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Color Atlas of Pathophysiology

病理生理学彩色图谱

181 Color Plates by Rüdiger Gay and Astried Rothenburger

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basic sciences

Color Atlas of Pathophysiology

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Preface

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

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

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

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

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

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

Würzburg and Tübingen, Germany
January 2000

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For Jakob

Stefan Silbernagl

For Viktoria and
Undine, Karl, Philipp, Lisa

Florian Lang

1 Fundamentals

S.Silbernagl and F.Lang

Cell Growth and Cell Adaptation

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

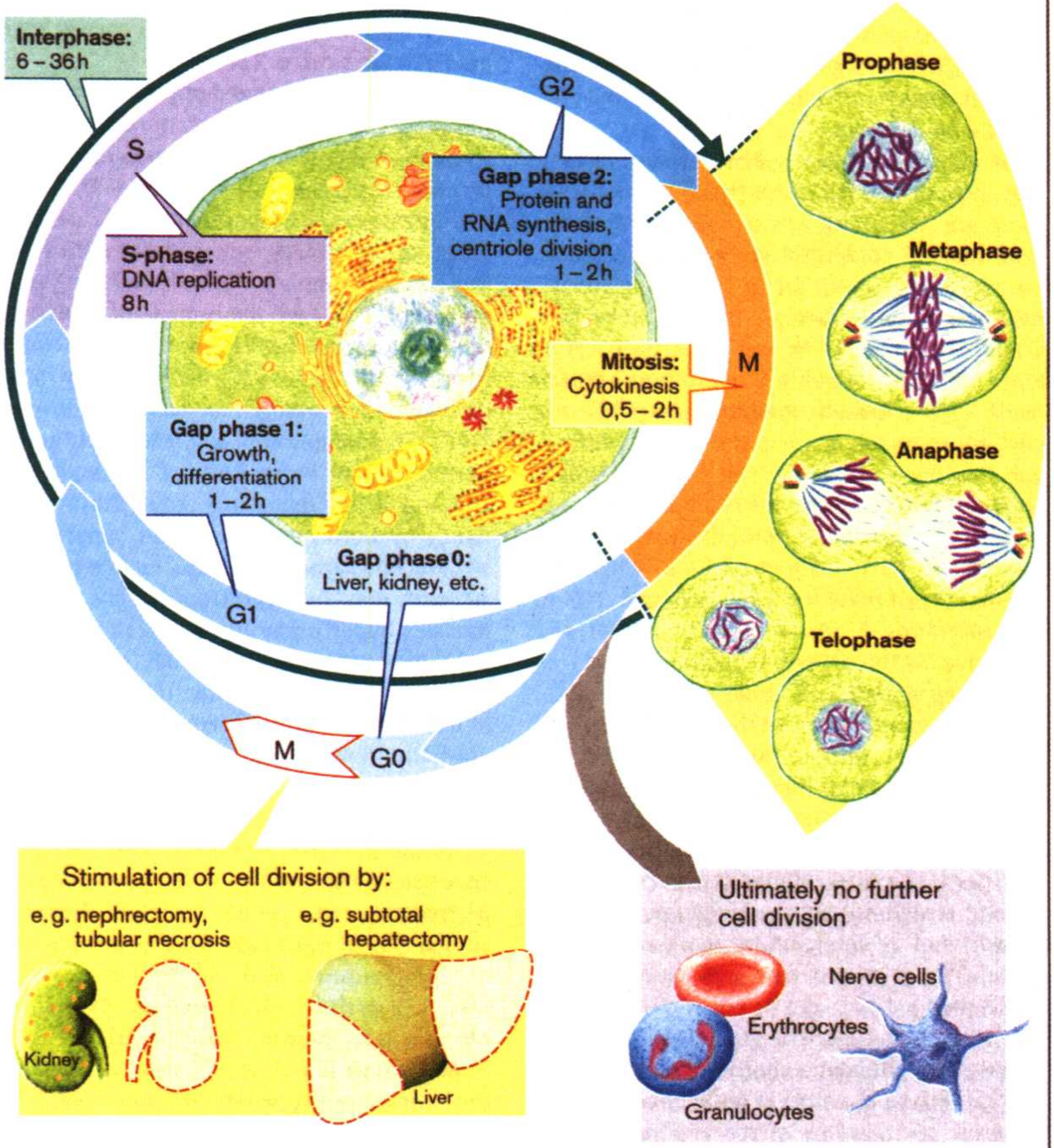
With the exception of the germ cells, whose chromosome set is halved during meiotic division (*meiosis*), most cells divide after the chromosome set has first been replicated, i.e., after mitosis (so-called indirect division of the nucleus) followed by division of the cell (*cytokinesis*). In this process every cell capable of mitosis undergoes a **cell** or **generation cycle** (→ **A**) in which one mitosis (lasting ca. 0.5 – 2 h) is always separated from the next one by an **interphase** (lasting 6 – 36 h, depending on the frequency of division). Most importantly, the cell cycle is governed by certain cycle phase–specific proteins, the *cyclines*. They form a complex with a protein kinase, called cdc2 or $p34^{cdc2}$, 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 synthesis). 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. 28 ff.). One daughter cell (stem cell) usually remains undifferentiated, while the other becomes differentiated into a cell which is no longer capable of dividing, for example, an erythrocyte or granulocyte (→ **A**). Spermatogenesis, for example, is also characterized by such *differentiated cell division*.

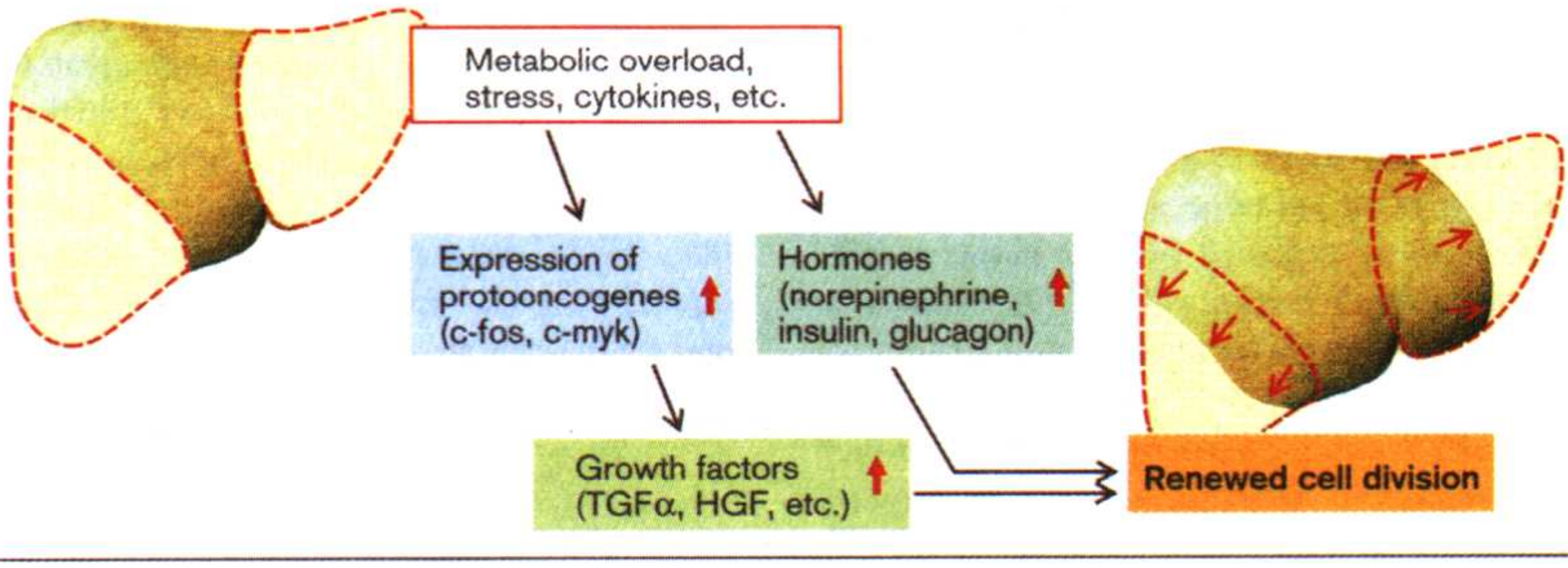
The cells of some organs and tissues do not normally proliferate (see below). Such **stable** or **resting cells** enter a resting phase, the G_0 *phase*, after mitosis. Examples of such cells are the parenchymal cells of the liver, kidneys, and pancreas as well as connective tissue and mesenchymal cells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

A. Cell Cycle



B. Compensatory Hyperplasia



The GF receptors 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. 14).

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

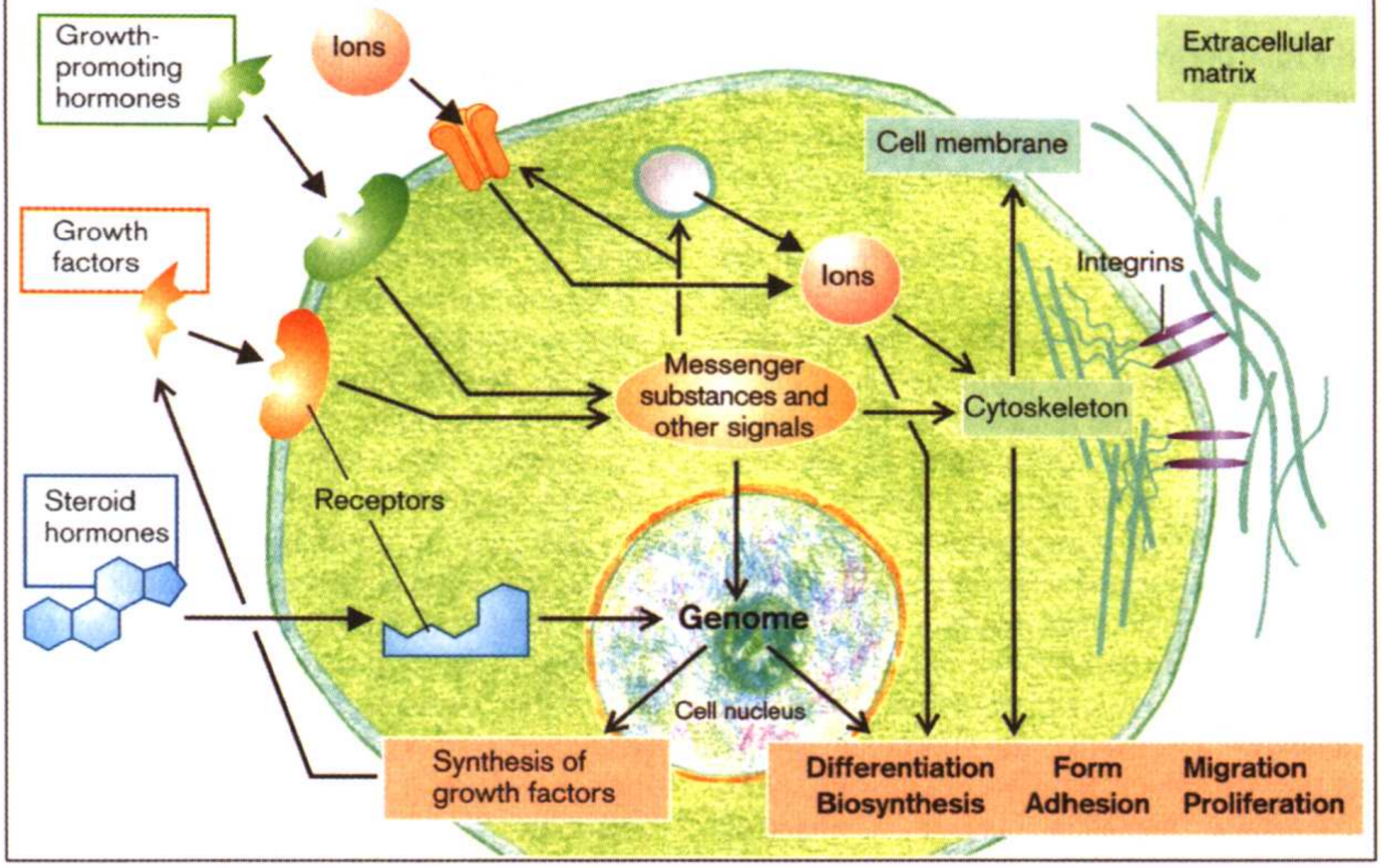
The regeneration of labile and stable cells does not necessarily mean that the original tissue structure is reconstituted. For this to happen the **extracellular matrix** must be intact, as it serves as the guiding system for the shape, growth, migration, and differentiation of the cell (→ **C**). The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

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

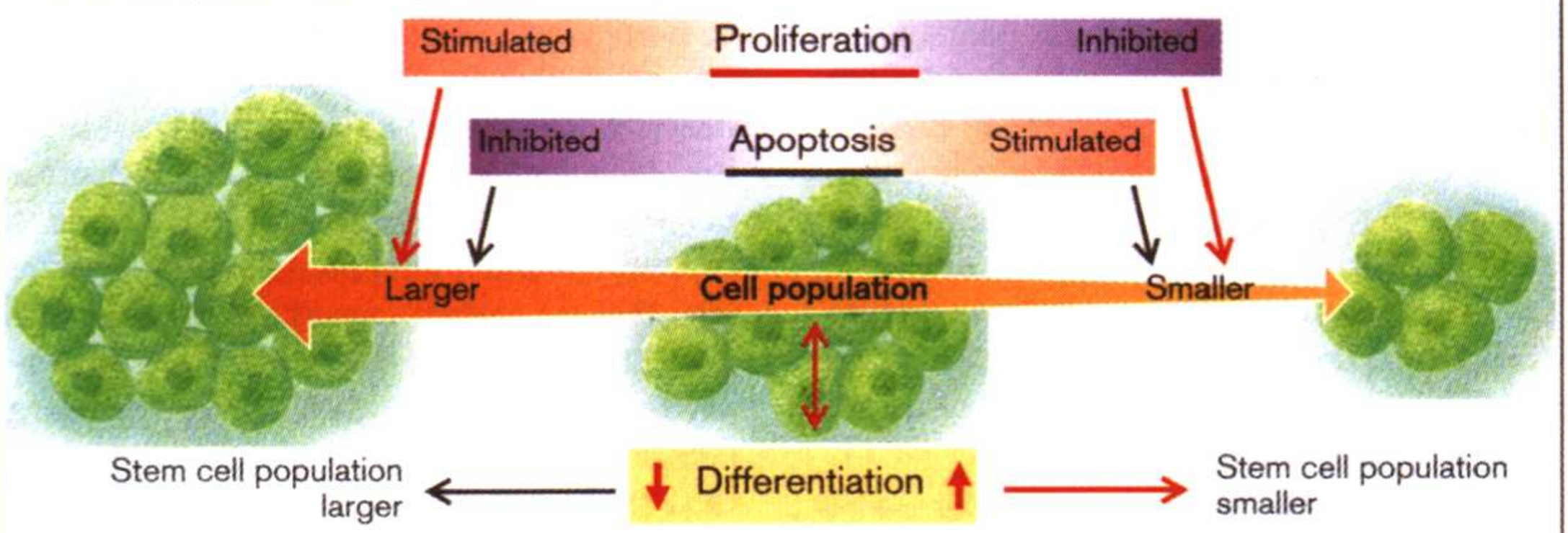
Adaptation to changed physiological or unphysiological demands can be achieved through an increase or decrease in the **number of cells** (*hyperplasia* or *aplasia*; → **D, E**). This can be triggered by *hormones* (e.g., development of secondary sex characteristics and growth of mammary epithelium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

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

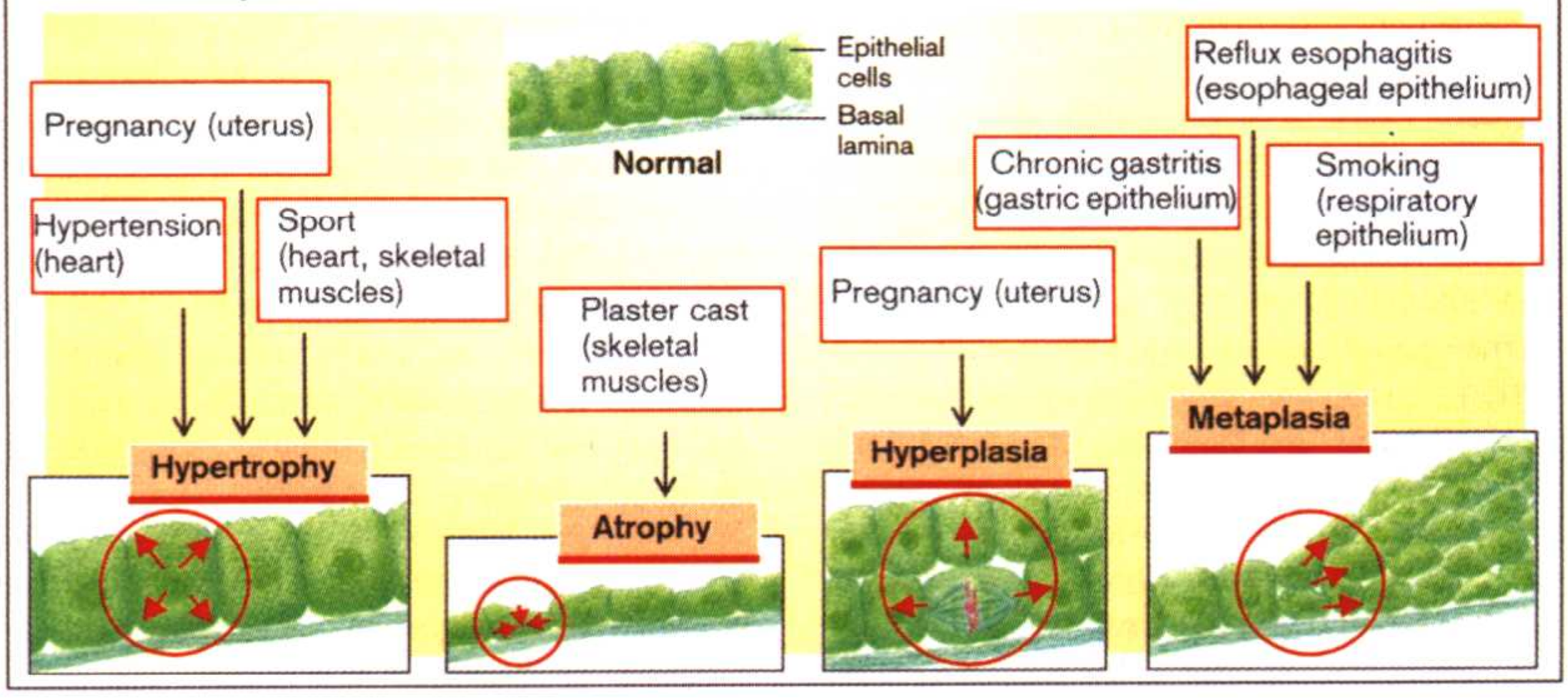
C. Regulation of Cell Proliferation, Motility and Differentiation



D. Changes in Cell Population



E. Cell Adaptation



Abnormalities of Intracellular Signal Transmission

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

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

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

Numerous **peptide hormones** use cyclic adenosine monophosphate (**cAMP**) as second messenger in such a way that, mediated by a *stimulating G protein* (G_s), *adenylyl cyclase* (AC) is activated and thus more cAMP is formed (→ **A1**). cAMP activates *protein kinase A* (PKA), which phosphorylates, among others, enzymes and transport molecules. cAMP can also be involved in gene expression via PKA and phosphorylation of a cAMP-responsive element-binding protein (CREB). cAMP is converted to noncyclic AMP by intracellular *phosphodiesterases* and the signal thus turned off. The following hormones act via an **increase in intracellular cAMP concentration**: corticotropin (ACTH), lutotropin (luteinizing hormone [LH]), thyrotropin (TSH), prolactin, somatotropin, some of the liberines (releasing hormones [RH]) and statins (release-inhibiting hormones [RIH]), glucagon, parathyroid hormone (PTH), calcitonin, adiuretin ([ADH] 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 to some extent the 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) (→ **A2**). 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. 150). *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, inhibit phosphodiesterase and thus the breakdown of cAMP, which also leads to an increase in cAMP concentration (→ **A4**). The xanthine derivatives are used therapeutically, among other drugs, to cause the bronchial musculature to dilate in asthma by raising the cAMP concentration.

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

Other intracellular transmitters are 1,4,5-

inositol trisphosphate (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 so-called 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 (→ **A6**). 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** stimulates protein kinase C (PKC), which is also activated by Ca^{2+}. PKC 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.

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

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

Insulin and numerous growth factors activate **tyrosine kinases** (→ **A10**), which transmit cellular effects via other kinases, enzymes, and transport proteins. The tyrosine kinases can themselves be part of the receptor, or can attach themselves to the receptor on activation. Kinases frequently act by phosphorylating other kinases and thereby trigger a *kinase cascade*. Thus, the mitogen-activated protein kinase (MAP kinase) is activated by another kinase (MAP kinase 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.

Other signaling molecules, such as the *small G proteins* (p_{21}Ras) or *transcription factors* (e.g., c-Jun, c-Fos, c-Myc, $NF_\kappa B$, AP-1), are important for signal transduction of growth factors (→ p. 14) and in apoptosis (→ p. 12).

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

Some mediators (e.g., the tumor necrosis factor [TNF] and CD95 [Fas/Apo1] ligand) activate acid sphingomyelinase, which forms *ceramide* from sphingomyelin (→ **A11**). Ceramide triggers a series of cellular effects, such as activation of small G proteins (e.g., Ras), of kinases, phosphatases, and 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. 12).

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