie diet may 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 enhances 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.

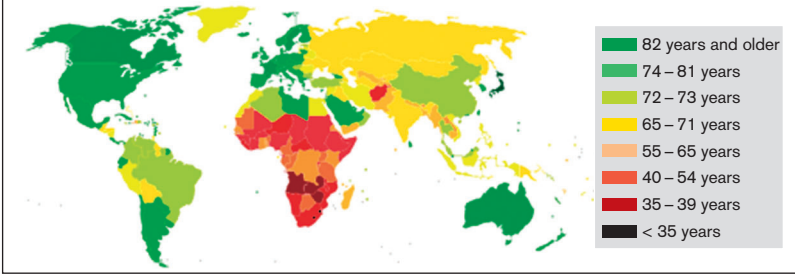
E. Telomere Shortening/Dysfunction and Replicative Senescence



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**).

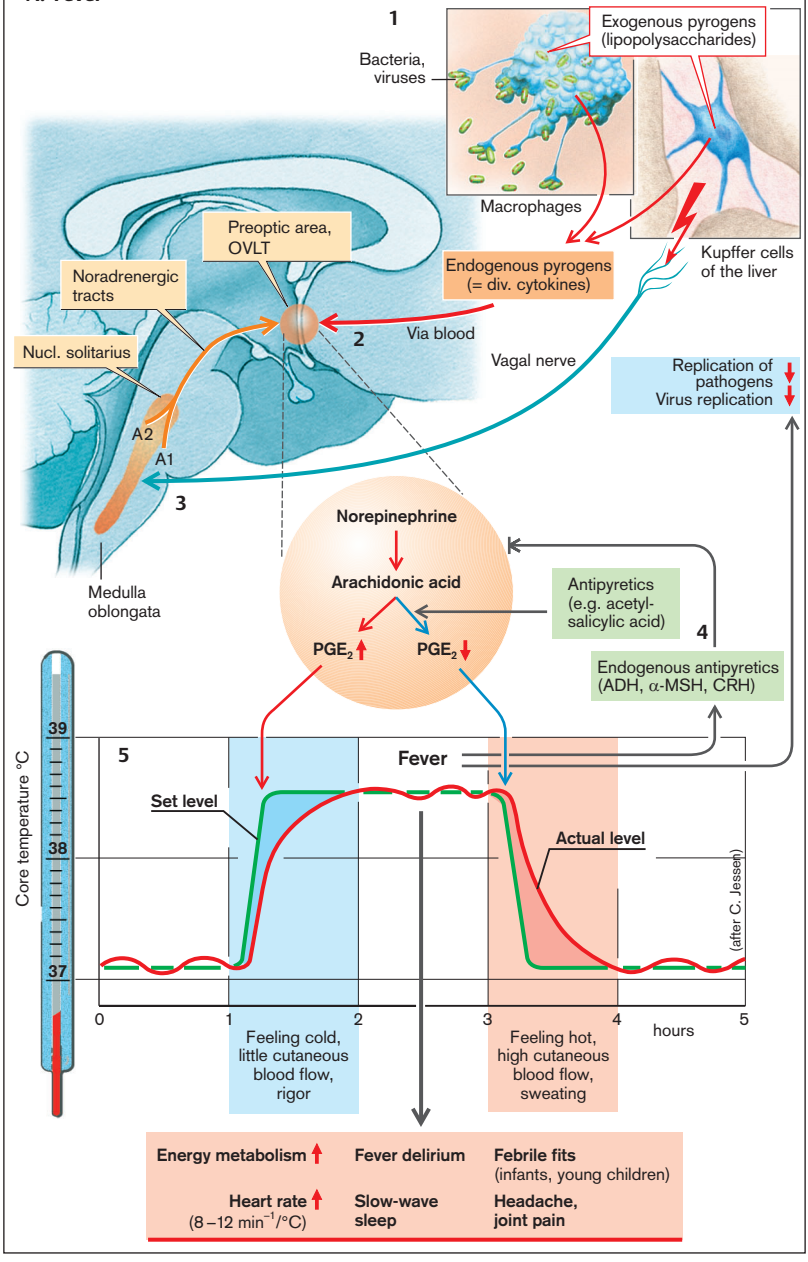
Fever is particularly common with infections in the course of the *acute-phase reaction* (→ p. 52 ff.) in which fever-inducing substances (pyrogens) cause a change in the set point. **Exogenous pyrogens** are constituents of pathogens, among which the lipopolysaccharide complexes (endotoxins) of gram-negative 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 TNF-α (cachectin) and TNF-β (lymphotoxin), the macrophage-inflammatory protein MIP 1 and many others. It is thought that these cytokines (with a molecular mass of 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 *preoptica area* and the *vascular organ of the lamina terminalis* (VOLT) by means of prostaglandin **PGE_2** (→ **A 2**). Some cytokines (e.g., IL-10) are also responsible for limiting the rise in fever (to ca. 41 °C). Fever-reducing drugs (*antipyretics*) are effective here. For example, acetylsalicylic acid inhibits cyclooxygenases 1 and 2, which catalyze the production of PGE_2 from arachidonic acid.

As after i.v. injection of lipopolysaccharides (components of the cell wall of gram-negative bacteria) 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 also activate the preoptic area and the VOLT 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 A1 and A2 noradrenergic cell groups. These in turn project from the ventral noradrenergic tract to the fever-regulating neurons in the preoptic area and VOLT (→ **A 3**). Norepinephrine that has been released there causes the formation of PGE_2 and thus fever. This also brings about the release of antidiuretic hormone (ADH; V_1 receptor effect), α-melanocyte-stimulating hormone (α-MSH), and the corticotropin-releasing hormone corticoliberin (CRH), which counteract 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. 54 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


1
Bacteria, viruses
Exogenous pyrogens (lipopolysaccharides)
Macrophages
Kupffer cells of the liver
Preoptic area, OVLT
Noradrenergic tracts
Endogenous pyrogens (= div. cytokines)
Via blood
2
Nucl. solitarius
Vagal nerve
Replication of pathogens
Virus replication
A2
A1
3
Medulla oblongata
Norepinephrine
Arachidonic acid
Antipyretics (e.g. acetyl-salicylic acid)
PGE2
PGE2
4
Endogenous antipyretics (ADH, α-MSH, CRH)
5
Fever
Set level
Actual level
Core temperature °C
39
38
37
0
1
2
3
4
5
hours
(after C. Jessen)
Feeling cold, little cutaneous blood flow, rigor
Feeling hot, high cutaneous blood flow, sweating
Energy metabolism
Heart rate
(8–12 min−1/°C)
Fever delirium
Slow-wave sleep
Febrile fits
(infants, young children)
Headache, joint pain

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 cavernous sinus, 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 in 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.

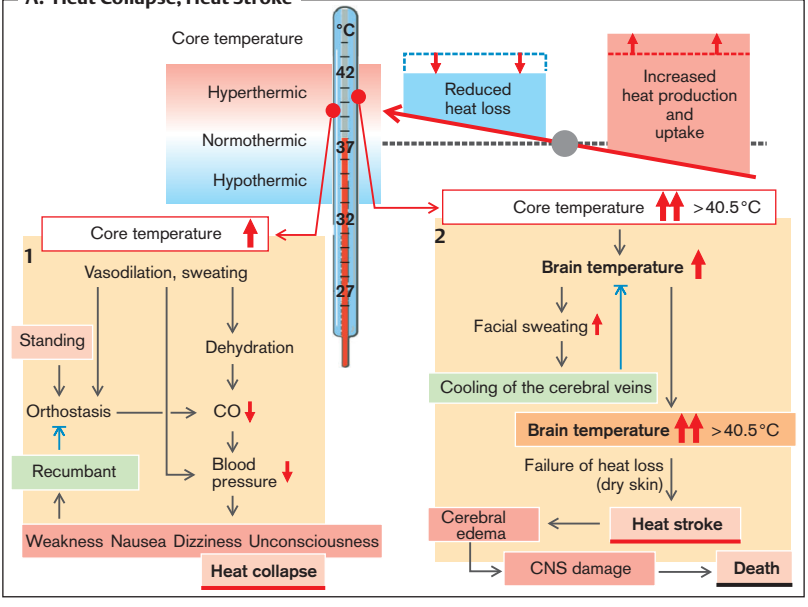
Malignant hyperthermia (→ **B**) is the potentially lethal result of heterogeneous genetic defects of sarcoplasmic Ca^{2+} transport, in which the Ca^{2+}-releasing channel (*ryanodine receptor*) is affected. Some inhalation anesthetics (halothane, enflurane, isoflurane) and depolarizing muscle relaxants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

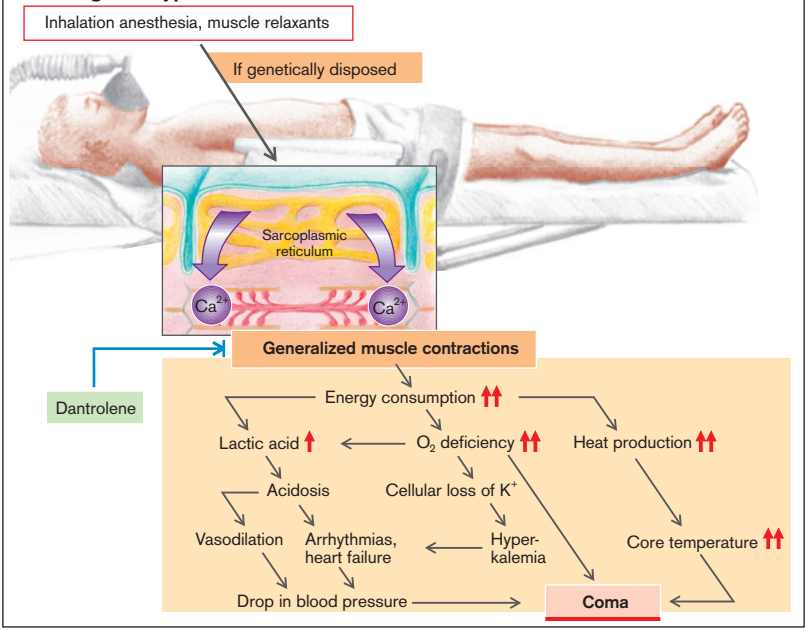
Sun stroke must be distinguished from hyperthermia. It is caused by direct sun radiation on head and neck and causes nausea, dizziness, severe headache, cerebral hyperemia, and serous meningitis and may end fatally.

Contact or radiant heat may cause first degree, second degree, or third degree **burns** (reddening, blisters, or necrosis, 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 ratio of body surface area to mass, 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 naked 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 erratically, 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 ↓↓

Muscle tremors

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)

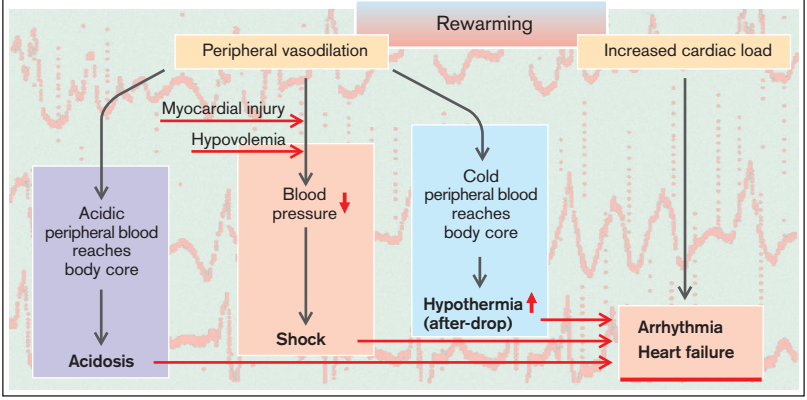
Psychiatric illness, hypothyroidism, Parkinson's disease

°C
37
35
33
31
29
Core temperature

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



Overview

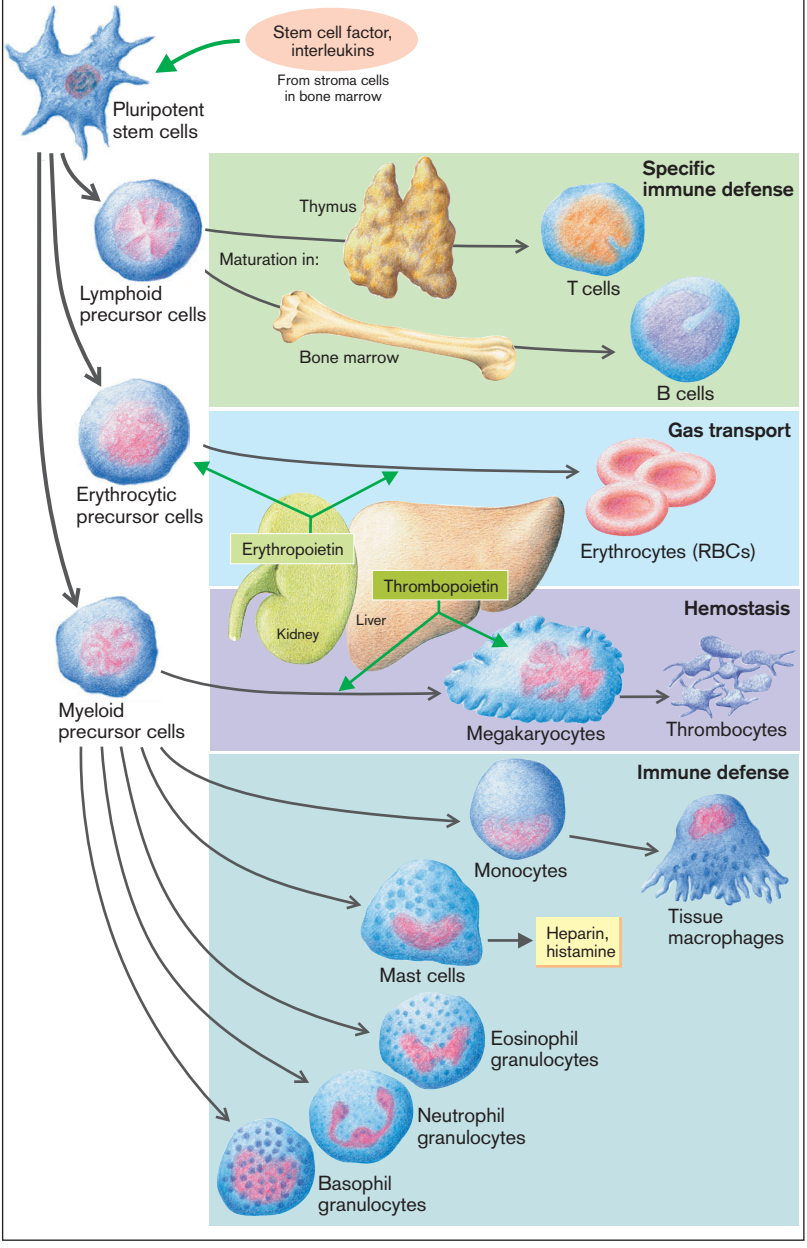
Total blood volume correlates with the (fat-free) body mass (→ Table below) and averages 3.6 L in women and 4.5 L in men. The blood's **tasks** include *transporting* various substances (O_2, CO_2, nutrients, metabolic products, vitamins, electrolytes, etc.), the transport of heat (heating, cooling), *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. 33, 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. 34), and *thrombopoietin* (secreted by the liver) for megakaryocytes and platelets (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, by transforming growth factor β (TGF-β) and tumor necrosis factor α (TNF-α).

Total Blood	Blood volume (L)	♂ 0.041 · kg body weight + 1.53	♀ 0.047 · kg body weight + 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.)	
Platelets	Number ($10^9/L_{blood} = 10^3/\mu L_{blood}$)	♂ 170 – 360;	♀ 180 – 400
Plasma proteins	(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. 31, A) and reach the bloodstream as nucleus-free and mitochondria-free, disc-shaped cells (ca. 7.5 × 2 µm). They can be severely deformed within the blood capillaries, which greatly facilitates both their passage and the exchange of substances and gases with the surrounding tissues. RBCs that have recently entered the blood will retain net-like residues of organelles (*reticulocytes*) for another one or two days. With a normal RBC *life-span* 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).

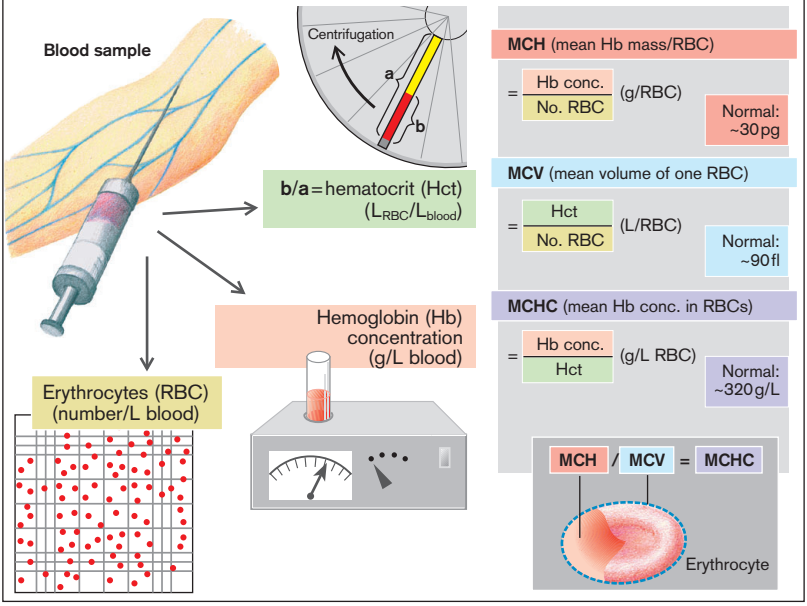
The RBCs regularly leave the arterioles in the pulp of the **spleen** and reach the small pores in the splenic sinuses. Old and abnormally fragile erythrocytes are separated out and destroyed in the region of these pores. The fragments are phagocytized by the macrophages in the spleen, liver, bone marrow, etc. and broken down (**extravascular hemolysis** in the reticuloendothelial system [**RES**], or more precisely, the mononuclear phagocytic system [**MPS**]; → p. 48). The liberated *heme* is broken down into *bilirubin* (→ p. 182), and the liberated iron is reused (→ p. 40). If there is **intravascular hemolysis**, Hb that has been released can to a certain extent be bound to *haptoglobin* (→ p. 40). 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 classification 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 erythrocyte 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 erythropoiesis-inhibiting interleukins (*secondary anemia*), among other substances; 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. 36); 6) abnormal Hb synthesis (*microcytic hypochromic anemia*; → p. 38 ff.).

A. The Erythrocyte Parameters MCH, MCV, and MCHC



B. Forms of Anemia