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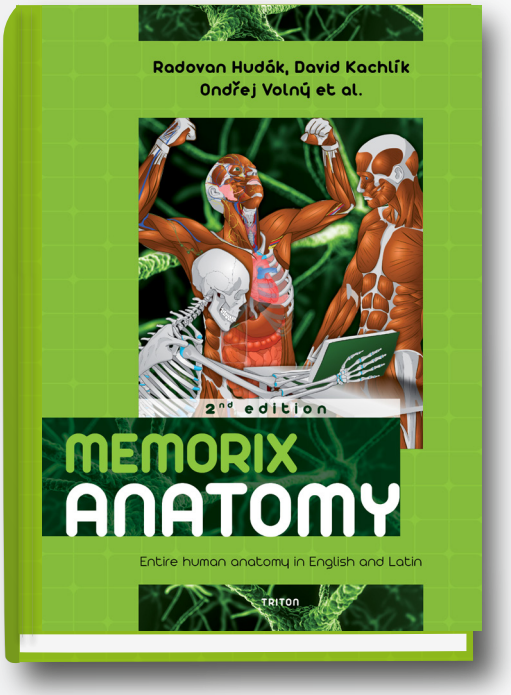

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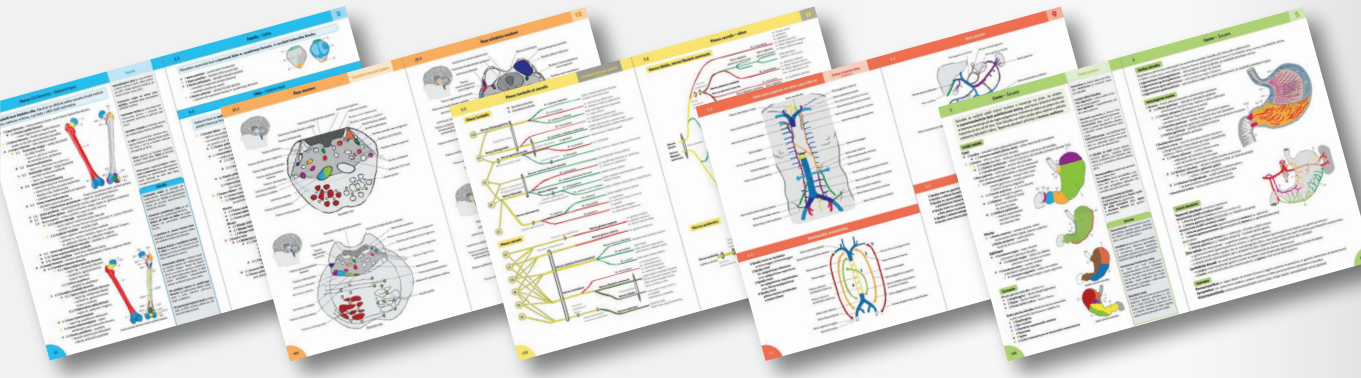

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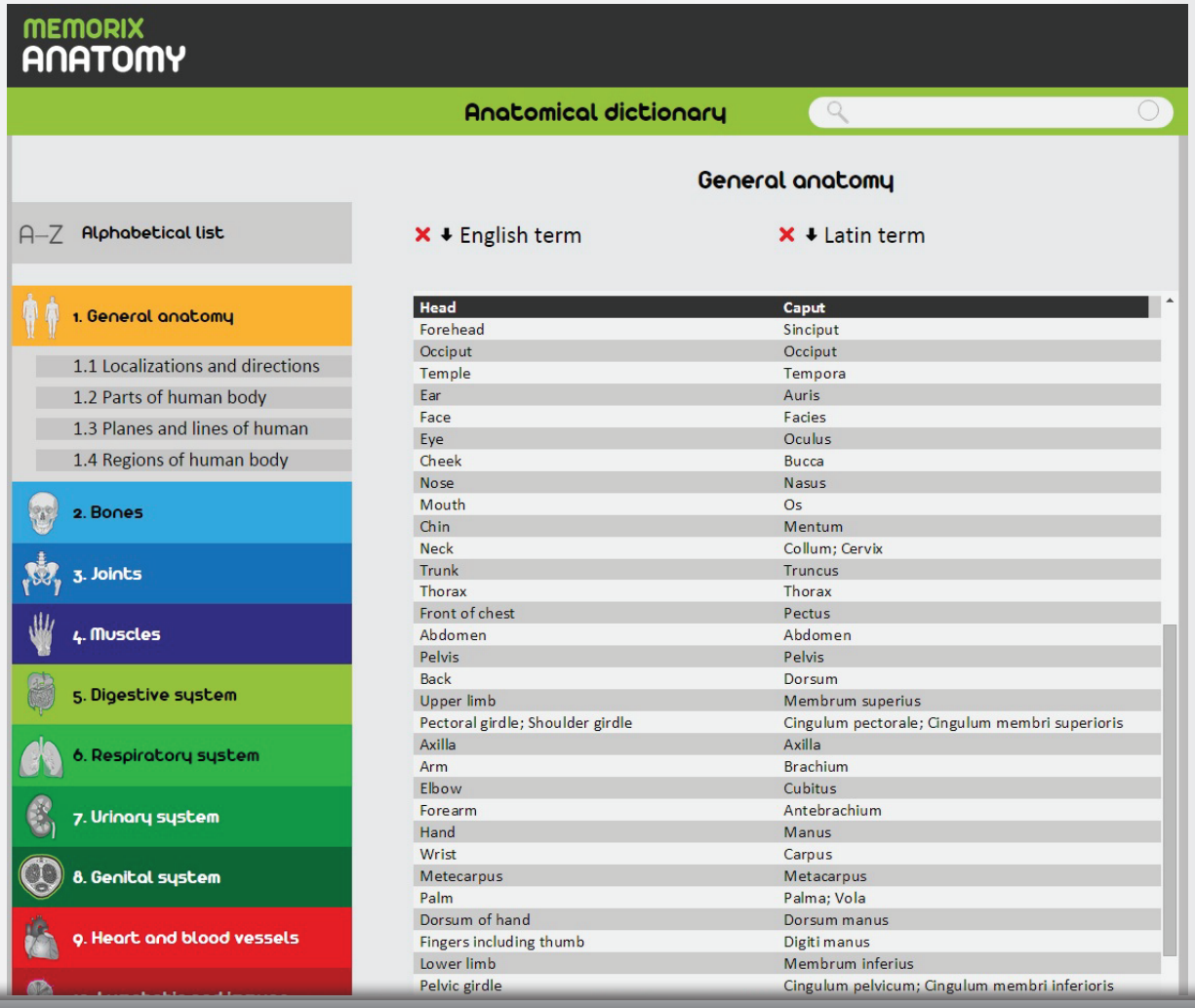

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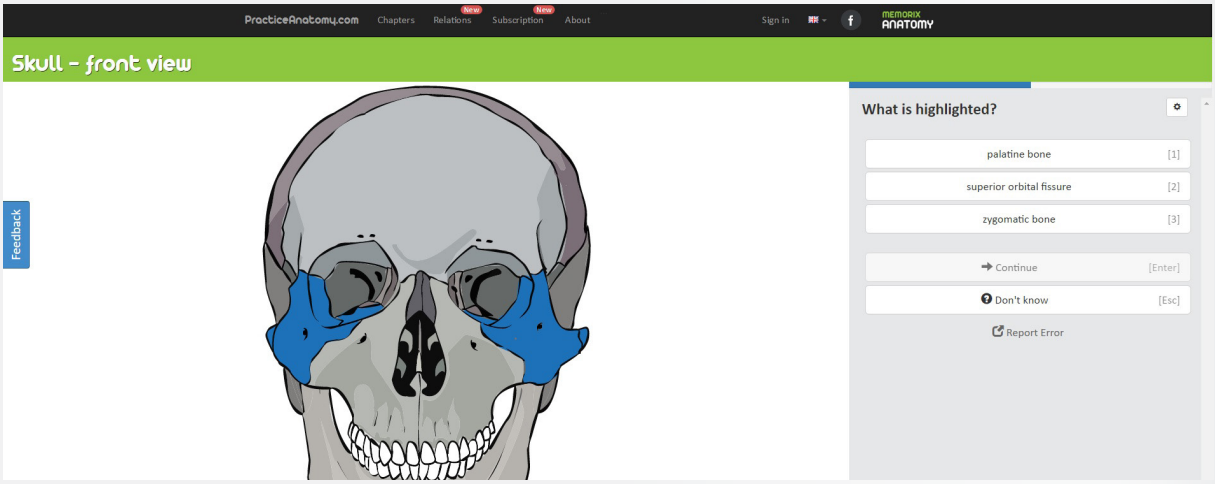

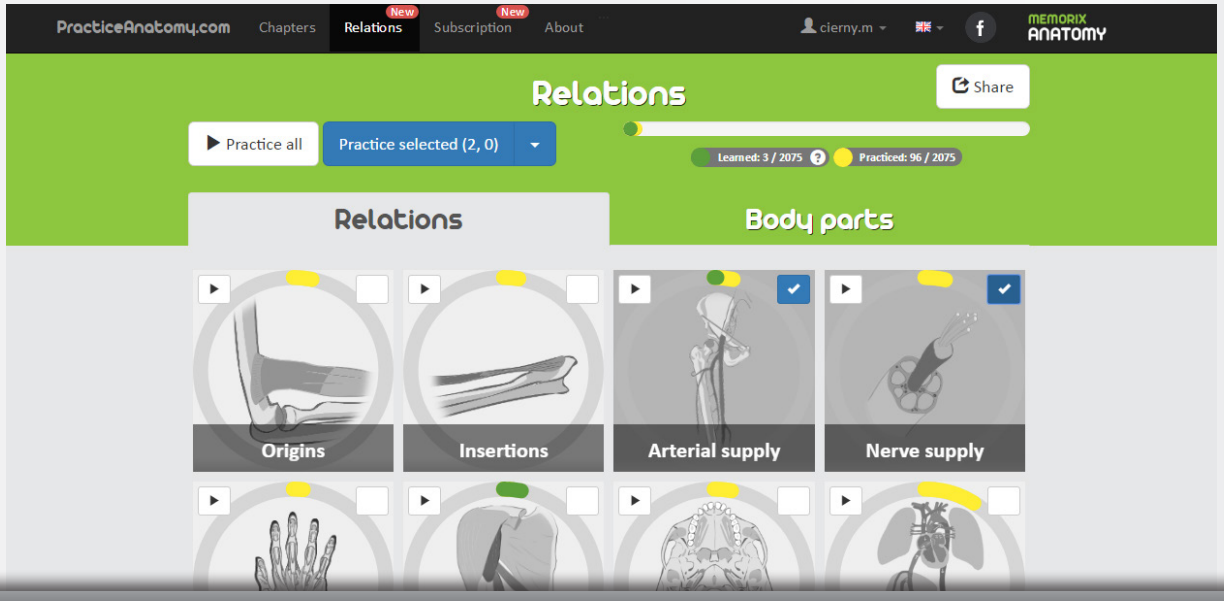

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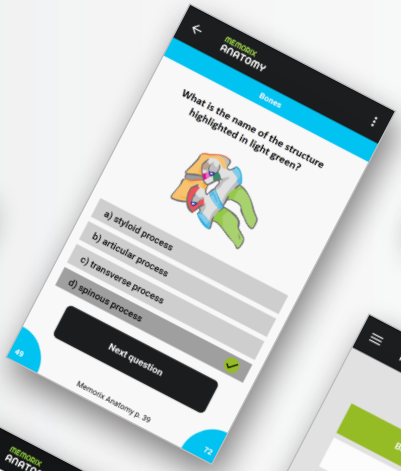

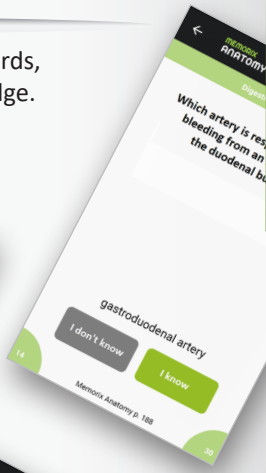

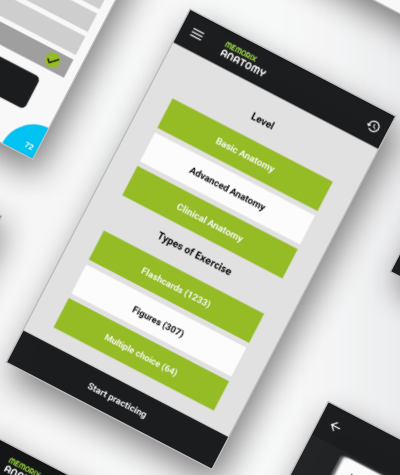

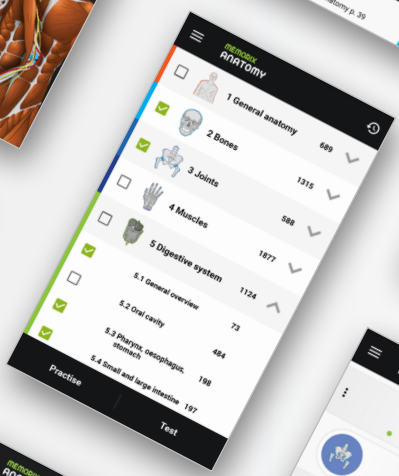

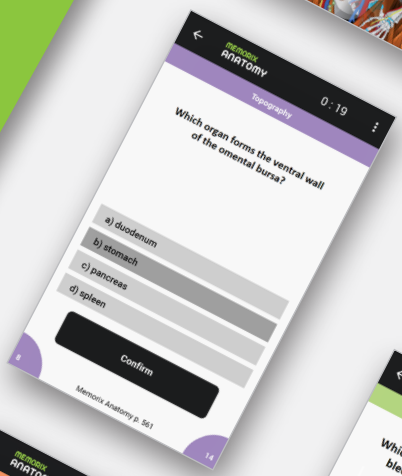

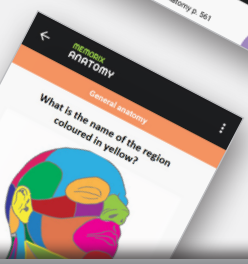

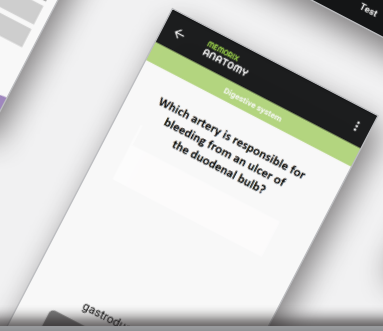

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and can light up for the smallest things.

Jan Balko
Zbyněk Tonar
Ivan Varga
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MEMORIX HISTOLOGY

1st edition

MEMORIX

Jan Balko, Zbyněk Tonar, Ivan Varga et al.
MEMORIX HISTOLOGY

Copyright owner and publisher of the E-book:
MEMORIX s.r.o.,
Plzeňská 1270/97, 150 00 Praha 5, Czech Republic
www.memorixhistology.com

Managing editor: Radovan Hudák
English version chief coordinator: René Novysedlák
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Illustrations: Jan Balko, Šárka Zavázalová, Radovan Hudák
Microphotographs: Zbyněk Tonar, Ivan Varga, Richard Adamčík
Elektronograms: Ivan Varga
Typesetting: Radovan Hudák, René Novysedlák, Petr Stojčev
Design: Radovan Hudák
Cover: Radovan Hudák, Renata Brtnická

Publisher of the print book:
Stanislav Juhaňák – TRITON,
Vykáňská 5, 100 00 Praha 10
www.tridistri.cz

ISBN 978-80-906331-2-4

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We live in times with easy access to information, **its quantity being so vast that it is almost impossible to cover it**. New information channels that have emerged in recent decades, **such as televisions and mobile phones** and especially the Internet, constantly provide new knowledge**. Even traditional forms of information transfer, such as** books recently experienced an unprecedented boom**.** Almost every theoretical institute at medical schools published a book or translated one of successful foreign titles**. The result is that we are slowly getting lost in this sea of information**. The more choices we have, the harder it is to choose **which teacher to believe, which books are worthy investing the time, what should be the basis of decisions in the exam and clinical practice** etc. This fact has resulted in the so–called **decision paralysis.** In medicine, it means that we are not able to decide what to learn, so in the worst case we do not learn from anything.

Book full of compromises

At the primary and secondary schools, we are used to the situation where **the vast majority of information provided during lessons or written in books** was the same. We could be confident that **if we acquire the knowledge, we will know everything** correctly. It's different at the college. In every field there is much basal **information**, presented by every teacher or doctor in the same way, but then, there is much of information **under discussion for many reasons**. Most often it has never been 100% verified or there have been some scientific discoveries. **In histology, the subjective opinion of histologists plays a big role,** they can see various shapes of cells in the microscope. Students who are used to learn dogmas **get lost in the mixture of information, lose their energy to study new things and worry that they will never have a chance to learn it**. The students will then get even more confused when the **professor lectures the lessons learned from his/her experience and the latest scientific articles**, **assistants teach according to the recommended literature and** student lecturers **recommended the** notes**prepared from students of higher grades.**

This **information gap** motivated us to try to **create study materials that meet the requirements of all the parties involved**. We invited **younger and more experienced histology specialists, pathologists, clinicians, of course, but also many students**. We tried to make a book that would contain **histological information both from available literature, the latest scientific papers, as well as from renowned histology specialists**. Pathologists and clinicians **gave emphasis on the quality of clinical correlations**, reflecting their importance for the medical practice. **Young doctors and students were trying to make the text readable and interesting**. Because only a **comprehensive, correct and graphically friendly textbooks can truly motivate students** to spent much of their youth with it, and older doctors to come back to it with love.

Memorix Histology is a textbook of huge compromises. If we put in all the information suggested by the authors and reviewers, it **would contain approximately 2,000 pages**. If we put in little information, it would not be respected in the academic sphere. **We believe that Memorix Histology will become a successful and popular textbook** and bring joy to all interested in this colorful morphological study.

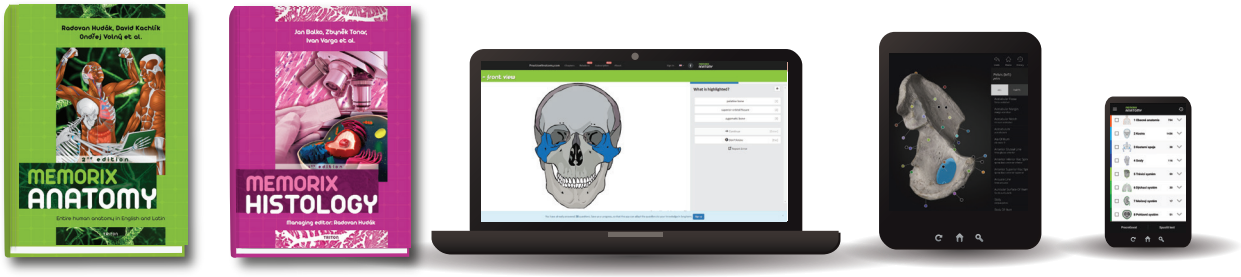
The idea of the Memorix

It's been 5 years since we completed the first edition of Memorix Anatomy. Since then, we have managed to prepare the **improved fourth edition of the Czech** and **the second English edition**, which got to various countries after a short time. There is already a Polish and Italian Memorix Anatomy and soon, the Hungarian version will be released. In addition, we embarked on the development of the **anatomical online dictionary (www.anatomicalterm.com),** which will be expanded by **many terms in various languages over the next years**, **but by the descriptions and images of anatomical structures**. Furthermore, **together with the group Adaptive Learning,** consisting of IT enthusiasts, we prepared a **web application www.practiceanatomy.com**, where you can revise the anatomy at your computer. Our newest and largest projects include **Memorix Anatomy QUIZ** mobile application, which will make anatomy revision more pleasant, anywhere, on Android and iOS and **Anatomyka**, the interactive 3D human anatomy atlas, allow you explore and interact with human anatomy in all its breathtaking complexity!

We do not want to brag with the list of our problems. Of course, we are proud **about them, but above all, we want to show that the** idea of Memorix does not lie only in publishing books. **Our aim is to** motivate all the students and teachers **to lose their fears and cooperate on the development of** study materials**. The list of options is virtually infinite (books, applications, videos, audio etc.) and it is impossible to fully appreciate the contribution. And lastly, we have a question: Why to be afraid to be successful and develop successful projects?** Success is not a coincidence. It is a choice everyone can make.

Look at our website **www.memorixanatomy.com**

Radovan Hudák
Prague 11. 6. 2018



Dear colleagues. **You are holding the first edition of the Memorix Histology**. **Never before, the people interested in the study of this specialization had a wider choice of high–quality printed and electronic study materials than today.** Despite that, or rather due to that, **a group of authors and graphic designers stemming from new graduates, students and teachers decided to contribute to histology education** in a way tested in the previous versions of Memorix Anatomy. **Do you want to know more about your body than you can see with the naked eye?** If so, read on. **Histology is interesting, and it deserves this attention.** This book has been written to help histology get your attention. In return, it will bring you the **knowledge of what is hidden under the microscope**.

Why are we studying and teaching histology?

Histological approach to knowledge of the human body is the link between the macroscopic **anatomy, developmental biology (embryology), cell biology, physiology, biochemistry and other areas** of the study of medicine and science. This makes it extremely useful and many generations of students can confirm that **efforts devoted to the study pay off many times in subsequent and related fields**. Only part of physicians actively use their knowledge and skills in cytology, tissue science, and microscopic anatomy in their diagnostic and therapeutic practice. But all those who seek understanding of anatomy during their education **find a logical explanation of relationships and mechanisms between cell organelles, cells, extracellular matrix and tissues**. **At a level hidden to an unarmed human eye, a microscope can explain much of what is observed during the development of the embryo and fetus, with anatomical autopsy, study of chemical reactions or homeostasis feedback loops. Histology, thanks to its explanatory capabilities,** not only satisfies the age–old human curiosity and desire for knowledge of hidden things, but it has structured the thinking of doctors for several centuries**. Like anatomy, histology teaches us to watch,** note, recognize and describe what they see**. It makes us observers and motivates us to think about how the observed structure of tissues and organs is related to their function. This helps us** remember a relatively large amount of subject thanks to logic, built on a solid foundation**. At the same time, it teaches us to think about the causes and consequences from the microscopic level to the level of the whole organism, which is the** key in shaping the thinking of future physicians, regardless of their specialization**. Learning to think and solve complex problems necessarily implies not to be tied up with the practice of a single specialization, but rather to learn how to use the study of acquired knowledge and skills according to the situation.** Only their combination provides the doctors and scientists the ability to think independently and critically **and to move the boundaries of knowledge. We provide this contemplation to our students as a response to the frequent and legitimate question "**where they will use histology **". Another explanation is available on the next page in the article on "The use of histology in pathology and clinical fields"**.

The histological approach to discovering the human body is a link between macroscopic anatomy, developmental biology (embryology), cellular biology, physiology, biochemistry and other areas of study of medicine and the natural sciences.

What to put into the histology textbook?

From its beginnings, **histology is a field of research into the structure, function and development of cells, tissues and organs**. It borders on many disciplines, but **the knowledge in each of them is constantly growing and overlapping**. Some faculties in our countries and abroad teach two different subjects – **the field of tissue science (general histology)**, and **separately, most commonly within anatomy, the microscopic organ structure (special histology)**. In other countries, both are included in one exam, often with embryology. Whether histology is taught and tested as a separate subject or integrated into multidisciplinary learning blocks, its role of explaining and interconnecting remains the same.

The selection of the knowledge we finally decided to include in the book was based on the mapping of the penetration between the matter taught at the medical faculties in the Czech Republic and Slovakia. Our goal was not to remove **any medically significant knowledge from our own histology in the narrower sense of the word** – as it belongs to its tradition and as it is included in the internationally recognized classification of terms – **Terminologia Histologica**. **Where the interpretation of histology already bordered on the following subjects** (e.g. with biochemistry or physiology), **we did not go too far beyond the histology, and** we remained only within the morphological foundations of the matter in a simplified form so that the students could extend the knowledge acquired in histology in these further subjects, so that the acquired knowledge would not need changes and corrections in the future.

The book would not come without the support of our reviewers from many sites in both republics. Thanks to their feedback, we have **removed some errors, refined and supplemented the interpretation or clarified confusing areas**. A number of ideas for **extending the chapters, which we did not included into the final version**. Often these were the same expanding remarks that the authors of the chapters themselves had originally included, but they did not go through the narrower selection for the final editions of the chapters, so that the section of the book remained readable and faithful to the overall concept of the textbook. **Embryology notes** are not a permanent and standardized part of all chapters, **but are only mentioned in selected cases** (e.g. tissue division according to the origin, in the nerve or reproductive system, etc.). **Without the knowledge of the development, it is impossible to understand the structure and functions of the human body.** However, we could not include and explain the development and ontogenetic associations in all the discussed organs and we refer to relevant embryology books. **If we used all the remarks of the reviewers, the extent of chapter would be disproportionately increased, diminishing the legibility and clarity**. There are many other references in the references recommended at the end of the chapters. On the other hand, we have received a number of proposals for the exclusion of certain areas. We are aware of the variety of teaching styles, the choice of test specimens and the test questions at individual faculties. We therefore encourage students to follow the recommendations of their teachers in these areas.

Texts, diagrams, atlas and microscopy

Effective study of histology requires the combination of several types of study materials with practical activities. The text books, scripts or lectures are used as the source of terms, their definitions and explanations of their relationships. **This reading and listening part cannot be skipped** as **even the most talented student cannot describe a preparation without the relevant terms**. The text part of our book **uses the internationally accepted terminology (Terminologia Histologica), while trying to respect both the common and newer forms of the Czech terminology**. All the terms are explained and staged so that the student does not lose the overview of the level. **The decision algorithms** included in several chapters are not the only possible ones, they do not include all the organs and are not intended for memorizing, but as **an inspiration for the questions, which are suitable for distinguishing preparations from different organs**.

The knowledge is illustrated using schemes to capture the shapes, proportions and typical staining of histological structures, which is often a useful lead reflecting their chemical composition. There are at least three reasons to create these schemes. **Schemes help us understand what to expect in the actual preparations** and increase the likelihood of finding the relevant structures in the preparation. **Schemes serve as a guide and inspiration for drawing of the actually observed cells and tissues**. Finally, **drawing of diagrams increases our attention to detail when using the microscope**. A well–drawn scheme can summarize the knowledge gained from observing many real–world specimens. In addition to the hundreds of schemes included in the book, you can also find recommendations on how to draw your own schemes and note your observations. **Schemes in the book are not quite photorealistic, and in selected cases, they depict the structures, which** would require replacing the lens in the microscope, disproportionately at various scales. Rather than memorizing, they are intended to inspire readers for their own observations. The advantage of schemes is the possibility to **depict the knowledge gained by observing a large amount of preparations,** which is one of the differences from photography, showing always only one particular segment of the cut.

Whether we watch **histological specimens through a microscope, or study their digitized, scanned virtual form**, we will encounter the restrictions associated with cartoon schemes. **Actual preparations appear to be less clear**; it is often difficult to find the boundaries between cells **and we need to acquire and not to lose the orientation when using different lenses**. Good tool are **the photomicrographs at the end of chapter**. For readers, we **carefully selected the preparations and images magnifications with regard to their readability,** so that they can serve as a start line for practical lessons. However, with the current range of the book, the images do not form a coherent atlas, and there is no need to include images of all the specimens and all magnifications showing the objects of interest. That is why we recommend using other printed or electronic histological atlases for practical microscopy. For microscope control and effective description of the preparations, we offer the readers the guidance in the chapter **Microscopy techniques**.

Effective study of histology requires the combination of several types of study materials with practical activities.

Microscope – window into the micro–world

Until microscopes were invented, improved and became a part of the education of physicians and naturalists, **the concepts of the internal structure of the body, its functioning, the causes and mechanisms of most diseases were cloudy or vice versa boldly speculative**. Microscopes are devices that have fundamentally shifted and are still moving the limits of human knowledge. **We cannot even imagine how the medicine would look without microscopes today**. The way microscopes expand our horizons, forces us to face tasks beyond our routine and everyday experience, especially in the introduction to histology (and other disciplines such as microbiology and physiology). We do not have direct contact with objects as small as cells or fibers and extracellular matter molecules. **Initially, we lack the idea of the dimensions and patterns**, which, unlike our macrocosm, **control the processes at the cellular and even smaller level**. We lack the terms for the descriptions of units generated by processing and staining of sections, **we have to distinguish a number of artificially induced changes in the preparations (artifacts)**. During its existence, histology nurtured **a rather effective terminology**, which has a similar role like. the small multiplication table in math – only its mastering opens more horizons where we can work and move. **The rate of use of microscopy at secondary schools is very diverse** , approach to teaching the basics of classical languages (Latin and Greek) in secondary schools and medical faculties are different and histology is included into different semesters of the curriculum of medical faculties. **Since we consider the knowledge of the key terms essential** (without the terms, one cannot create a meaningful sentence and without the original sentence, no response at the test, let alone during a discussion with the teacher)**, we followed the following principles when writing Memorix**: **All terms are explained as clearly as possible in place of the first occurrence, and only then they are placed in context**. **Simpler terms are preceded by more complicated ones**. Where it is absolutely necessary to explain the concept and there is no stable Czech term**, we provide the original Latin or English terms in the text**. Because the required level of Latin in histological terminology may vary at various faculties, at the end of the book, there is a Latin–Czech Cytological dictionary **of less frequently used terms**.

We were very pleased with the favorable reactions to the first edition and a number of suggestions for further improvements, which we happily incorporated into the second edition of the Memorix. Based on the experience of students and teachers, we have made **hundreds of both smaller and larger amendments and clarification of the text, we have added 56 new microphotographies, added some schemes** and took into account the comments of the main clinical reviewer in the areas that help use information from histology in other fields of medicine study.

We therefore present this book to you, our readers. Our goal is to make your life more enjoyable and to encourage you to study deeper. Your suggestions for improvements or additions are welcome at the web site **www.memorix.cz**. The whole team of Memorix Histology wishes you effective time spent with the book and the microscope:

Jan Balko, Zbyněk Tonar, Ivan Varga
Prague, Pilsen, Bratislava, 11. 6. 2018

Due to the content and terminological demands of histology, we need to learn it very effectively. It is therefore useful to create **a system** that **makes revising faster and easier**. Although each student has their own system of learning, we have created the so–called **Memorix learning system** which can serve as a good inspiration. But since you are studying medicine (or a related field), you are bound to know that even the best system does not replace hundreds of hours you have to devote to learning. **Besides Memorix, your studies will need a "steel skull and lead bottom"**.

Steps of the Memorix Education System

1. **Syllabus and introductory texts** – at the beginning of a chapter or a unit, make a simple overview of its content
   – read the introductory spreadsheets of the contextual text that will tell you the story of the chapter and introduce the main terms
   – browse subchapter names, read the sentences in the opening windows of subchapters, and take a quick look at the main texts and pictures
   – write a few questions the text should answer (you can find an inspiration in the questions at the end of the chapter)
   – create a learning plan according to the scope of the chapter (how many hours you spend with one page, how many days you will learn for, etc.)

2. **Main contents** – scroll through the main contents of all subchapters to the smallest detail
   – read the introductory sentences once again and go through the main texts with pictures where you can find answers to your questions
   – underline what matters to you, make excerpts, redraw images, create mind maps

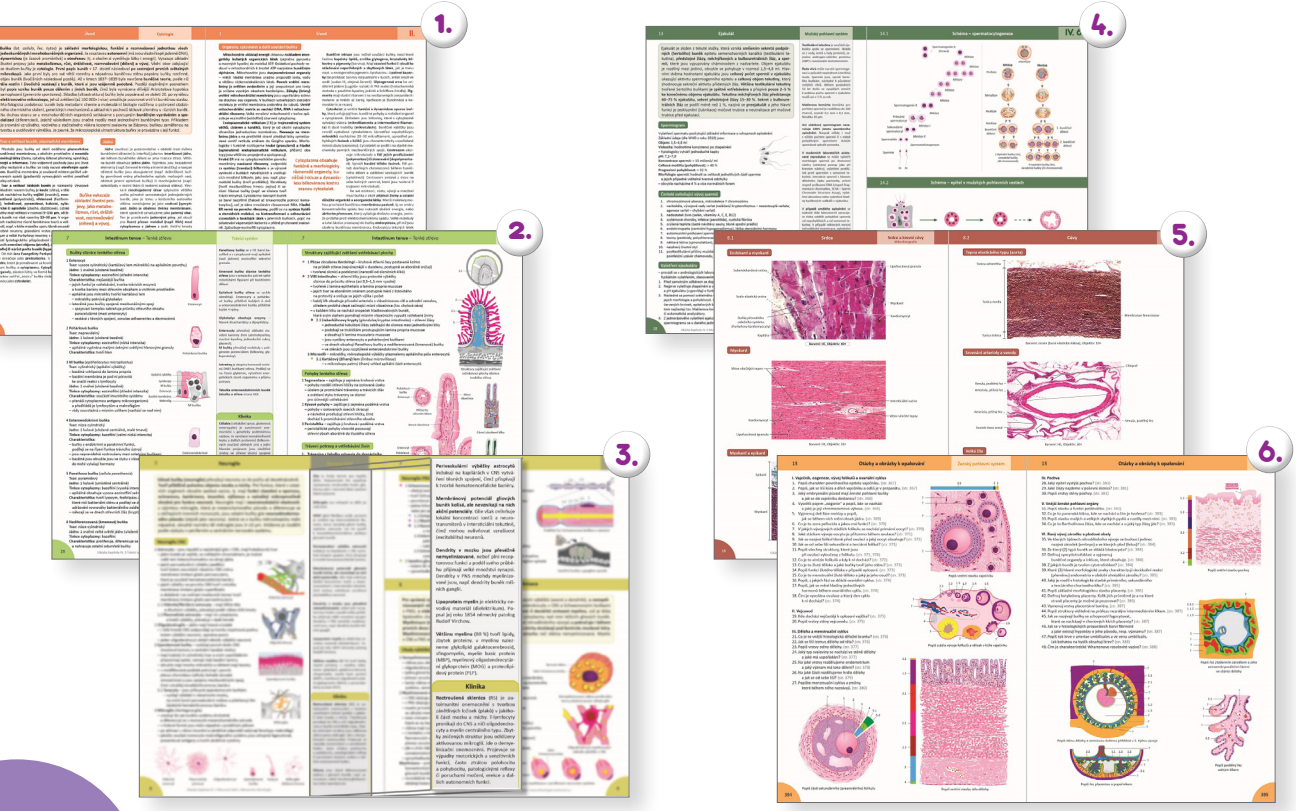
3. **Points of interest and clinical information** – after browsing the main content, see the information in the middle column
   – less important information, examples and outdated terms can make it easier for you to memorize your curriculum
   – read the clinical correlations to know which knowledge you will need the most as a physician

4. **Schemes, tables, and decision algorithms** – look at the clearly arranged information after the main text
   – decision algorithms will help you find the right way to search for cells or tissues in light microscope

5. **Electronograms a micrographs** – electronograms at the end of the Cytology chapter, micrograph in all other chapters
   – large annotated images will show you a real picture of histological structures seen in electron and light microscopy

6. **Questions and images to revise** – review questions and images to revise and make sure you understand the topic well

7. **Present the acquired information** – aloud and systematically, present the information you have learned to yourself or your classmates



Histology is not only intended to educate students about the microscopic body structures and research purposes. This is a **science with a wide practical use**. All tissues collected from patients must be histologically examined – these procedures are performed by doctors **at the pathology department who draw histopathological conclusions**, i.e. **examination of tissues obtained** from diseased, but **predominantly from living patients**. Definitive **diagnosis of malignant and many non–malignant diseases comes from pathologists**, although the lay public generally has no idea about the necessary processes. Collected materials include the tissues of almost all organs of the body in very different scale – **from cytological smears and puncture or lavage of effusions, through endoscopic sampling, curettage and excision, to surgical removal (resections) of any scale**. **Almost all medical fields** cooperate with the pathology daily and thus **come into contact with histopathologic terminology**. Therefore, it is necessary to learn it if we want to understand the findings in our patients.

I. Nature of material

Histopathology examinations on pathology departments are divided according to the nature of the acquired material – **necropsy, biopsy and cytology**. The results of all these methods go to the clinician who requested (indicated) them.

1. **Necropsy indicates tissue samples of dead patients** collected by a pathologist at autopsy to help determine the cause of death and to clarify the circumstances.
2. **Biopsies include any samples collected from living patients**, representing a wide range of materials from e.g. excised skin moles, through endoscopically removed material and curettage to the biopsy of whole organs (routine example is the appendix, uterus or gall bladder during the most common surgical procedures), and organ units (e.g. transplantation, amputation and cancer). Biopsy diagnostics is the predominant part of the workload of a pathologist and allows the definitive diagnosis of a number of diseases, especially tumors. Depending on the findings, the clinician continues to follow up on the patient's progress and when deciding about the treatment.
3. **Cytologic diagnosis** indicates the methodology that evaluates **individual cells isolated from tissues**. This discipline extends to other specializations and is used e.g. in the departments of gynecology and pneumology. Collected materials include a variety of cell surface swabs, cells aspirated using needles, punctuates or lavage of exudates and body cavity contents and cysts. Since cytology only evaluates cells without their tissue relationships, it does not inform about the microscopic structure of respective organs or their layers.

II. Sampling

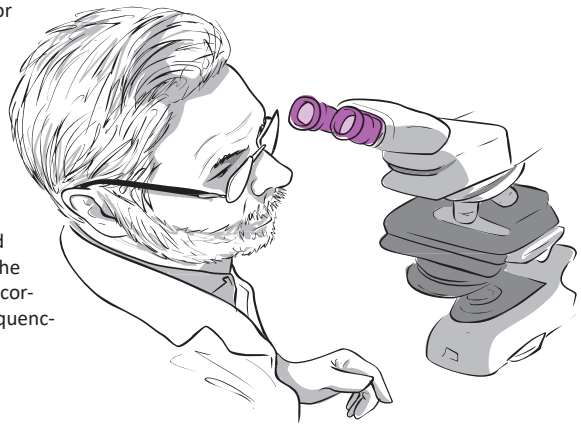
For the clinicians, the familiarity with the preparation of histological specimens is particularly useful **during the collection of the material**. It is imperative to know the medium, the collected tissue should be put into to ensure the preservation and enable the transfer, and to know how it is to be treated. All of this can be illustrated in an example of surgically removed appendix (appendix vermiformis caeci) in common inflammation (appendicitis).

After removing it in appendectomy, the surgeon must have it subsequently **fixed in formaldehyde solution in an appropriate volume (optimum volume ratio of 1:10 – tissues to formol)** and sent to the pathology department. Conversely, **other material should be sent to non–fixed, or frozen** (e.g. intraoperative biopsy) or stored in other media (for electron microscope examination, genetic tests). Any error in this process leads to the degradation of the material and further hinders the diagnosis with the corresponding consequences.

III. Diagnostics

Standard preparations, encountered during histology studies (clear staining with hematoxylin–eosin) are usually used in the histopathology diagnostics. If necessary and in cytological methods, useful staining may be added, which is also discussed in the chapter **V. Microscope techniques**. In many cases, **immunohistochemical and histochemical methods** are commonly used.

1. **Immunohistochemistry** mainly helps **decode cancers,** which has a fundamental role in determining their prognosis and treatment.
2. **Histochemical methods** allow to clarify **pathological processes of metabolism**.
3. **Other special procedures** , used mainly in the pathology of nerves and muscles, include **polarization and electron microscopy**.



Pathologist during biopsy diagnostics

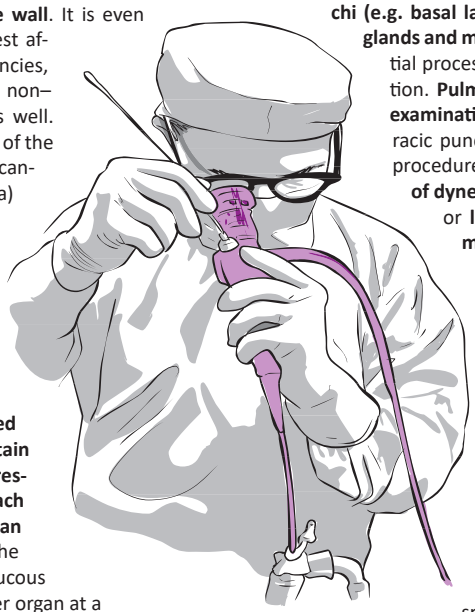
The above–described text implies another, also important significance of histology, especially for medical students. Histology is crucial for the subsequent study of pathology and other subjects in the following difficult years**.** Pathology **deepens the acquired knowledge about the physiological body structure at the microscopic level.** It shows morphological changes of tissues in disease states**. The success at the pathology examination in many institutes includes** the recognition of preparations with the basic pathological findings**. Other preclinical disciplines, where you will** work with histological terms, are embryology, physiology and pathophysiology**. As for the clinical subjects, particularly** oncology, hematology, internal medicine and gynecology.

As already indicated, **clinical medicine widely uses microscopic diagnosis of living patients** in the collaboration with the department of pathology. **Many histopathological findings are routine for pathologists** and clinicians come into contact with the resulting findings very often. The understanding of the descriptions of microscopic characteristics of disease states requires **good understanding of the histological structure of the organs**. We have prepared several examples of frequent cases categorized by clinical disciplines with a description of the basic knowledge in histology a clinician must cover.

Internal medicine

Almost all internal fields **abundantly use biopsy, particularly oncology and hematology,** but also pneumology, gastroenterology, nephrology, endocrinology, hepatology and others. **The physician in this field must know the histological structure of the organs he/she is specialized in** to fully utilize the results of the pathological evaluation to determine the extent of the damage and the next steps.

Gastroenterology is one of the most common referents for biopsy thanks to the introduction of endoscopy. It is necessary to know the wall structure of the entire digestive tract, because the penetration of local tumor affects the prognosis and treatment**. A** tumor affecting only the epithelium (carcinoma in situ) behaves and is managed in a different way than **invasive adenocarcinomas infiltrating the wall**. It is even necessary to accurately state the deepest affected layer of the wall. Besides malignancies, **precancerous (preceding cancers)** and non–tumorigenic processes are examined as well. E.g. goblet cells in the esophagus instead of the squamous epithelium are a high–risk precancerous condition (intestinal metaplasia) **and the patient should be further monitored (follow–up). Histology is used to determine the presence and type of inflammation of the esophagus, stomach and intestines (Crohn's disease, ulcerative colitis, microscopic colitis and others), including their severity (degree of esophagitis, gastritis, enterocolitis, proctitis) based on the degree of inflammation in certain layers of the organ wall. The eventual presence of a causative pathogen in stomach inflammation (Helicobacter pylori) can also be proven microscopically.** Also, the examination of polyps, ulcers, ectopic mucous membranes (mucosa presence of another organ at a specific location of the examined organ), and other conditions are the common problems biopsy helps solve. Without the knowledge of histology, the internist cannot truly understand **the description**.



The gastroenterologist performs biopsy using an endoscope

In pulmonology, the most common indications are **bronchial and lung tumors,** which again have different prognosis based on the affection of the bronchial walls. Likewise, asthma (asthma bronchiale) and other obstructive lung diseases are characterized by their findings with various **changes in the microscopic structure of the bronchi (e.g. basal lamina widening, increased number of glands and muscle layer in asthma)**. Also, all interstitial processes require histopathological examination. **Pulmonology also widely utilizes cytology examination of pleural effusion,** obtained in thoracic punctures. An example of very specialized procedures is **electron microscope examination of dynein arms in cilia** in Kartagener syndrome or **lamellar bodies in the granular pneumocytes** in defective synthesis of surfactant.

Nephrology frequently requires the help of pathologists, including the use of highly specialized techniques **(electron and polarization microscopy)**. This happens mostly in the **diagnostics of glomerulopathies, which cannot be understood without the knowledge of the structure of renal corpuscles**. **Transmission electron microscope** (TEM) specifically helps reveal **the damages to the filter barrier and is also used before the transplantation of kidney**. Also, endoscopic cold biopsy of the urinary bladder and urinary cytology are the "daily bread" of a pathologist.

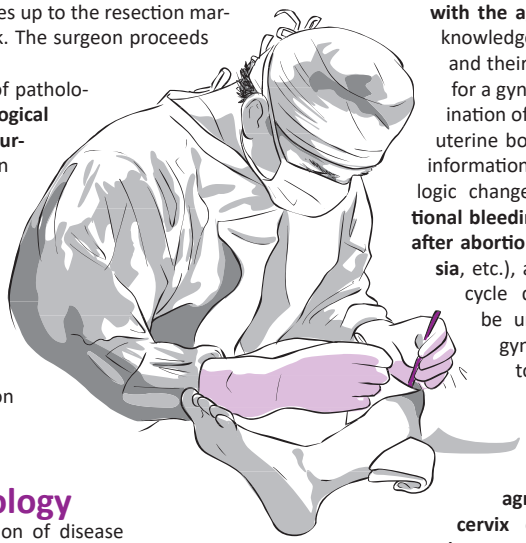
Hepatologists perform **percutaneous liver biopsy** requiring **various special staining method in the microscopic examination** (**PAS** to confirm glycogen storage disorder, **Berlin blue** for iron accumulation, **trichrome** for fibrosis and others) to help diagnose a wide range of disorders from inflammations, cirrhosis, tumors to complex metabolic diseases and storage disorders.

Endocrinology calls for pathologists especially in the resection of **thyroid gland due to the hyperplasia (goiter), inflammations and tumors**. Endocrinologists always receive the description of the structure and **lining of the thyroid gland follicles,** helping them clarify the process.

Surgery

The requirements for histopathological examinations performed by surgeon overlap partially with the internal ones due to the similar use of endoscopic techniques. Further, surgeons supply biopsy station with numerous **resection samples of organs and tissues from all body parts**. As already said, each excised and resected tissue or organ sample must be examined. Whether **the appendix in the inflammation** (appendicitis), **gallbladder affected by gallstones** (cholelithiasis), **limb in case of amputation, or in major procedures in transplantations and oncological affections**. The surgeon will then receive extensive descriptions of the resected samples with information about the microscopic form of the process and the resulting diagnosis. This description is particularly important **in tumor diseases**, where the **depth of penetration, and metastatic affection of lymph nodes and distant organs are evaluated**. The results are reflected in the **TNM classification of** the extent of tumor spread: T – the extent of the tumor, N – metastases in regional lymph nodes, M – distant metastases, determining the type of the management. It also evaluates whether the disease process reaches up to the resection margins or whether the surgeon has removed the whole bulk. The surgeon proceeds based on all the reported information.

Another service offered to surgeons by the department of pathology is the **intraoperative biopsy**. This is a **rapid histopathological evaluation of the disease process directly during the surgery of the patients**. It enables to clarify whether it is an inflammatory or cancerous tissue change and informs the surgeon **whether he/she has resected the whole** bulk, or whether the process still exceeds the border of the removed sample**. Once the result is reported, the procedure may be completed or continued, extending its scope (more radical approach).** The technique of frozen sections is used during intraoperative biopsy. It significantly speeds up the tissue processing, because the sections are sliced and dyed without the need for fixation and embedding into paraffin blocks.



Surgeon during tissue resection

Gynecology

Another pillar in histopathological diagnostics is gynecology. The most commonly investigated samples include **curettage of the cervix and uterine body**. The cervix can be affected by a wide range of pathological processes which differ **by location (exo– or endocervix)**. **Each of these areas is lined by a different type of epithelium** and their interface is subject to various pathological changes. **The border of the epithelium moves with the age (ectropium)**. The knowledge of these linings and their changes is essential for a gynecologist. The examination of the curettage of the uterine body mucosa provides information on both the pathologic changes (**mostly dysfunctional bleeding, embryo remains after abortion, polyps, hyperplasia**, etc.), as well as menstrual cycle dating, which must be understood by every gynecologist at the histological level. As for more extensive gynecological examination, let's state **the diagnostics of uterine cervix conization samples (resection of the affected part of the cervix in the shape of a cone), placenta after birth and resected uterus with the uterine tubes and ovaries (adnexa) after hysterectomy with eventual adnexectomy**. Other organs of internal and external female reproductive system are sent for histopathological examination. Routine gynecological examination includes the **cytological diagnosis of cervical smear**, which is useful for the early detection of metaplasia and precanceroses, often preceding the developing tumor.

Oncology

comprises a large **region of the tumor issue** within the internal fields. There are many types of tumors, which are divided **based on their microscopic morphology,** which matches their histogenesis. **Each tumor stems from certain cells of the tissue of various organs**. It often at least partially retains its original morphological features. Describing these histological features and determining the type (and possibly the subtype) of the tumor allows for an accurate diagnosis, which can be used by the oncologist to initiate an appropriate and targeted treatment regimen. As already indicated, **the extent of the cancer in the affected organ and its surroundings** (staging) **and its microscopic differentiation** (grading) are evaluated. A more accurate cancer diagnosis is often based on **specialized staining (mucicarmine, PAS, trichrome, Congo red)** , **immunohistochemical examination** and in many cases **even genetic testing**. The knowledge of histological terminology and microscopic anatomy helps oncologists navigate through the findings.

Hematology

The recognition of disease processes in hematology is an extension of pathology. Blood disease diagnostics is complex and requires laboratory testing in cooperation with microscopic examination**. The histopathological diagnosis often necessitates specialized methods** – flow cytometry, immunohistochemical and genetic analyzes**. Specialized staining is always used in** trepanobiopsy (bone marrow aspiration)(cholesterol acetate esterase, Giemsa staining and silver reticular fibers).

Pediatrics

Children can also undergo **biopsy examination** similar to adults. The spread of the disease is different, but not less important, so the pediatrician should be familiar with descriptions of the histopathological findings. **Organ structure of the smallest children shows a range of histological differences when compared to an adult**.

Dermatovenerology

Skin excisions are also histopathologically confirmed. Macroscopic evaluation is inaccurate in many cases; often, the diagnosis is difficult to determine even microscopically. The **cooperation of the histopathologist and a clinician is really important for proper diagnosis**. Routine cases include **excised birthmarks (nevi), inflammatory diseases of the skin and small skin tumors**.

Designing the concept, creating curriculum and dealing with the publishers were only a fraction of the work at the beginning of the development of our textbook. All this was followed by **writing the texts, drawing the pictures** and the **professional typesetting**. At the end, we went through **dozens of reviews from histologists, pathologists, clinicians, students, as well as laboratory technicians and other academician** primarily from medical schools and hospitals in the Czech and Slovak Republic. On this long journey we needed a lot of help, so at this point, we would like to **thank everyone** who stood at the development of this revolutionary histology textbook.

First of all, we would like to thank the chief coordinator of the English version of the Memorix Histology **René Novysedlák** and the co-authors who sacrificed an incredible amount of time and energy with us to create this unique histological book. Co-author **Richard Adamčík** brilliantly created and edited texts in the Muscle tissue and Senses and skin chapters, where he focused on the skin section. **Bětka Blanková** perfectly described the Male reproductive system, Female reproductive system and Endocrine system chapters, but also contributed to sections devoted to glands in the Epithelial tissue chapter. **Martin Gavač** has systematically elab- orated on most of the chapter on Epithelial tissues and further creat- ed the comprehensive chapter on the Digestive system. We are immensely grateful to **David Kachlík**, who, in addition to writing the Respiratory system chapter and most of the chapter of Senses and skin chapter, actively participated in the creation of all other chapters. His contribution consisted mainly in the unification of histological terminology, which was not an easy task at all.

As for graphic design, we would like to thank the chief illustrator **Jan Balko** and the graphic artist **Šárka Zavázalová** who contributed a number of illustrations in the epithelial, connective and nervous tissue chapters, and also created the pictures in the Nervous system chapter.

We are extremely grateful to **Pavel Filip, Azzat Al–Redouan and Adam Whitley** for proofreading and copy editing of the entire contents. They spent extraordinary care on every word and term to read in the book as a fairy tale.

From the depth of our histological heart we sincerely thank everyone, who helped us bring Memorix Histology to reality.

Equally we would like to thank co-typesetters **René Novysedlák** and **Petr Stojčev** whom greatly helped **Rado Hudák** with the typesetting of 560 pages of this book.

We thank the main reviewers, **Vojtěch Kamarád, Marian Adamkov, Jan Petrášek**, all the academic and clinical reviewers and reviewers and feedbacks of students for carefully reading the chapters and providing valuable comments. Thank you for your remarks and patience, for helping unifying the terminology, for discussing the selection of the necessary information, and for resolving the contradictions that we have encountered in the referenced literature. Here we would like to thank especially **Ondřej Daum, Michal Miko, Andreas Arend, Renata Šimkūnaitė-Rizgelienė, Geoffrey Meyer, Aymann Ghallab, Daniel Bohmer, Maria Grazia Palmerini** for their helpful reviews. Namely thanks to all reviewers on the right side of this spread.

We thank the superiors and colleagues of our workplaces, with whom we share the burden of teaching and research work and whom are often our role models and inspiration. Namely we would like to thank **David Kachlík**, head of the Institute of anatomy of the 2nd Faculty of Medicine, Charles University, **Roman Kodet**, head of the Department of pathology, 2nd Faculty of Medicine, Charles University, **†Luděk Vajner** and **Jiří Uhlík**, former and current head of Institute of Histology, 2nd Faculty of Medicine, Charles University, **Milena Králíčková**, head of the Institute of Histology, Faculty of Medicine, Plzeň, and **Štefan Polák**, head of the Institute of Histology, Faculty of Medicine, Komenský University, Bratislava.

We are also thankful to **histological laboratory staff** at our sites, whom help was indispensable when creating the preparations used for the routine work and the development of educational materials. Their skill, diligence and patience are irreplaceable and represent the basic pillar of the quality of histological work and teaching.

Our appreciation goes also to **our predecessors and teachers** for their work in the field of histology, for the education of genera- tions of physicians and scientists and for the records on which we may count on.

We are also thankful to the **authors of the referred textbooks, atlases and scientific articles and our colleagues** for their ideas, consultation, advice and constructive criticism. Thank you to our associations and scientific fields, such as the **Czech Anatomical Society, Slovak Anatomical Society, Czech Cyto– and Histochemical Society and Czechoslovak Microscopy Society** for organizing congresses, support of scientific work and mobil- ity of young researchers, organizing training courses, providing the space for discussion of the morpholo- gy courses and other activities.

We also thank the Memorix PR team, **Ľuboš Repka** and **Slávka Sotáková**, Memorix mobile app coordinator **Ester Bartl** and managers **Avetis Švamberk, René Novysedlák, Martin Mikeš** for the very important work they are doing in Memorix company.

Thank you to **Stanislav Juhaňák** and all employees of the publishing house Triton, who take care of successful printing the book and getting it to retail shelves.

Last but not least, our thanks go to the rector of Charles University **Tomáš Zima** and vice–dean of the 2nd Faculty of Medicine, **Roman Kodet**, for being the godparents of our textbooks, thus expressing recognition and support to our work.

And with the greatest love, we thank our friends, families and beloved ones for their patience, tolerance and support, which enabled us to work on this textbook. Thanks to our girlfriends or wives, namely **Gabriela Holubová, Kristína Demjanovičová, Martina Tonarová and Mária Vargová** for standing at our side even in the moments when we, instead of romantic walks and a joint dinner, spent days and nights working with microscopes and computers to write "some pink book" for you.

Radovan Hudák, Jan Balko, Zbyněk Tonar, Ivan Varga

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59 Medical students

20 Other contributors

... worked hard creating MEMORIX HISTOLOGY for You!

If I learn all the time, I will know much and I will become a great doctor**. And because there is a lot to learn in medicine, I cannot waste time with other activities. This is one view of the study of medicine. The second one says that** it is not just knowledge which makes a successful doctor**.** The expertise gained during the study is an important building block, but certainly not the only one**. A good doctor has to master** professional **communication, time management, but also the management of the entire health care team. Only after the school, many graduates find out how difficult it is to coordinate the investigation of dozens of patients over several hours, or** how strenuous it is to clearly explain the diagnosis and subsequent treatment to the patient**.** Student clubs **provide excellent conditions during the study for the development of these** so called soft skills**.** By organizing projects, **you can learn** to manage your time, improve your communication skills **but also meet** a number of complications that you have to solve**. I spent many years in Motolák and IFMSA CZ, and they helped me much gain experience and contacts**. **Without this stage of life, I would probably never go into large projects such as the creation of books Memorix Anatomy and Memorix Histology**.

Radovan Hudák

Motolák is the student heart of the 2nd Faculty of Medicine. Each year, it organizes more than 40 projects focused on culture, sport, study, arts and volunteering. Musical group Ježci or volunteers in the Week of reading regularly make the long moments of children and seniors in the hospital more pleasant. The exhibition of pictures and photos of students and teachers called MotolArt presents the artistic talent of future and current doctors. (The main graphic artist and both graphic artists of Memorix also exhibit their paintings at MotolArt). The Faculty ball and the Steamer for graduates are among the biggest cultural events at the faculty. The project promoting science in a café called Medicafé gradually spread from Motol, thanks to IFMSA CZ, to most of the faculties of medicine in the Czech Republic.

IFMSA CZ is a part of the largest student organization in the world (IFMSA). In the Czech Republic, it has local branches at all medical faculties. Projects such as Teddy bear hospital, World AIDS Day, World Diabetes Day, 4Life, Medicafe, and Smokefree Party allow medical students to get to the issue of public health and education during their studies. Thanks to its membership in the multinational organization, the support of faculties and clinical departments, it facilitates exchange scholarships throughout the world. Every year more than 300 Czech medical students are sent to a clinical or research internship.

Trimed makes the 3rd Faculty of Medicine what it is – family–like and friendly. It strengthens the relationship between the students and educators at various events, such as the Representation ball, Steamer and many others, it extends the horizons of medical students through various study projects and adventure courses, and helps prospective graduates find employment at the annual work fair. Younger students are helped with seamless entry to the faculty, and the older ones can enjoy nice movements between the study sessions.

The Association of Czech Medical Students is the oldest student organization in the country with more than 150 years of tradition. Still, it has a young beating student heart – the purpose of the association is to care for the cultural, social and scientific life of the medical students of the 1st Faculty of Medicine, Charles University. Traditional activities include Mikuláš in the General University Hospital, a picnic in the garden of the Department of Psychiatry or the care for foreign students.

The Association of Medical Students at the Masaryk University is a student organization with more than ninety–year history. Traditionally, it organizes the Representation ball of the Faculty of medicine with Matriculation, the Student Scientific Conference, various lectures and social evenings with guitar.

The Association of Medical Students at the Palacký University organizes the project You do not know, you will not save!, which allows participants to virtually practice the basics of first aid. The night sports tournament of medical students always shakes stiff limbs with the slogan "healthy body, healthy spirit."

SloMSA, as a member of the international organization (IFMSA), mediates clinical and research internships for more than 150 Slovak medical students every year worldwide. In addition to internships, it also organizes interesting projects such as First gynecological screening, Stop AIDS, Men's Issues, Teddy Bear Hospital and many others.

The Association of physicians of SZU mediates voluntary internships at SZU departments clinics and surgical suturing seminars. It also focuses on projects for the general public through lectures at secondary schools or the project 5 minutes for your health.

The Association of Medical Students in Bratislava (BSM) is an association of more than 300 medical students at the Medical Faculty of Komenský University in Bratislava. The association supports the medical students in their studies, personality growth, and enhances the possibilities of education by organizing courses, seminars and lectures in various fields, not only in medicine.

The Association of Medical Students in Martin (MKM) is an association with a long tradition that helps students develop in many projects ranging from sports activities, lectures at schools, education courses to medical students.

The Association of Medical Students in Košice (SMMK) is an interest organization for students and graduates of the Faculty of Medicine of Šafárik University in Košice, who are interested in developing the scientific, cultural, social and sports life at the faculty. The mission of the association is to provide spiritual growth, cultural and social life as well as to increase the professional level of students and thus contribute to enriching the personality of the future physician.

The Association of Dentistry Students of the Czech Republic (SSSČR) is intended for all the students of dentistry. It publishes the StuDent magazine, organizes projects in Healthy Czech Republic with Healthy Teeth, International Dental Student Congress and sends students for foreign internships.

The Association of Physiotherapy Students brings together all students of physiotherapy in the Czech Republic, it organizes the projects as FyzioCafé, Physiocamps, Physiomeetings and other conferences and workshops. It provides foreign internships for students of physiotherapy.

Motolák
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www.motolak.org

IFMSA CZ
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ASF
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SSSČR
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www.ssscr.cz

Radovan Hudák
managing editor and author

Impossible – what is it? For everyone it's different, and **that's the problem**. When I was at elementary school, I loved basketball so much that I wanted to play it professionally. **I was told I could not make it, but I did not believe them.** I went to Košice for sports grammar school and I played junior extraliga. Then I wanted to go from a sports school in the eastern Slovakia **to the 2nd Medical Faculty of Charles University in Prague** and once again, everybody laughed at me, that I cannot make it. **Once again, I worked hard, and I made it**. When I was putting together the team of Memorix Anatomy five years ago, **I only smiled when someone said that what we want to do is virtually impossible**. Because what is impossible? Just what **does not motivate us to create the "possible"**. I'm filling my dreams, no matter how real they are for others, and that's what I want. **Believe in yourself, work hard, and you can even make the impossible work**.

Jan Balko
editor and chief illustrator

It is said that there are two kinds of textbooks. **"American model"** is a book that tries to sell itself to the reader and attract him/her **with readable text with numerous pictures and diagrams, so that his studies go smoothly**. **The second model is the so–called "Russian" –** textbooks that simply provide the material and "**who does not understand it, has got nothing to do here**". I firmly believe that we have managed to create the first model. I do not want to describe **the incredible amount of work at length we devoted to it**. I'd rather find a spot in silence somewhere in the corner, and I believe that **all texts and pictures** which we have prepared with co–authors, **will make your studies of this beautiful, yet underrated science, histology, simpler**. As **a pathologist**, I also know that **histology is not an unnecessary discipline, but rather a fundamental building block for understanding the pathology** – associated science, every physician will work with. And do not look for anything cynical in this statement.

Zbyněk Tonar
editor

It was embryology that brought me to histology. For the thesis at the end of my studies as a biology teacher, **I needed to learn to cut, stain, work with microscope and photograph histological sections** and embryos of various mammals. **Teachers and researchers from the Faculty of Medicine in Plzeň** helped me, advised and **inspired me for this field** so much that I graduated from the faculty. **As a medical student I was involved in research and in lecturing at the Institute of Histology and Embryology and I do so until today**. **I still enjoy working with the microscope.** With its help, histology provides a unique insight into many medical disciplines and **enables me to find answers to unanswered questions**. I focus **on quantitative histology of blood vessels of humans and microscopic evaluation of experiments in animals** where we want to understand **the nature of certain diseases** and to test whether it is possible to treat the conditions. I like music, books and sports.

Ivan Varga
editor

It's now been almost four years since I got the first chapter of Memorix Anatomy to review. The team of authors consisted **mostly of medical students, which was revolutionary!** I thought **how wonderful it would be to write in a histology book in similar spirit**. We managed to inspire the Rado Hudák to organize a team of authors from several medical faculties from the Czech Republic and Slovakia. It was a formidable task, and **in addition to the actual creation of chapters, we spent weeks with discussion over the accuracy of different views. Our graphic designers repeatedly edited pictures based on our requests**... Today, however, it seems that **my wish was fulfilled**. **Neurohistologist Ramon Y Cajal compared the various cells of the neural tissue to "fragile and elegant butterflies of the soul"** in 1937. I believe that **you will also see similar gorgeous cells in your microscopes** and that the exploration of the human body will bring you more joy than trouble.

Richard Adamčík

author

I got my first **microscope at the age of 10** and this moment **probably predestined my whole further journey**. My whole youth was accompanied by the verve for all natural sciences and a dream to become a scientist. **My heart drew me, for some reason, to the medicine** where I reopened that magical window into the microscopic world. **From the second year of my studies, I work as a lecturer at the Department of Histology and Embryology** of the Faculty of Medicine in Hradec Králové and precisely **this desire to share my knowledge** brought me to **the team of this revolutionary textbook**.

Alžběta Blanková

author

My journey to histology was not a straight and not planned at all. A chance brought me to her and my direction **was gradually shaped by meeting with people who taught me to see the beauty of the micro–cosmos.** They gave me the opportunity **to develop the ability and participate in scientific projects**. I was lucky because they became great friends and **histology has become a passion I have tried to pass on to my students**. I hope I at least partially succeeded and that **Memorix can not only improve the studies, but also seduce the reader to the same path that we took**.

Martin Gavač

author

Unlike Rado, I **I'm no workaholic**. **I did not want to go for medical studies,** because medicine requires hard work. But eventually, the other professions seemed so boring, that I filed the application. **After the histology examination, I got an offer to work as a lecturer**. Even if against my nature to minimize my efforts, I accepted the offer. **It is similar to the philosophy of Memorix**: **the information is given simply, clearly and understandably**. Thanks to the excellent figures, histology studies are from now a piece of cake**. Enjoy learning from it!**

David Kachlík

author

Anatomy is my love. During the study, I found that **without histology and embryology, it is not well understood** and I decided that **as a teacher, I will pass on the information about the structure of the human body through functional and clinical morphology** that highlights **the context and meaning of each part of the human body**. **Histology plays an irreplaceable part here,** similarly to the **scientific research**, which fills the other half of my career. **The cell rules the world,** whether we want it or not, so let us subdue it to make it serve us well.

Šárka Zavázalová

illustrator

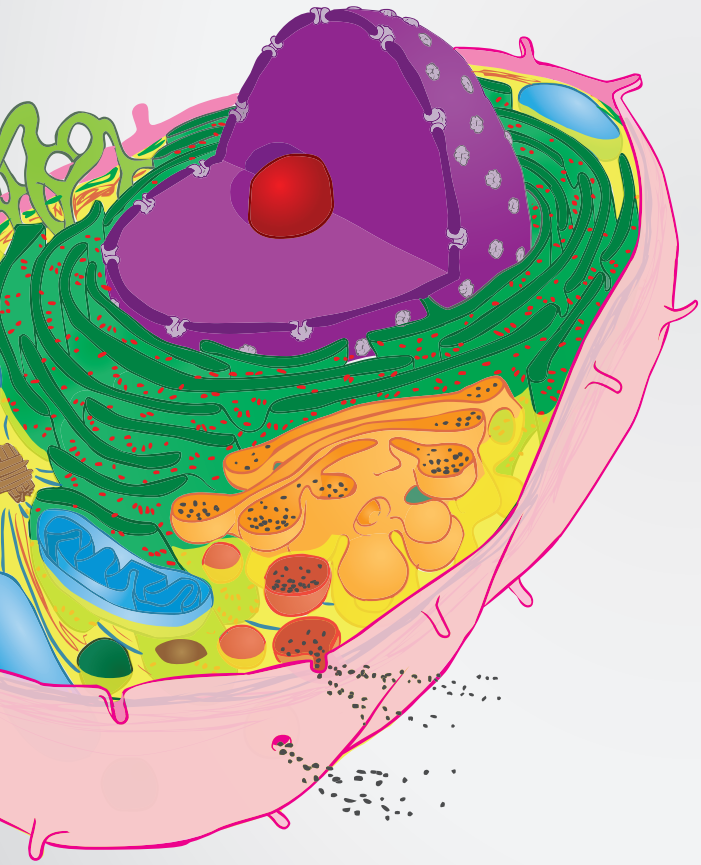
I confess that in the first year of medical school in histology, I **enjoyed only drawing the histological slides into my notebooks during the class**. It was supposed to help us **remember the observed structure**. Though it would certainly be much easier, if the schematic images had already been created. **During the development of Memorix, I was trying to help in this area**. And though I **thought that I will never meet microscopes in medical practice,** I have another confession to make – I like using them, when, as **an ENT specialist, I look into the ears of my patients**.

"If you cannot explain it simply,
you do not understand it well enough."

Albert Einstein

Memorix Histology

II.
Cytology



Ivan Varga
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Cell (Lat. *cellula*, Gr. *kytos*) is the **basic morphological, functional and reproductive unit of all unicellular and multicellular organisms**. It is **self-replicating** (it has its own copy of nuclear DNA), **dynamic** (it changes in time) and **an open system** (i.e. it exchanges substances and energy with the external environment). It exhibits basic life characteristics such as **metabolism, growth, excitability, reproduction (division) and development**. **Cytology** is the field of life science concerning the study of cells'structure and function. The **first description of the cells** in the 17th century followed **the invention of the first light microscopes**. The plant cells were the first to be described due to their larger dimensions and noticeable cell wall; the discovery of animal cells followed later. The **cell theory** was proposed in the years 1837–1839, claiming that the **bodies of plants and animals were composed of cells that are similar to each other**. Later, further findings on the origin of cells only by division from other cells**, thus confuting the earlier Aristotle hypothesis of spontaneous fertilization** (generatio spontanea*).* The structure (ultrastructure) of the cell was described in the 20th century after the invention of electron microscope, its magnifying power (up to 100,000× or more) allows the observation of the internal cellular structure. The morphological similarity of cells has been extended through chemistry and molecular biology methods by the confirmation of similar chemical composition, genetic mechanisms and basic processes of metabolism among different cells. On the other hand, multicellular organisms are characterized by gradual cellular maturation and specialization **(differentiation) resulting in significant differences between individual cell types.** An example is the comparison of a skeletal muscle fiber carrying an excitatory, conductive, and contractile function; with a glandular cell carrying formation and release of excretions function. It is obvious that microscopic ultrastructure of the cell is related to its function.

Shape and size of cells, cell membrane

Although cells are separated from the surrounding environment by the **cell membrane**, they constantly exchange substances **with the environment** (nutrients, metabolic wastes, excretion), **energy, and information**. These mutual processes are necessary for the life of the cell and the cell can therefore be called an **open system**. At the same time, the cell membrane is a place of carefully maintained gradients that define the internal environment of the cell from the external environment.

Human cells are of various shapes and sizes. From developmental point of view, the basic shape of the cell is spherical**, but in the body we find** ovoid**,** polyhedral**,** spindle-shaped **(fusiform), stellate, pyramidal, cuboidal, columnar or squamous** (pavement). Human cells have a size in the range of **5–150 µm**, but most cells have the size of **10–30 µm**. There are various combinations of shapes and sizes in the organs, for example, the cerebellar cortex contains extremely small neurons in the granular layer with a diameter of 5 µm closely adjacent to large 120 µm Purkinje cells. Physiological adaptation and also pathological conditions in some cells include **reduction in size (atrophy), increase in size (hypertrophy), or increase in number of cells (hyperplasia).**

The cell exhibits basic life characteristics such as metabolism, growth, excitability, reproduction (division) and development.

From the time of **Jan Evangelista Purkinje**, the living content of the cell is referred to as **protoplasm**. Within the cell, we distinguish the **nucleus**, which is thought to be the cell's coordination and information center, and **cytoplasm**. **Cytoplasm** contains numerous **organelles**, reserve substances in the form of **cytoplasmic inclusions**, and the dynamic internal "skeleton" of the cell composed of proteins, referred to as **cytoskeleton**.

Nucleus

Nucleus is observable in the phase between two cellular divisions (in the interphase) as the so-called "interphase nucleus", its nuclear envelope disappear during cellular division. Most cells contain **one nucleus**. Exceptions include nucleus-free elements (e.g. red blood cells and platelets), and some cells with two nuclei (e.g. umbrella cells of the transitional epithelial layer of the excretory urinary tract, some hepatocytes of the liver) or multinucleate (e.g. osteoclasts in bone tissue or skeletal muscle fibers) . If the **multinucleate object** is formed by the merging of more originally separated mononucleated cells, as is the case in skeletal muscle fibers, we refer to it as a syncytium**. The nucleus is enveloped by two membranes**, collectively referred to as a **nuclear envelope**. It contains protein-lined openings – **nuclear pores**, which serve as a medium for **controlled transfer of molecules (e.g. RNA) between the cytoplasm and the nucleus** and vise versa. The inner matter of the nucleus, the so-called **nucleoplasm**, consists of **chromatin** and a three-dimensional scaffold of **intermediate filaments**, called the fibrous lamina. Chromatin is made of DNA strands bound to histone and non-histone proteins. The nucleus contains also a nucleolus producing *ribosomal RNA*. Even in the most common staining (hematoxylin and eosin), the cell's proteosynthetic activity can be estimated using a light microscope based on the characteristics of its nucleus. If the lightly packed form of chromatin, **the euchromatin** (less compact, hydrated, accessible for transcriptional enzymes, with lower intensity of basic stains) predominates, with a noticeable nucleolus (or two or three nucleoli), the cell is in **proteosynthetic activity**. The predominance of tightly packed form of chromatin and intensely stained **heterochromatin** assume **low DNA transcription activity**. The proportion of euchromatin and heterochromatin depends on both the cell type and the stage of its development.

Organelles, cytoskeleton and other components of the cell

The mitochondria store the energy obtained **by decomposition of energy-rich organic substances** (especially pyruvate and fatty acids) to ATP molecules. Oxidative processes leading to the production of ATP in mitochondria are called **cellular respiration**. Mitochondria are **double membrane-bound organelles** - the outer smooth membrane is easily permeable for ions, water and most low-molecular substances. **The inner membrane surface is extensively folded** and its ion permeability is reduced by the high cardiolipin content. **The invaginations (cristae) of the inner mitochondrial membrane** are perpendicular to the long axis of the organelles. In cells producing steroid molecules, the inner membrane is folded into tubules. **The mitochondrial matrix contains DNA, RNA and mitochondrial ribosomes.** Large numbers of mitochondria in the cell lead to eosinophilic (acidophilic) cytoplasmic staining.

Endoplasmic reticulum (ER) is **a three-dimensional system of sacs, cisterns and tubules**, which is delimited from the surrounding cytoplasm by a simple membrane. **It is adjacent to the nuclear envelope** and passes the substances synthesized inside the reticulum on the opposite side towards the Golgi apparatus. Morphologically and functionally, we distinguish between **rough (granular) and smooth (agranular) endoplasmic reticulum**, both of which are mostly interconnected and collaborated. **Rough ER posses ribosomes** on the cytoplasmic surface of the membrane, is responsible for **protein synthesis** (translation) and is highly developed in cells producing and releasing proteins such as plasma cells (antibodies), fibroblasts (produce the extracellular matrix of connective tissue proper), or serous exocrine cells (e.g. digestive enzymes in the pancreas). The cytoplasm of such cells is basophilic (purple to dark blue in hematoxylin and eosin staining), reflected by the amount of presented ribosomal RNA. **Smooth ER has no ribosomes** on their surface, it is involved in the **synthesis of lipids and steroid molecules, biotransformation and degradation of foreign and toxic substances** in liver cells, events. the storage of calcium ions in skeletal muscle fibers reflects an eosinophilic staining appearance of the cytoplasm.

The Golgi apparatus (complex) is a set of mutually parallel flat vesicles and saccules, which are bounded by one membrane. At its cis-face (entry face), it absorbs transport vesicles from the endoplasmic reticulum, and converts the proteins and lipids contained in these vesicles into its final forms. From the trans face (exit face), it releases the vesicles intended for export out of the cell, merging with the cell membrane (**exocytosis**). Other newly formed vesicles remain in the cell and, with the help of the enzymes contained within them, serve as lysosomes. **Lysosomes and peroxisomes** are single membrane-bounded organelles that contain enzymes involved in cell digestion and other metabolic processes. A lysosome produced by the Golgi apparatus is referred to as the primary lysosome; a lysosome with an active digestion as the secondary lysosome, which, after digestion, becomes a residual body (tertiary lysosome or telolysosome).

The cytoplasm contains functionally and morphologically diverse organelles, cytoplasmic inclusions and a dynamic protein framework called the cytoskeleton.

Cytoplasmic inclusions are non-living substances of the cell that are not bound by membrane. This group includes **lipid droplets, glycogen granules, protein crystalloids and pigment granules**. They have **storage functions** or **are used to store unneeded and residual substances**, as is the case for lipofuscin, an endogenous pigment. **Lipid droplets** can be visualized using fat-soluble staining, but not by water soluble staining agents (Sudan stains, Oil Red). **Glycogen granules** may be visualized using iodine (Lugol solution) or PAS reaction (histochemical method using periodic acid and Schiff's reagent). **Pigment granules** have their own color even in unstained sections: melanin is brown to black, lipofuscin is yellow-brown, and hemosiderin is rusty.

The cytoskeleton is the **internal functional and dynamic cell support** that determines its shape, cellular movements, and organelles distribution in the cytoplasm. The basis is formed by the proteins creating fibers (**microfilament and intermediate filaments**) or hollow tubes (**microtubules**) in the cytoplasm. Cellular protrusions are also cytoskeleton-reinforced. In the core of immotile **microvilli**, we find 20–30 microfilaments; the central part of motile **cilia** and **flagella** contain characteristically arranged microtubules (axoneme). The cytoskeleton also participates in the construction of strong intercellular joints. **Centrosome** anchors microtubules **and controls their prolongation (polymerization) or shortening (depolymerization).** It forms the **basal bodies of the cilia**, controls the movement of daughter chromosomes during cellular division and the separation of the daughter cells (cytokinesis). Centrosome consists of two perpendicular centrioles made up of 9 triplets of microtubules.

The existence, growth, development, and multiplication of the cell **require nutrients and other important organic and inorganic substances received from the external environment**. Smaller molecules can get through the cell **membrane passively**, i.e. in the direction of the concentration gradient without the need for energy supply, or using **active transport** mechanisms, which require the supply of energy, as it works against the electrochemical gradient. Large molecules and solid particles penetrate the cell via **endocytosis**, where they are surrounded by the cell membrane. The endocytosis of the fluid is called **pinocytosis**; the endocytosis of larger particles is called **phagocytosis**. In addition to the intake of nutrients, phagocytosis is also the basis of non-specific innate immunity. Significantly phagocytic cells include **macrophages** in the connective tissue proper (originating from white blood cells called monocytes) and **neutrophilic granulocytes**.

Some cells are able to move actively. The ameba movement, where the cells move using cytoplasmic protrusions (**pseudopodia**) is observed in the moving cells **during the embryonic development or in the white blood** cells passing through the ground substance of the connective tissue. In particular, microfilaments are involved in the formation of pseudopodia. Sperm cells use **flagella** for the movement. Its internal structure corresponds to the cilia, and contains specifically arranged pairs of microtubules with associated "motor protein", dynein.

Reproduction and cell death

The cell cycle consists of two main periods: cell division (mitosis, M-phase) and interphase period. **Mitosis** is genetically controlled by progressively forming proteins called cyclins. During mitosis, the cell nucleus is first divided (karyokinesis) followed by the cytoplasm to form the daughter cells (cytokinesis). Five basic phases are newly distinguished: **prophase, prometaphase, metaphase, anaphase and telophase**. The period between two cell divisions is called **interphase**. It consists first of the **G1 phase**, with significant protein production and cell increase in size. It is followed by the **S phase** with nuclear DNA replication, and then the **G2 phase**, which represent a gap between DNA synthesis and mitosis, when the DNA is checked and repaired. **G0 phase** is the period when the cell actively synthesizes proteins, functionally matures (differentiates and specializes), performs its activity, but does not show signs of preparation for further cell division. **Some cells of the human body remain, after the initial period of reproduction, for the most part of their lives in the G0 phase**, such as neurons or cardiac muscle cells. **Meiosis** takes place only in the formation and maturation of the male and female sex cells (gametes), i.e. during spermiogenesis and oogenesis. It includes two rounds of cell division to produce four daughter cells, each with half the number of chromosomes as the original parent cell. The resulting gametes contain each chromosome in only one copy.

In the interphase period between two mitoses, the cells produce proteins and double their DNA.

The stem cells are diverse populations. Some are already **important during early embryonic development** and give rise to all other cell types (omnipotent or totipotent stem cells) or a group of cell types (pluripotent cells). During the postnatal development, we find so-called **adult somatic stem cells** in the tissues and organs, which have the ability to form the precisely-defined cell group mostly for tissue regeneration, and are therefore referred to as **multipotent progenitor cells**. Stem cells are undifferentiated with the **ability of self-renewal (auto-replication)**, where the mitotic division produces **two non-equivalent daughter cells (asymmetric mitosis)**. The term plasticity refers to the ability to differentiate morphologically and functionally to various other cell types. An example of a somatic multipotent stem cell is the hematopoietic stem cell forming all other blood cells, but also mast cells in the connective tissue proper.

Negative stimuli (oxygen deficiency, high temperature, poisons) leading to irreversible damage to the cell causing cell death, known as **necrosis**. Intracellular contents, including enzymes, are expelled into the surrounding environment through the damaged cell membrane, moreover necrosis is accompanied by an inflammatory reaction of the surrounding tissue. **Apoptosis** is a different process (silent or programmed cell death). Old cells undergo apoptosis after its depletion of mitotic potential and at the end of its life cycle (shortening of chromosomal telomeres), supernumerary cells (selection), damaged cells or cells where apoptosis is triggered by the contact with some immune cells. Apoptosis is important **in remodelations of tissues and organs** during **the prenatal development** (for example, the separation of the fingers in the development of the hand and the leg). It can be likened to cellular "suicide" that does not damage the surrounding cells and does not elicit inflammatory responses in the surrounding environment. **The cell actively disintegrates (fragments)** into smaller apoptotic bodies, which are still covered by a surface membrane, and the cell content is not expelled into the external environment. Multiple mechanisms of apoptosis induction (through the "death receptor", via mitochondria or endoplasmic reticulum) lead to cascade activation of serial enzymes called caspases that cleave the components of the cytoskeleton, the nuclear fibrous lamina and the cell cycle regulating proteins.

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Eukaryotic cells are about 10 times larger and 1000 times more bulky than prokaryotic cells.

According to one hypothesis, the original eukaryotic cells absorbed smaller prokaryotic cells during evolution. They could use them for the growth of their membrane, the proteins to form the cytoskeleton and create organelles.

According to the endosymbiotic theory (symbiogenesis), the original eukaryotic cells absorbed aerobic bacteria approximately 1.5 billion years ago, which are the basis of mitochondria. Similarly, the chloroplasts of plants were formed by the absorption of photosynthetic bacteria or cyanobacteria.

Jan Evangelista Purkinje discovered many new structures in the human body. For example, in 1838, he was the first to describe a region of the middle brain - substantia nigra with neurons containing neuromelanin pigment.

The Czech scientist, Purkinje's name is integrated in the name of the Czech Medical Association of Jan Evangelista Purkinje, the Jan Evangelista Purkinje University in Ústí nad Labem (Czech Republic) and the Purkinje Institute in Prague, the seat of the Institute of Histology and Embryology of the 1st Faculty of Medicine, Charles University.

The nuclear genome (DNA in the nucleus) contains approximately 30,000 genes, which occupy only 2% of the genome of the nucleus. Approximately 27,000 genes encoding proteins and 3,000 genes encoding different types of RNA have been described. The remaining 98% of the nuclear genome was formerly referred to as "non-coding" DNA, but it often has significant regulatory functions that have not yet been fully understood.

The term chromosome comes from the Greek words chromos - color and soma - body, because it is intensely stained with basic stains.

The discovery of cells whose size is below the resolution power of the human eye closely followed the assembly of the first light microscopes. The term **"cell" (cellula**) dates back to 1665 to the English scientist **Robert Hooke**, who described the tiny cavities observed in tree cork using a microscope, as their shape resembled the prayer cells of monks. Even the fact that he only observed the cell walls of dead plant cells did not prevent the spread of this name. Approximately ten years later, a variety of cells were described by a Dutch merchant and amateur naturalist **Antonie van Leeuwenhoek**, who published the observation of protozoa, spermatozoa, red blood cells, and muscle fibers in the journal of the British Royal Society. An important milestone in the description of intracellular organelles was the year 1933, when German scientists Max Knoll and Ernst Ruska created the first transmission **electron microscope**.

The cell theory

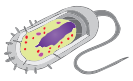
1. **It was created by the botanist Matthias Jacob Schleiden and zoologist Theodor Schwann in 1838–1839**
   – basic structural (morphological) and functional unit of living organisms is the cell
   – plant and animal cell are basically similar
2. **In 1885, this thesis was extended by the German pathologist Rudolf Virchow**
   – a cell can only arise by the division of a pre-existing cell (*omnis cellula e cellula* = "all cells (come) from cells")
3. **The Czech scientist Jan Evangelista Purkinje is considered as a co-author of the cell theory**
   – in 1825,he discovered the germinal vesicle (*vesicula germinativa*) of the bird egg, in fact, it was the first description of the egg cell nucleus
   – in 1837, he gave a lecture about the granular structure of the nerve tissue, where the "granules" were the nerve cells
   – in 1839, he named the living content of the cell as "protoplasm"
4. **In the 20th century, it was added that all cells have**
   – a very similar structure and contain organelles with identical or similar functions
   – very similar chemical composition and undergoing similar biochemical metabolic processes
   – universal genetic code
   – similar cell division, where the genetic information is duplicated and one copy is transmitted to each of the daughter cells
   – a common evolutionary history, where prokaryotic cells developed as the first ones, followed by eukaryotic cells

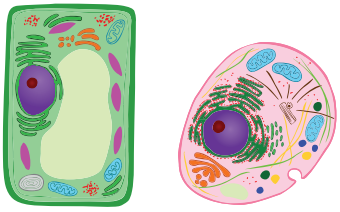

Rudolf Virchow


Jan Evangelista Purkinje

Basic cell types according to the organization of the nucleus

1 **Prokaryotic** - examples are bacteria, cyanobacteria and archea (archaebacteria)
   – single-cell organisms, size in micrometer units
   – morphologically without membrane-bound nucleus (without nuclear envelope) called nucleoid (nucleus-like, prokaryotic chromosome), is composed of one circular double-stranded DNA molecule (without histone binding)
   – cytoplasm it can also contain circular DNA molecules called plasmids
   – ribosomes of prokaryotic type (sedimentation constant 70S)
   – no cytoskeleton
   – surface covered by the cell membrane and cell wall, may be surrounded by a capsule
   – asexual reproduction, usually by binary fission, without the appearance of chromosomes (this type of direct cell division is sometimes called as amitosis)
   – evolutionarily the original type
2 **Eukaryotic** - cells of protozoa, plants, fungi, animals (including humans)
   – more complex structure, tens of micrometers
   – the nucleus is separated from the cytoplasm by the nuclear envelope
   – DNA is organized into chromosomes during cell division
   – larger ribosomes (sedimentation constant 80S)
   – contain numerous organelles that can be separated from the cytoplasm by the membrane
   – contain a cytoskeleton
   – the surface is covered by the cell membrane, the cell wall can be present (in plants and fungi) or absent (animal cells)
   – the mechanism of division is mitosis, or meiosis in the formation of sex cells (gametes, sperms and eggs)
   – differentiation and specialization of cells in multicellular organisms, thereby distinguishing sets of cells (animal tissues, plant tissues)

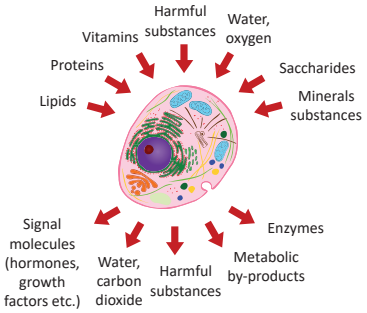

Bacteria
Prokaryotic cell


Plant cell
Animal cell
Eukaryotic cells

The cells are in constant connection with the external environment where they exchange matter, energy, and information. The **cell** controls the intake and output of substances and **gains energy by converting the received energy-rich nutrients** into energy-poor substances. It uses energy to maintain balance between its internal environment and its external environment. The cell contains its own **genetic memory** in the form of DNA. The processes of macromolecule formation and metabolic transformation are encoded in it. Turning the genes on and off (activating and deactivating) during the cell's life controling its differentiation, acquisition of observable features (phenotype) during specialization, intercellular interactions as well as cell death.

The flow of substances

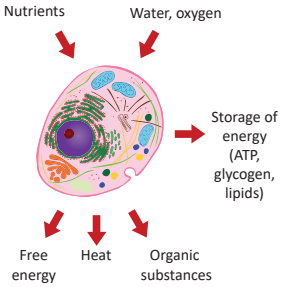
1 **The cell selectively receives various substances from** the external environment, chemically converts them (metabolism) and excretes certain substances out (metabolic wastes or molecules intended for transport in the form of secretion)
2 **It controls biochemical processes** and enzymes affects the course of chemical reactions
3 **It transports the molecules through the cell membrane**
4 **It acquires larger solid particles** through phagocytosis **and droplets of fluid using** pinocytosis



Flow of substances between the cell and its surroundings

Energy flow

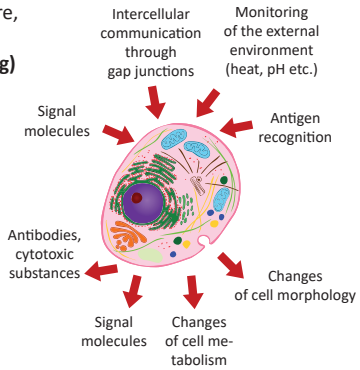
1 **It achieves the stability of the internal environment** (cellular homeostasis)
2 **Energy is utilized in the form of a free energy** in chemically demanding reactions, exerting mechanical and electrical work (e.g. cell division, cell movement, substance transfer)
3 **A large amount of free energy is used by the cell for the synthesis of its own macromolecules**
4 **Energy released as heat** is radiated by the cell into the surroundings
5 **Energy can be stored in the cell for a short time** in energy-rich (macro-energy) bonds of compounds, e.g., ATP and creatine phosphate
6 **Energy can be stored in the cell for medium durations** in the form of polysaccharides (glycogen)
7 **Energy can be stored in the cell for a long time** mainly in the form of fats (triglycerides)



Energy flow between the cell and its surroundings

Information flow

1 **Cells can perceive changes in the environment**, such as the changes in temperature, pH, osmotic pressure, activity of electrolytes, levels of chemicals etc.
2 **Cells communicate with each other (intercellular signaling)**
2.1 **Communication via direct contacts** through lockable gap junctions, which connect cytoplasm of adjacent cells and allow for low-molecular substances influx
2.2 **Communication via signal molecules,** e.g., hormones, transporters, cytokines and other information molecules
2.3 **Mutual differentiation and recognition of cells** via protein and glycoprotein membrane antigens or polysaccharide molecules
2.4 **Changes of membrane electrical voltage can spread** along the cell membrane (action potential of nerve and muscle cells)



Information flow between the cell and its surroundings

The transport of a molecule through the cell membrane is either in the direction of the concentration (or electrochemical) gradient, i.e. without the need of an energy supply, or against the direction of the electrochemical gradient using membrane-bound transporters (which requires coupling with a power source).

Some cells acquire energy in long-term anaerobic glycolysis. Examples are red blood cells, which do not contain mitochondria. Glycolysis occurs in the absence of oxygen in skeletal muscle during strenuous load. The resulting accumulation of lactic acid in the cytoplasm causes a decrease in the pH, associated with muscle weakness and pain.

The highest effectiveness of ATP production in the cell is achieved by oxidative (oxygen-consuming) phosphorylation coupled with the gradual transfer of electrons in the respiratory chain of the inner mitochondrial membrane. The resulting ATP and other energy-rich molecules are then transferred to different parts of the cell.

Some cells (e.g. hepatocytes) are able to synthesize glucose (gluconeogenesis) from glycerol, lactic acid (Cori cycle) or some amino acids.

The resulting glycolysis product in the cytoplasm is pyruvic acid under aerobic conditions. It enters the mitochondria where oxidative decarboxylation generates acetyl, binding to the coenzyme A and entering the Krebs cycle.

Signal molecules bind to receptors that are a part of the cell membrane (in the case of peptide or protein molecules) or in the cytoplasm, from which they travel to the nucleus and affect transcription (steroid hormones).

Immune system cells allow the detection of a foreign antigen and trigger an immune response resulting in antigen phagocytosis, specific antibody production, or cytotoxic agents release.

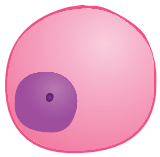
White blood cells have a spherical shape only while in blood plasma. After the transfer from the vessels to the connective tissue proper (diapedesis), they move using their protrusions (pseudopodia) and thus become irregular in shape.

The highest columnar cells arranged in one layer are found in the lining of the gall bladder.

The human body is built from cells forming **a morphological and functional whole unit**. However, each cell type has different **size and shape**. The phylogenetical original shape of an animal cell was probably **spherical** or similar to that of **human cells found freely in the fluid medium (e.g. white blood cells in blood plasma).** The spherical shape is best suited **for balancing the internal tension of the cytoplasm with the surface tension of the cell membrane**. **The shape of the cell** adapts both to changes in the environment and to **the cellular function during the evolutionary development (phylogeny) and during the development of the individual (ontogenesis)**. Surface lining and covering epithelial cells, tightly adjacent to each other, are usually **polyhedral**. Depending on the height of the cell, we distinguish **squamous (pavement), cuboidal or columnar epithelial cells.** In the body we find **elongated spindle-shaped (fusiform)**, cells or cells **with shape similar to pyramids or stars (pyramidal and stellate).** The cell size ranges from 5–150 microns, but most cells are 10–30 microns.

External morphology of cells

1 **Spheroidal / spherical shape** (*cellula spheroidea*)
– e.g. white blood cells, oocyte (egg), cartilage chondrocytes
2 **Ovoid/oval shape** (*cellula ovoidea*) – derived from spherical
– e.g. a mast cell or a plasma cell of the connective tissue
3 **Polyhedral shape** (*cellula polyhedralis*)
– cell compressed from multiple sides
– cross section resembles a polygon
– e.g. hepatocytes forming cords
3.1 **Polygonal shape** – two-dimensional view of polyhedral cells on a histological section
4 **Columnar/prismatic shape** (*cellula columnaris*)
– similar to a cylinder or prism, the height of the cell exceeds the width
– e.g. the epithelium of the digestive tract from the stomach to the pectinate line of anal canal, epithelium of the uterine tubes and the uterus
5 **Cuboidal shape** (*cellula cuboidea*) – all the cell dimensions are comparable
– e.g. thyroid follicular cells, striated ducts of major salivary glands or ducts of sweat glands
6 **Squamous shape** (*cellula squamosa/plana*)
– cell height is negligible compared to other dimensions
– e.g. the lining of the parietal layer of Bowman´s capsule and loops of Henle of the nephrons, endothelial cells lining blood and lymph vessels, mesothelial cells lining serous cavities (pericardial, peritoneal and parietal cavity)
7 **Fusiform shape** (*cellula fusiformis*) – elongated, spindle-shaped
– e.g. smooth muscle cells, fibrocytes and fibroblasts (these can combine the fusiform shape with numerous cytoplasmic processes)
8 **Stellate shape** (*cellula stellata*)
– similar to star, the projections of the cytoplasm are evenly spaced along the circumference of the cell
– e.g. motor neurons of the anterior spinal horns, astrocytes of the central nervous system
9 **Dendritic/branched shape** (*cellula dendritiformis*)
– resembles a tree, with numerous irregular cytoplasmic projections
– e.g., antigen-presenting dendritic cells in the lymphatic organs, osteocytes in bone tissue
10 **Pyramidal shape** (*cellula pyramidalis*)
– like a pyramid or truncated pyramid
– e.g., serous cells of the pancreas and salivary glands, pyramidal cells of the cerebral cortex
11 **Goblet shape** (*cellula caliciformis*) – shape of a bowl-shaped drinking cup without handles
– e.g., mucus-producing goblet cells in the epithelium of the digestive and respiratory system
12 **Pear-like shape** (*cellula piriformis*)
– Purkinje neurons in the cortex of the cerebellum
13 **Biconcave disk** - a flattened, bilaterally indented sphere
– shape resembling an oblate spheroid with two concave surfaces, one on the top and on the bottom
– characteristic shape of red blood cells


Spherical shape (oocyte)


Spherical shape (monocyte)


Ovoid shape (mast cell)


Polyhedral shape (hepatocyte = liver cell)


Columnar shape (enterocyte = intestinal absorptive cell)

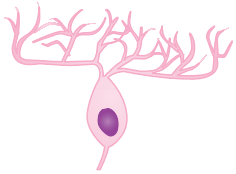

Cuboidal shape (pneumocyte type II)

Squamous shape (pneumocyte type I)


Spindle-like shape (smooth muscle cell)


Stellate shape (multipolar neuron)


Dendritic shape (osteocyte)


Pear-like shape (Purkinje neuron)

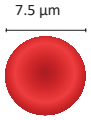

Pyramidal shape (serous cell of the pancreas)


goblet shape (goblet cell)

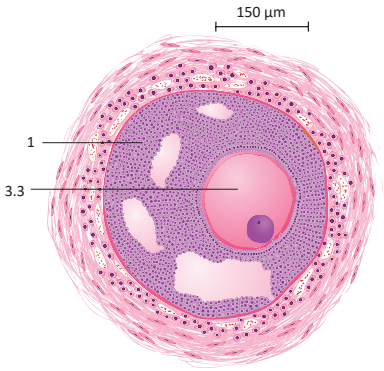

Biconcave shape (erythrocyte)

Cell size

1 **Small-sized cells** - diameter up to 10 µm
– e.g. small lymphocytes, erythrocytes, follicular (granular) cells of the ovarian cortex
1.1 **The diameter of an erythrocyte is 7.5 µm** (7.2–7.6 µm)
– as erythrocytes are present almost in all organs and tissues, they serve as an orientation structure in light microscope for size estimation of other cells and structures
2 **Medium-sized cells** – diameter 10–30 µm
– the majority of cells
3 **Large-sized cells** – some cells significantly exceed 30 µm
3.1 **Diameter of up to 100 µm**
– e.g., bone marrow megakaryocytes
3.2 **Diameter of 80–120 µm**
– e.g., motor neurons of the anterior spinal horns and Purkinje neurons in the cerebellar cortex
3.3 **Diameter of up to 120–150 µm** – oocyte
– the largest cell of the human body



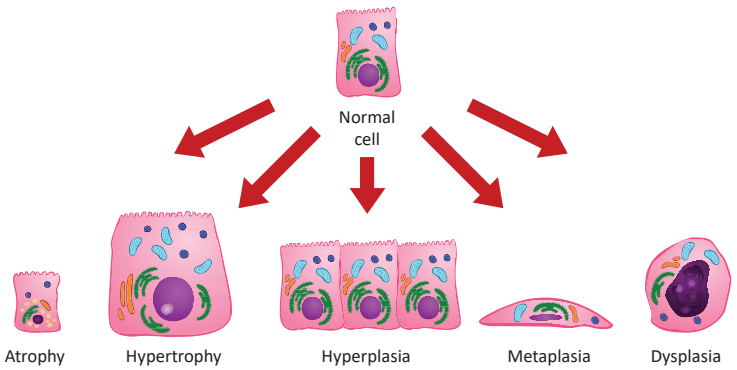
Oocyte diameter



The diameter of an oocyte and granular cells in a tertiary / antral follicle in ovarian cortex

Changes in size, shape, function, and cell number

– a cell can morphologically adapt to physiological processes (growth, aging, growth of the uterus and mammary gland during pregnancy); undesirable pathological stimuli (chronic irritation, inflammation, viral infection, etc.)
1 **Atrophy** – reduction of cell volume
– e.g. during starvation, damage to innervation, and reduced metabolic activity of the cell
2 **Hypertrophy** – increased cell volume
– physiologically in the uterus during pregnancy (smooth muscle cells enlarge up to 10x)
– pathologically, hypertrophy e.g. of cardiac muscle in high blood pressure
3 **Hyperplasia** – increased cell count as a result of cell proliferation
– physiologically in the mammary gland during puberty and pregnancy, smooth muscle of the uterus during pregnancy (hyperplasia is accompanied by hypertrophy)
4 **Metaplasia** – reversible transformation of one differentiated cell type into another differentiated cell type
– e.g. the substitution of columnar cells with cilia to the squamous cells in the epithelial lining of the respiratory tract in smokers or change of columnar cells to squamous cells in the epithelial lining of the gallbladder due to irritation by biliary stones (cholelithiasis)
– initially, it is reversible; after the negative stimuli disappear, the original shape can be restored in that location
5 **Dysplasia** - Disturbance of the physiological morphological and functional properties of the cell to such an extent that they may be a precursor to tumor growth
– dysplastic changes of epithelial cells may initially be reversible or vice versa continue into malignant epithelial tumor (carcinoma, adenocarcinoma)



Metaplasia of epithelial tissue p. 78.

In human histology, the term "egg" is reserved for the already haploid female sex cell. However, the oocyte completes its second meiotic division only during fertilization, i.e. when the egg is formed together with the second polar body. However, this egg already contains the genetic material of the sperm in its cytoplasm. Over the next few hours, the female and male pronuclei are formed, which will fuse together and create the zygote ("fertilized egg").

The smallest cells of the human body are considered to be the neurons in the granular layer of the cerebellar cortex, having a diameter of 4–5 µm.

The largest human cell is oocyte, with a diameter of about 150 µm. The longest cells, including the slender cytoplasmic projections, are motor neurons in the gray matter of spinal cord, which have axonal projections longer than 1 meter. Smooth muscle cells of the uterine wall reach up to 0.5 cm in length during pregnancy.

The largest animal cell is an ostrich egg that weighs approximately 1.4 kg at a diameter of 15 cm. The nerve cells of dorsal root ganglion in a blue whale are at least 25 m long and also the nerve cells of a giant squid (a deep-ocean dwelling squid) reach up to 10 meters in length.

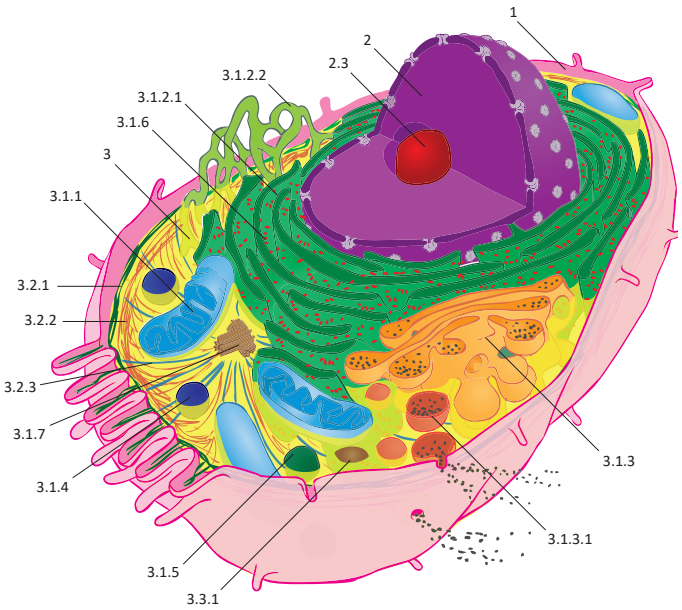
Most human body cells contain two chromosome sets, so they are diploid (2N). The haploid set of chromosomes (1N) is only present in gametes (sperm and eggs). Bone marrow megakaryocytes (platelet precursor cells) are polyploid cells and may contain 8–64 times the amount of genetic material compared to normal cells (16N to 128N).

Clinical notes

Aneuploidy is an abnormal number of chromosomes; for example, in chromosome 21 trisomy (Down's syndrome), there are three copies of chromosome 21 in the cells and a total chromosome count of 47 (instead of 46 for euploidy).

We call the living content of the cell **protoplasm**; it contains the **cell nucleus** and **cytoplasm**. The cell surface is the **cell membrane**, the main component of which are phospholipids forming a double layer, and proteins. **Some proteins are a permanent component of the membrane** (integrated, integral), others are easier to **separate from the membrane** (peripheral). Chemically and structurally similar membranes are part of other **organelles**, so it is possible to speak of a "universal" biological membrane (**biomembrane**). The **nucleus** is the coordinating and control center of the cell. It contains genetic information that is embedded in the molecular structure of deoxyribonucleic acid (DNA). The structure of nucleus changes significantly throughout the cell cycle. In the period between the divisions, the **interphase nucleus** has a distinct **nuclear envelope**, **nucleoplasm** and **nucleolus** (or more nucleoli). The **nucleoplasm** contains **chromatin** and **intermediate filaments network**, referred to as the **nuclear fibrous lamina**. Nuclear lamina represents the main **extrachromosomal structure of nucleoplasm**. During the cell division, the structure of the nucleus disappears and renews after the division is complete. **Cytoplasm** is the basic internal environment of the cell, consisting mainly of water (70–80%); it also contains ions (especially Na^+, K^+ and phosphate and chloride anions), amino acids, peptides and proteins, fatty acids, and nucleic acids. The cytoplasmic surface layer just below the cell membrane is referred to as the **ectoplasm**; the inner layer as the **endoplasm**. The endoplasm contains morphologically and functionally diverse **organelles** and **cytoplasmic inclusions**. **Hyaloplasm** or **cytosol** is the cellular cytoplasm without organelles and inclusions. Organelles can be divided according to the presence and nature of their membrane. **Organelles** are the site of enzyme activity, occurring in or on them to synthesize and subsequently modify amino acid chains, polysaccharides or lipids. These functions require energy. The components of the cytoskeleton **are microtubules, intermediate filaments and microfilaments**. They are involved in maintaining the shape of the cell, in the movement of organelles within the cell as well as in the movement of the cell as a whole. **Cytoplasmic inclusion** include **lipid droplets, protein crystals (crystalloid inclusions) and pigment and glycogen granules**. Inclusions are **storage** units or they accumulate **unnecessary substances**.

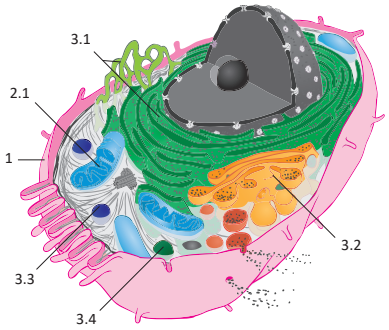
- 1 **Plasmalemma / membrana cellularis** – plasmalemma / cell membrane
- 2 **Nucleus**
  - 2.1 **Tegumentum nucleare** – nuclear envelope
  - 2.2 **Nucleoplasma** - nucleoplasm/karyoplasma
  - 2.3 **Nucleolus**
- 3 **Cytoplasm** – semi-liquid internal environment of the cell containing cellular organelles, cytoskeleton and cytoplasmic inclusions
  - 3.1 **Organelles**
    - 3.1.1 **Mitochondria**
    - 3.1.2 **Endoplasmic reticulum**
      - 3.1.2.1 **Rough / granular endoplasmic reticulum**
      - 3.1.2.2 **Smooth / agranular endoplasmic reticulum**
    - 3.1.3 **Golgi apparatus / complex**
      - 3.1.3.1 **Vesicles**
    - 3.1.4 **Lysosome**
    - 3.1.5 **Peroxisome**
    - 3.1.6 **Ribosome**
    - 3.1.7 **Centrosome**
  - 3.2 **Cytoskeleton**
    - 3.2.1 **Microfilaments**
    - 3.2.2 **Intermediate filaments**
    - 3.2.3 **Microtubules**
  - 3.3 **Cytoplasmic inclusions**
    - 3.3.1 **Pigment granules**
    - 3.3.2 **Lipid droplets**
    - 3.3.3 **Crystalloid inclusions**
    - 3.3.4 **Glycogen granules**



The cell membrane is a part of every eukaryotic cell**, it separates the cell from the external environment and maintains a different environment inside and outside the cell** (membrane gradients). **A similar membrane** is also a **part of several organelles** – it separates them from the cytoplasm and participates in the physiological and biochemical involved processes. Both the cell membrane and the organelle membranes are collectively referred to as biological membranes (**biomembranes**). The following description focuses on the cell membrane, but it mostly also follows the general characteristics of other biological membranes.

Biomembranes

- 1 **Cell membrane**
- 2 **Organelles with two membranes**
  - 2.1 **Mitochondria**
- 3 **Organelles with one membrane**
  - 3.1 **Rough and smooth endoplasmic reticulum**
  - 3.2 **Golgi apparatus / complex**
  - 3.3 **Lysosomes**
  - 3.4 **Peroxisomes**
- 4 **Structures with nonconstant membrane**
  - 4.1 **Cytoplasmic inclusions**



Cell membrane and biomembranes

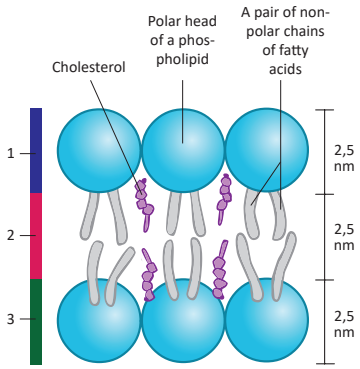
Cell membrane function

1 **Selectively permeable barrier**
2 **Building (support) function**
3 **Separation function** – separation of extracellular and intracellular environments
4 **Forming and maintenance of electrical membrane potential**
5 **Quick transmission of information** – such as nerve and muscle cell signals
6 **Information function** - anchoring of cell receptors and transmission information between the internal and external environments of the cell
7 **Intercellular communication**

Cell membrane structure

– the average thickness is 7.5–10 nm
– detailed structure not distinguishable at the level of light microscopy, the membrane seems like a thin homogeneous line on the surface of the cell
– under a transmission electron microscope, it has a three-layer (trilaminar) structure
– the three-layer membrane structure is created artificially in tissue processing for the electron microscope

- 1 **Lamina densa externa**
  – external dense lamina
  – impermeable for electrons
- 2 **Lamina intermedia lucida**
  – Middle lucent lamina
  – permeable for electrons
- 3 **Lamina densa interna**
  – Internal dense lamina
  – impermeable for electrons



Phospholipid double layer of biomembrane

The original model of the membrane is the "lipoprotein sandwich model" formed in the middle by a phospolipid bilayer that lies between two layers of globular proteins . This hypothesis dates back to 1935, when it was defined by English scientists Hugh Davson and James Danielli (Davson-Danielli model).

The three-layered structure is created artificially in the preparation of samples for transmission electron microscope analysis using heavy metal salts (osmium has a higher affinity for hydrophilic phospholipid heads on the membrane surface than for hydrophobic chains in the middle).

The ratio of lipids and proteins in the membrane is usually 1:1. However, in the myelin sheaths surrounding the nerve fibers, this ratio is approximately 4:1 and in the case of the internal mitochondrial membranes with high enzyme content, it is 1:4.

There are five phospholipid groups in the biological membrane: phosphatidylcholine (lecithin), sphingomyelin (sphingolecithin), phosphatidylethanolamine (cephalin), phosphatidylserine (serincephalin) and phosphatidylinositol.

A higher proportion of cholesterol reduces cell membrane fluidity, i.e. the cholesterol leads to stiffening of membranes. A higher proportion of cholesterol also reduces the permeability of the membrane in concern of water and water-soluble small molecules permeability.

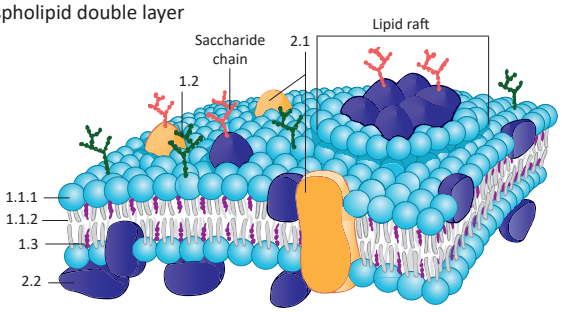
Glycolipids include cerebrosides, gangliosides and sulfatides.

The fluid mosaic model compares the movement of protein and lipid molecules in the biomembrane to the icebergs movement in the sea. Protein and lipid molecules can move (drift) freely in the biomembrane in a way comparable to that of icebergs (protein analogy) in the sea (phospholipid bilayer). This model was described by American biologists Garth L. Nicolson and Seymour J. Singer in 1972.

The cell membrane and the membranes of all separate organelles originate from the unicellular stage of human development, i.e. from growing and dividing membranes and organelles of a fertilized egg (zygote).

Molecular structure of the cell membrane

1 **Membrane lipids**
- 1.1 **Phospholipids**
  - 1.1.1 **The polar (hydrophilic) head**
    – iby phosphorylating the alcohol with the residual trihydrogen-phosphoric acid, it generates negative charge
    – in an aqueous medium, the hydrophilic portions are spontaneously oriented toward the aqueous phase around the cells, thus forming a phospholipid double layer
  - 1.1.2 **A pair of non-polar (hydrophobic) fatty acid chains**
    – passively rotating to the inside of the membrane
- 1.2 **Glycolipids** – one of the hydroxyl groups of alcohol has a monosaccharide or oligosaccharide component bound to it
  – usually on the outer surface of the cell membrane
- 1.3 **Cholesterol** - is a steroid molecule present in animal cell membranes; affects stability and decreases the fluidity of the membrane



Molecular structure of the cell membrane

2 **Membrane proteins**
- 2.1 **Integrated (transmembrane)**
  – pass the entire phospholipid bilayer
  – are amphipathic / amphiphilic (have both hydrophilic and hydrophobic domains)
  – difficult to separate from the membrane
- 2.2 **Peripheral** – bound by covalent bonds to membrane lipids, or non-covalent bonds to integral proteins, or are electrochemically attached (basic with positive charge directly or acidic with negative charge over Ca^{2+} ions)
  – easier to separate from the membrane (e.g. by pH changes)

Function of membrane proteins

1 **Structural and cohesive function** – involved in intercellular junctions
2 **Transport proteins (carriers) and ion pumps** – transfer of small molecules such as glucose, amino acids, ions
– often an active transport requiring energy
- 2.1 **Na^+-K^+-ATPase** – ensures low intracellular Na^+ concentration
  – contributes to the formation of electrical membrane potential
- 2.2 **H^+-K^+-ATPase** – on the membrane of lining cells of stomach glands, it transfers H^+ to the inside environment of the stomach, thus contributing to the formation of HCl
- 2.3 **Na^+-K^+-$2Cl^-$ co-transporter** – transfers the stated ions into the cytoplasm

3 **Ion channels** – hydrophilic pores in which inorganic ions influx through while engulfed within their solvent according to the concentration gradient (i.e. without the need for energy, facilitated diffusion)
– may be in open or closed state, their activation is possible:
  – by membrane electrical potential change
  – by coupling with the receptors respective ligands are bound to (hormones, neurotransmitters and other signal molecules)
  – mechanical stress (in the mechanoreceptors)
4 **Water transfer via aquaporins** (special protein channels with controllable flow)
5 **Receptors capable of binding signal molecules, neurotransmitters and hormones** – leading to physiological changes in the cell (e.g. G-protein coupled receptors with a system of intracellular secondary messengers)
6 **Enzymatic function** – catalysis or reactions on the membrane surface (e.g. disaccharidase on the surface of absorptive intestinal cells)
7 **Glycoproteins work as antigens** (recognition of body structures and foreign structures using antibodies)
8 **Oligosaccharides and polysaccharides work as lectins** (saccharide-recognition of cellular surfaces)

Fluid mosaic membrane model

– the molecules of the phospholipids are not interconnected, allowing their lateral movement (membrane fluidity)
– integrated proteins can move both transversally and laterally within the membrane
– frozen sections technique can be used to investigate the spatial distribution of proteins, where we observe integral proteins as granules inside the membrane using the scanning electron microscope
1 **Lipid rafts** - functional clusters of membrane lipids and proteins formed by shifting
  – rafts are used in signal transfer, transfer of substances through the membrane and immunocompetent cell activities

Glycocalyx

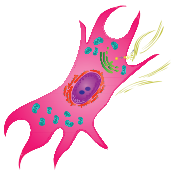
– a summarized name referring to the carbohydrates covering / coating the outer surface of the cell membrane
– visible under an electron microscope as a fur-like coating surrounding the surface of the cell
– ranging from a few dozen to hundreds of nanometers from the membrane, consists particularly of glycolipids and glycoproteins
– important in cell recognition, can have enzymatic activity, and prevents physical contact of neighboring cells

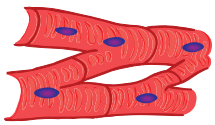
The cell nucleus is the genetic and information center of eukaryotic cells. Stimulates the formation of other cytoplasmic organelles; the nuclear genes encode a portion of the mitochondrial proteins – mitochondria have their own genes and multiply partially independently from the nucleus (semi-autonomously). It contains the complete genetic information of the individual, but only a fraction is transcriptionally active at a certain point in time. It governs cellular activities such as growth, division, metabolism. The nucleus changes according to the cell cycle phase. **The interphase nucleus** is found between the two cell divisions. **The mitotic nucleus** is present during the cell division period, when both the nuclear envelope and nucleolus (multiple nucleoli) disintegrate, chromatin condenses and arranges into chromosomes.

Nucleus size and number of nuclei

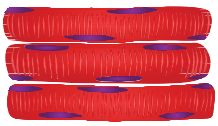
– it is the largest cellular structure with diameter of 4–30 µm
– larger in younger cells
– often decreases its size during cell differentiation

1 **Mononucleate cell** (*cellula mononucleata*) – most of cells of human body
2 **Binucleate cell** (*cellula binucleata*)
  2.1 **Some cardiomyocytes** (cardiac muscle cells)
  2.2 **Some hepatocytes** (liver cells)
  2.3 **Some surface umbrella cells**
    of the transitional epithelium of the urinary tract
  2.4 **Some parietal cells** of the proper gastric glands
    forming hydrochloric acid (HCl)
  2.5 **Some plasma cells** of the immune system
3 **Multinucleate cell** (*cellula multinucleata*)
  – may have several to several tens of nuclei
  – **Syncytium** – a multinucleate cell
    created by merging of originally separate cells
    (fusion of cell membranes and cytoplasm)
  3.1 **Osteoclasts** (cells degrading bone matrix)
    – created by the fusion of monocyte precursors
      derived from bone marrow
  3.2 **Giant multinucleate cells**
    – in response to foreign bodies that
      are formed by the merging of macrophages in the neighborhood
      of a foreign material or similar
      Langhans cells in tuberculosis infection
  3.3 **Skeletal muscle fibers** - have up to hundreds of nuclei
    – they were created by merging of mononucleate myoblasts
      during the development of the skeletal muscle,
  3.4 **Syncytiotrophoblast** – is on the surface
      of the blastocyst (developing stage of embryo) implanting
      into the uterine mucosa and covers
      the surface of the chorionic villi of placenta
4 **Anucleate cell** (*cellula anucleata*)
  – some specialized cells
  – they lose their nucleus during their development
    and cease to meet the cell definition
  4.1 **Erythrocytes** (red blood cells)
    – in one developmental stage in the bone marrow
      are called orthochromatophilic erythroblast (during
      differentiation), they extrude their nucleus (enucleation)
  4.2 **Keratinized squamous surface epidermal cells**
    – dying and dead cells filled with keratin,
      where the nucleus disintegrates
  4.3 **Thrombocytes** – platelets also do not have a nucleus,
      but unlike previous cells, they never had it,
      because they are only fragments of protrusions
      of cytoplasm of bone marrow megakaryocytes


Mononucleate cell
(fibroblast)


Binucleate cell
(cardiomyocyte) - above


Multinucleate cell
(osteoclast)


Multinucleate fiber
(skeletal muscle fiber)


Anucleate cell
(erythrocyte)

Nucleus is the Latin term, **karyon** is the Greek term for nucleus.

The first to observe an animal nucleus was J. E. Purkinje in a bird egg in 1825 and called it the "germinal vesicle".

The term "cell nucleus" was defined by a Scottish botanist Robert Brown, who described it in plant cells in 1831.

Chromos is the Latin term for color, because chromosomes are intensely stained using basic stains / dyes.

About 20 % of human liver cells normally contain two nuclei and this ratio increases with age. Even mononucleate hepatocytes may be polyploid (tetraploid to octoploid). Higher numbers of binucleated and polyploid hepatocytes are present in chronic viral infections of the liver (hepatitis B and C) or in the final stages of hepatic cirrhosis (diffuse nodulation of liver due to connective scar tissue subdividing liver into regenerative nodules). **The interphase nucleus was formerly referred to as "resting"**, which is misleading because in fact the nucleus during the transition between cell divisions is ensuring active transcription of DNA into different types of RNA needed for proteins synthesize. In which the cell is preparing for further division and its DNA content is duplicated.

Multinucleate cells may form by fusing originally separated cells (*syncytium*) or by dividing the nucleus (endomitosis) without subsequent cell division (without cytokinesis, thus forming a *plasmodium*). Examples of plasmodia are the long, branching and filamentous hyphae of some fungi or the developmental stages of the *Plasmodium* genus (cause of malaria). **Since the shape of the nucleus** often corresponds to the shape of the whole cell, we can perform an easy deduction (the shape of nucleus is well visible in the microscope) to estimate the shape of the whole cell (the cellular border - the cell membrane is poorly visible in routine staining methods). **The number of nuclear segments increases with age of the cell in neutrophilic granulocytes**. A young neutrophil has an unsegmented rod-shaped nucleus, the oldest forms have 4–5 lobes.

Clinical notes

In pathology, not only the size, stainability and the shape of the nucleus are evaluated, but also its location. The distribution of nuclei in multiple planes may be a sign of dysplasia in some epithelium types.

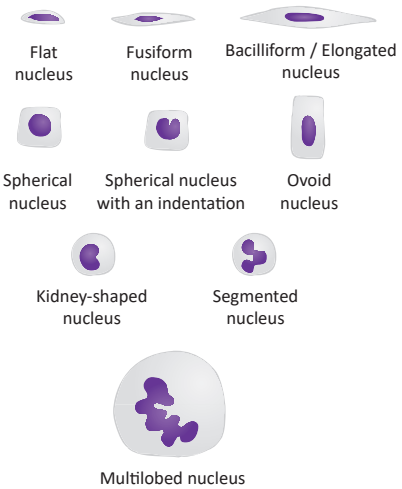
Nuclear – cytoplasmic ratio

– is the ratio of the volume (size) of the nucleus to the volume of the cytoplasm
– in a given cell population at the same stage of development, it is a relatively stable value
1 **Immature (precursor) cells** - during development, they usually have a large nucleus and little cytoplasm (4:1 ratio)
2 **Mature cells** - usually have the nuclear-cytoplasmic ratio of 2:1 or 1:1
– cytoplasm volume increases, where they accumulate storage substances
– the exception being e.g. lymphocytes with a large spherical nucleus and only a small amount of cytoplasmic (4:1 ratio)
– the increase in the Nuclear – cytoplasmic ratio is typical for dysplastic and malignant tumor cells

Lymphocyte with nuclear-cytoplasmic ratio of 4:1

Nucleus shape

– the shape of the nucleus usually copies the shape of the whole cell
1 **Flat nucleus** (*nucleus planus*) – in flat cells, e.g. squamous epithelium
2 **Fusiform nucleus** (*nucleus fusiformis*) – in spindle-shaped cells
3 **Bacilliform/elongated nucleus** (*nucleus bacilliformis*) – in spindle-shaped cells
– with the long axis parallel to the long axis of the cell
4 **Spherical nucleus** (*nucleus sphericus*)
– in spherical, polygonal and cuboid cells
5 **Nucleus with an indentation / indented nucleus** (*nucleus indentatus*)
– in contractile cells (smooth, cardiac and skeletal muscle, myoepithelial cells of the exocrine glands)
– indentations are observable only in an electron microscopic level
5 **Ovoid nucleus** (*nucleus ovoideus*) - in ovoid or cylindrical cells
6 **Kidney-shape / Reniform nucleus** (*nucleus reniformis*)
– in monocytes and macrophages
7 **Segmented nucleus** (*nucleus segmentatus*)
– in neutrophilic granulocytes (a type of white blood cell)
– segments are linked by chromatin bridges and their number increases during aging
8 **Multilobed nucleus** (*nuclues multilobatus*)
– in bone marrow megakaryocytes, contain more chromosomal sets within the nucleus

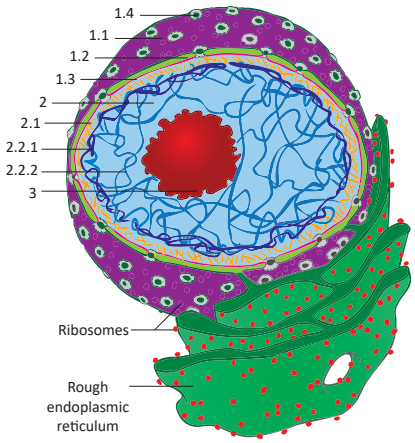


Interphase nucleus

1 **Nuclear envelope** (*tegumentum nucleare*)
- 1.1 **Outer nuclear membrane** (*membrana nuclearis externa*)
- 1.2 **Perinuclear space**(*spatium perinucleare*)
- 1.3 **Inner nuclear membrane** (*membrana nuclearis interna*)
- 1.4 **Nuclear pore**(*porus nuclearis*) and **nuclear pore complex** (*complexus pori nuclearis*)

2 **Nucleoplasm/karyoplasm** (*nucleoplasma*)
- 2.1 **Fibrous lamina** (*lamina fibrosa nuclearis*)
- 2.2 **Chromatin** (*chromatinum*)
  - 2.2.1 **Heterochromatin** (*heterochromatinum*)
  - 2.2.1 **Euchromatin** (*euchromatinum*)
- 2.3 **Nuclear body** (*corpusculum nucleare*)

3 **Nucleolus** (*nucleolus*)



Interphase nucleus

Nuclear envelope

– separates nucleoplasm from the surrounding cytoplasm
– consists of two membranes (internal and external) each with a thickness of approximately 8 nm
– between the membranes, there is a perinuclear space (*spatium perinucleare*) with an average width of 20–80 nm
– the outer membrane is covered with ribosomes (protein synthesis) and may be connected to the rough endoplasmic reticulum
– the perinuclear space directly communicates with the interior space of the endoplasmic reticulum cisterns
– the inner membrane is in contact with the nucleoplasm and is reinforced by a network of intermediate filaments referred to as the fibrous lamina
– the inner membrane is usually connected to the condensed (and more intensely stained) heterochromatin, but the area of nuclear pores contain euchromatin
– the nuclear envelope is not entirely contiguous, but it is perforated by nuclear pores

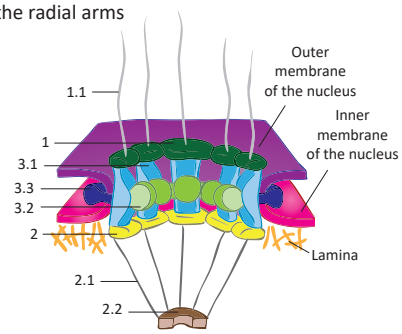
Nuclear pore

– a set of openings in the nuclear membrane for bidirectional communication and controlling the passage of substances between nucleoplasm and cytoplasm
– the pores are the site where the inner and outer nuclear membranes meet
– active and passive transmission of ions, mRNAs (and other RNAs), transcription factors, steroid hormones, ribosomes, histones and regulatory proteins
– the diameter of one pore is about 60–70 nm
– the pores cover 5–25% of the surface area of the nucleus
– one nucleus contains about 2 000 – 4 000, the number depends on the functional state of the cell
– due to the complex structure and interconnection of pores with the surrounding objects, it is newly referred to as the complex of the nuclear pore, the pore itself forms only the inner part of the complex

Nuclear pore complex (*complexus pori nuclearis*)
– consisting of more than 30 proteins (nucleoporins)

- 1 **Outer ring of the complex** - consists of 8 more complex granules
  - – the pores are therefore of octagonal shape
  - – granules are visible using electron microscope
    - 1.1 **Thin filaments** – run from the outer ring to the surrounding cytoplasm
      - – may be used as receptors
- 2 **Inner ring of the complex** - consists of 8 more complex granules
  - 2.1 **Radial arms** – 8 arms extend toward the nucleoplasm
  - 2.2 **Basket** (*canistrum pori*) - is suspended on the radial arms
    - – the innermost pore ring passes through its center

3 **Central canal** - the space between granules, where macromolecules pass up to 39 nm in size
– in the vicinity of the central canal, there are smaller, peripheral canals used for the uptake of molecules up to 8 nm
– protein units constituting the channel area:
- 3.1 **Column unit**
- 3.2 **Annular unit**
- 3.3 **Luminal subunit**



Nuclear pore complex

Nucleoplasm/karyoplasm

– under the electron microscope, it is possible to distinguish the fibrous and granular component
1 **Fibrous layer / fibrous lamina of** the **nucleus** – along the inner membrane of the nucleus
– forms a 3D network that determines the distribution of chromosomes in sectors
2 **Chromatin** – forms the rest of the nucleoplasm
– consists of a fine network of fibers of hydrated and de-condensed chromosomes
– consists of linear DNA molecules that are linked by histone and non-histone proteins
– fine filaments can produce visible nuclear bodies under the electron microscope

Fibrous lamina of the nucleus

– continuous network of fibers formed by the lamins, which belong to the intermediate filament group
– The 3D network forms crossings (*factories*) where the enzymes are collected in form transcripts (for mRNA synthesis) or replicosomes (for DNA synthesis)
– consolidate the nuclear envelope and maintain its shape, determine the position of the nuclear pores
– involved in the spatial arrangement of chromatin and forming the nuclear envelope after cell division
– consist of three different proteins: lamin A, B and C
1 **Lamin B** – anchors the entire fibrous layer of lamins to the inner nuclear membrane
– also holds the end portions of chromosomes (telomeres) to the fibrous lamina
– important in the disintegration of the nucleus in prometaphase and in the reconstruction of the nuclear envelope during telophase of cell division
2 **Lamins A and C** – organize the structure of nucleoplasm, help transform chromatin and maintain regions (territories) of individual chromosomes within the nucleus
– during cell division and deassociation of nucleus disintegration (are released from chromatin)

Over 1000 macromolecules pass through each pore in both directions during 1 minute.

According to the hypothesis of Mary Lyon from 1961, the inactivation of one of the X-chromosome pair in women prevents a double dose of genes found on the X chromosome (compared to men who have only one copy of the X chromosome). This chromatin region is referred to as sex chromatin (chromatinum sexuale) or Barr body. The X-chromosome from the mother is active in some female cells while the X-chromosome from the father is active in others (chromosomal mosaic).

The demonstration of the presence of Barr body in the nucleus has been used in the past for cytologic determination of gender (e.g. in the case of disorders of the development of a genital organs or for forensic medicine purposes).

Telomere plays the role of the "biological clock" of the cell: it is shortened with each division, which prevents further DNA replication after a certain number of divisions (e.g. 50), and the cell undergoes apoptosis, unless it has a telomerase capable of restoring the telomeres (as in the cells with unlimited number of divisions, e.g. stem or tumor cells).

Non-histone chromatin proteins include some enzymes (topoisomerase), "high mobility group" proteins that control transcription, replication and repair processes, or cellular memory modules.

Marginal chromatin is a designation for heterochromatin located just below the inner nuclear membrane.

Different types of chromosomes can be distinguished depending on the position of the centromere and the relative length of the arms.

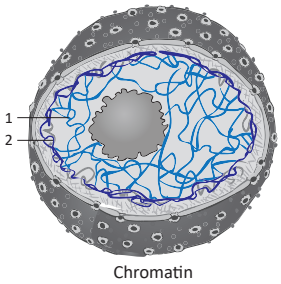
Clinical notes

Tumor cells have more nuclear pores and are in higher metabolic activity.

Laminopathies are diseases caused by a mutation in genes encoding the fibrous lamina of the nucleus. These include Emery-Dreifuss muscle dystrophy and premature aging syndrome (Hutchinson-Gilford progeria). The cause of progeria syndrome is a mutation in the lamin A gene. Affected children live approximately 13 years and die of complications typical of an old age (atherosclerosis, heart disease, senility, osteoporosis, etc.).

Chromatin

– according to the stainability and degree of condensation, the interphase nucleus contains:



Chromatin

- 1 **Euchromatin** – slightly condensed, only mild staining with basic stains
  - – transcriptionally active, represents up to 90% of chromatin in most cells in the interphase
  - – its DNA replicates at the beginning of the S-phase of the cell cycle
  - – stored genes are accessible to transcriptional enzymes and are transcribed into mRNA (the "active form" of chromatin)
  - – located in the center of the nucleus and in the area of nuclear pores
- 2 **Heterochromatin** – highly condensed
  - – intensely stained with basic stains / dyes, dark in the electron microscope (electron-dense)
  - – transcriptionally inactive, represents only 10 % of chromatin in most cells in the interphase
  - – its DNA replicates only in the late part of the S-phase of the cell cycle
  - 2.1 **Constitutive heterochromatin** – permanently in the condensed state; contains inactive genes
  - 2.2 **Facultative heterochromatin** – formed by the temporary condensed euchromatin
  - – one inactive X-chromosome in women is also a heterochromatin (gonosomes XX)
  - – **Barr body** – inactive X-chromosome in a female somatic cell microscopically visible in the form of a basophilic spot or a finger-like appendage on the nucleus
  - – well recognizable especially in some cells (e.g. oral cavity epithelium, neutrophilic granulocytes)

Structure of chromatin

1 **Histones** – structural and control function, they are basic proteins with a positive charge (contain, in particular, the amino acids lysine and arginine) which, due to the opposite polarity, bind to DNA

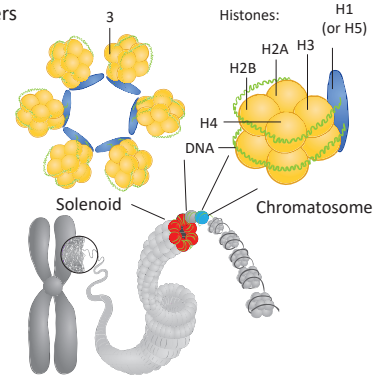
2 **Nonhistonic proteins** – predominantly have a control function and manage the internal nuclear organization

Organization of chromatin

– 5 types of histones – H1, H2A, H2B, H3 and H4 participate in the formation

– coupled pairs (dimers) H2A-H2B and H3-H4 form tetramers, their coupling produces octamers

– DNA winds around the octamer 1.75 times per each segment of about 146 base pair



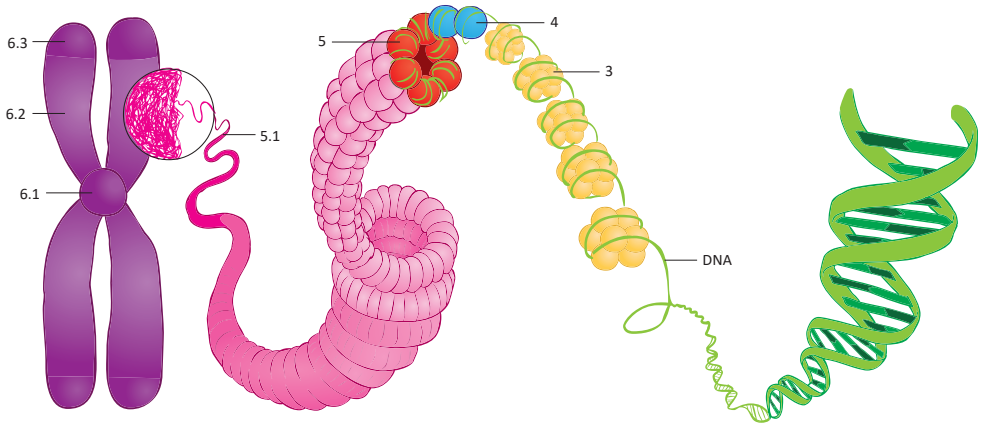
- 3 **Nucleosome** – basic functional and regulatory structure of chromatin
  - – forms by winding the DNA on the histone octamer
  - – H1 histone binds to the DNA between the nucleosomes after 20 base pairs
- 4 **Chromosome** – a chromatin unit composed of nucleosome and H1 histone
- 5 **Solenoid** – a circle formed by chromatosomes by combining H1 molecules
  - 5.1 **Chromatin fiber**
    - – 30 nm long spiral structure consisting of solenoids
    - – basic building block and functional unit of the chromosome

Chromosome – human somatic cells contain 46 chromosomes (23 pairs)

– chromosomes in the interphase nucleus are decondensed and hydrated (not observable), but occupy precisely defined areas (territories)

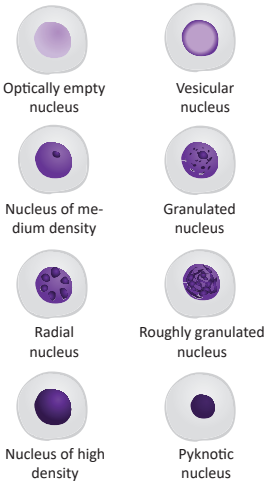
– regions of chromosomes rich in genes are stored closer to the center of the nucleus, regions with fewer genes are located closer to the nuclear envelope

- 6 **Chromosome** – a separate nuclear genome unit
  - – formed by a scaffold, which 30nm chromatin fibers are attached to
    - 6.1 **Centromere** – chromosome narrowing (primary constriction) - divides chromosome into two arms
    - 6.2 **Chromosome arm** – short arm and long arm
    - 6.3 **Telomere** – the end part of the chromosome, plays the role of the "biological clock" of the cell



Structure of chromosome and chromatin

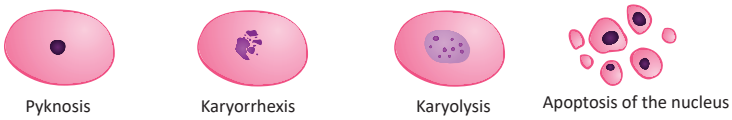
Density of the nucleus (chromatin)



1 **Optically empty nucleus**
– very pale (e.g. stem cells)
2 **Vesicular nucleus** – light with darker peripheral border (e.g. neurons, glandular cells)
3 **Nucleus of medium density** – medium dark (most cells)
4 **Granulated nucleus** – chromatin forms granules (e.g. a urothelial basal cell)
5 **Clock-face nucleus**
– darker (heterochromatin) regions around periphery of nucleus separated by lighter (euchromatin) regions like the numbers on a clock (plasma cell)
6 **Roughly granulated nucleus** – chromatin forms large granules (e.g. tumor cells)
7 **Nucleus of high density** – dark (e.g. cardiomyocytes)
8 **Pyknotic nucleus** – maximally condensed chromatin (e.g. sperm cells)

Nuclear morphology during cell death

1 **Pyknosis** (*nucleus pyknoticus*) – shrunk nucleus with concentrated chromatin
– basic agents produce noticeably dark staining
2 **Karyorrhexis** (*nucleus karyorhecticus*) – chromatin accumulation into numerous lumps of various size that collapse after the nuclear envelope bursts and release the content into the cytoplasm as a karyorrhectic spray
3 **Karyolysis** (*nucleus karyolyticus*) – nucleus content is gradually lost (is enzymatically degraded by endonucleases), but the nuclear envelope remains intact
4 **Apoptosis of the nucleus** (*nucleus apoptoticus*) – chromatin is condensed under the nuclear envelope (chromatin marginalization), followed by the breakdown of the nucleus



Nucleolus

– part of the interphase nucleus, does not have its own limiting membrane, size 1–5 µm
– not a permanent structure of the nucleus, disappears in the prophase, reappears in the telophase
– well visible by light microscope, intensely stained with basic stains
Shape: spherical, oval or irregular
Number: most often 1, or 2–3 (proteosynthetically active cells have multiple nucleoli)
Position: organized around the short arms of the chromosomes 13, 14, 15, 21 and 22, which include ribosomal RNA genes (the region of the nucleolus organizer)
Chemical composition: 80–85% protein, 5–15% DNA and RNA
Function: synthesis of ribosomal RNA and its posttranscriptional modification
– ribosomal subunits are formed here

Electron microscopic structure

1 **Granular component** – lighter part, consisting of granules – ribosome precursors
2 **Fibrous component** – darker part, contains fine fibers (ribosomal RNA precursors)
Nucleolonema: contains mesh-shaped portions of granular and fibrous component
Perinucleolar chromatin: a layer of heterochromatin around the nucleus
Intranucleolar chromatin: chromatin extending up to the core of the nucleolus

Types of nucleoli

1 **Nucleolus with distinct nucleolonemas** – the most common type
– very actively involved in the synthesis of rRNA
– alternating darker and lighter parts, in the proteosynthetically active cells
2 **Compact nucleolus** – Contains only few fibrous structures
– very active synthesis of rRNA, therefore it is present in proteosynthetically highly active, embryonic and tumor cells
3 **Ring-shaped nucleolus** – granules absent in the central area
– in resting, less active cells

Proteosynthetically active cells have a relatively large and pale nucleus, where less condensed euchromatin predominates. Euchromatin is widely used for transcription (transcription of DNA into mRNA). Chromatin is stained very poorly with basic stains. Cells have a noticeable nucleus (or more nucleoli). Their nuclei may have indentations that enlarge the nucleus surface. Typical examples are mesenchymal stem cells or pinealocytes of the pineal gland. The indentations are only visible using electron microscope.

The terms of cytoplasm, hyaloplasm, cytosol, and cytoplasmatic matrix are often used as synonyms, and their definition is not fully established.

Nissl substance (tigroid bodies) is the term for the prominent accumulation of rough ER and ribosomes in the cytoplasm of neurons that appear as basophilic granules after staining.

Characteristics of cells in special histology p. 202.

The nucleolus organizer region is a chromosomal region crucial for the formation of the nucleolus, separated from the remainder of the chromosomal arm by constriction (secondary constriction). The part of the chromosome which is present beyond the secondary constriction is called satellite body or trabant.

The Czech cytologist Professor Karel Smetana, senior (*1930) contributed significantly to the research of the nucleolus structure and function. Together with Professor Harris Busch, they wrote the world-renowned monograph "The Nucleolus" (1970).

Nuclear envelope (*tegumentum nucleare*) used to be referred to as nucleolemma or karyolemma. However, the "-lemma" suffix in histology usually denotes a simple membrane (e.g., plasmalemma) and does not describe the complex bilayer membrane of the nuclear envelope, which is also interrupted by pores.

Nucleoporins affect the transfer of substances through the nuclear pore complex – their receptors are able to recognize the presence of a 4-8 amino acid chain – "nuclear localization signal" .

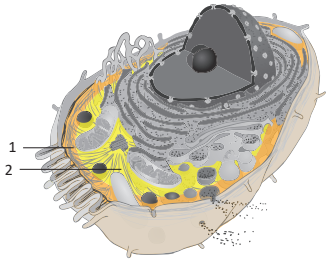
Cytoplasm represents the **basic inner cell environment.** It is **a semi-liquid content of cell surrounding the nucleus**, containing **70–85% of water** (except of fat cells, where the water content is lower). The cell is able to change the **cytoplasm viscosity** as needed from **colloidal solution** to **gel** and vice versa (viscosity is affected especially by the protein content and their binding to water). It looks homogeneous under the microscope or as finely granular amorphous (nonstructural) mass. The cytoplasm contains **organelles, cytoskeleton, cytoplasmic inclusions, and various chemicals**.

Structure

- 1 **Ectoplasm** – a thin layer of cytoplasm located under the cell membrane
  – is more viscous, metabolically less active and contains a network of actin fibers (cortical cytoskeleton, stress fibers) that support the cell membrane
- 2 **Endoplasm** – contains numerous organelles, metabolically active

3 **Hyaloplasm** – cytoplasm without organelles
– optically amorphous at the level of a light microscope (seemingly nonstructural)

4 **Cytosol / cytoplasm matrix** – basic cell matrix without organelles observable with an electron microscope



Parts of the cytoplasm

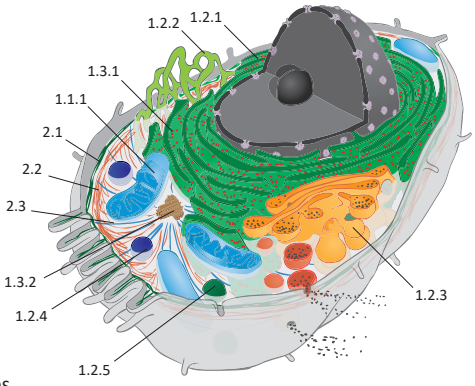
Content

1 **Organelles**
- 1.1 **Double-membrane bounded organelles**
  - 1.1.1 **Mitochondria** – double-membrane bounded organelle
- 1.2 **Single-membrane bounded organelles**
  - 1.2.1 **Rough endoplasmic reticulum** (RER)
  - 1.2.2 **Smooth endoplasmic reticulum** (SER)
  - 1.2.3 **Golgi apparatus / complex**
  - 1.2.4 **Lysosome**
  - 1.2.5 **Peroxisome**
- 1.3 **Non-membrane organelles**
  - 1.3.1 **Ribosome**
  - 1.3.2 **Centrosome**

2 **Cytoskeleton**
- 2.1 **Microfilaments**
- 2.2 **Intermediate filaments**
- 2.3 **Microtubules**

3 **Cytoplasmic inclusions** – are usually not covered by a membrane
– pigment granules, lipid droplets, protein crystalloid inclusions, glycogen granules

4 **Chemicals** – proteins, amino acids, saccharides
– potassium, magnesium, sodium and calcium cations
– phosphate and chloride anions and other low-molecular substances



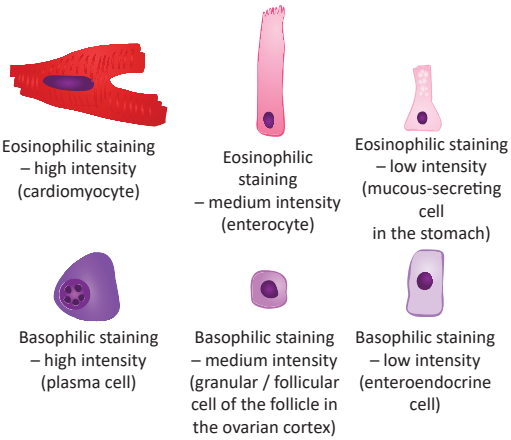
Content of cytoplasm

Staining of cytoplasm

– staining and its intensity are evaluated only in the most common staining technique in histology
– hematoxylin and eosin (HE) stain

1 **Eosinophilic (acidophilic, oxyphilic) cytoplasm** – cytosol of most cells contains mainly basic proteins stained with acidic eosin
– eosinophilia of the entire cytoplasm is enhanced in high mitochondria content

2 **Basophilic cytoplasm** – rough ER aggregates and ribosomes (containing large amounts of ribonucleic acids) stained with basic agents (e.g. hematoxylin)



Staining of cytoplasm and its intensity

Chemicals in cytosol

1 **Enzymes involved in biochemical processes** (glycolysis, protein synthesis, fatty acid synthesis, glycogen synthesis, part of a urea cycle, etc.)

2 **Proteasomes** - complexes of proteolytic enzymes for fast degradation of some proteins (e.g. cyclins during anaphase of mitosis)

3 **Intermediates of metabolism**

4 **Co-factors** – nicotinamide adenine dinucleotide (NAD) or its reduced form (NADH)

5 **Steroid hormone receptors**

Mitochondria are **the energy centers of cells**. They are the organelles **necessary for the conversion of chemical energy from nutrients** to the types of energy that can be utilized by the cell. Cellular respiration produces **energy-rich ATP molecules** using energy generated by the systematic decomposition of nutrients (glucose, fatty acids, etc.). Mitochondria are covered with two membranes and have a **variable shape** (rod, filament, oval to spherical). Mitochondria **contain their own DNA** and ribosomes**, making them semi-autonomous organelles (the formation of their proteins is partly independent of the nucleus). After fertilization, all sperm mitochondria dissipate (they are probably actively destroyed by oocyte lysosomes). Hence, all the** mitochondria in the embryo (even mitochondrial DNA) originate exclusively from the mother.

Endosymbiotic theory (symbiogenesis)

– from an evolutionary point of a view, mitochondria probably evolved from eubacteria, which lived in a symbiotic relationship within the cytoplasm of primitive eukaryotic cells

1 **External mitochondrial membrane** has a composition similar to cell membrane

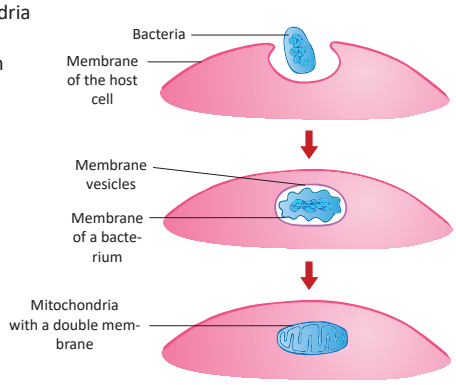
2 **The inner membrane** is comparable to the membranes of prokaryotic cells

3 **Mitochondria have their own genome** in the form of a circular molecule similar to prokaryotic DNA

4 **Ribosomes of mitochondria** are of prokaryotic type

5 **Mitochondria can synthesize some of their structural proteins themselves** (however, other mitochondrial proteins but are encoded in the nucleus)

6 **The number of mitochondria increases during cell division**



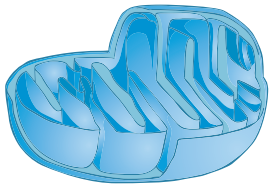
Endosymbiotic theory

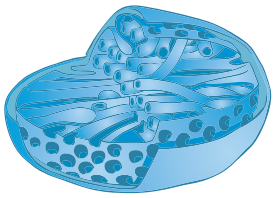
Types

– according to the type of internal membrane folding

1 **Mitochondria with cristae**
– the most common type of mitochondrial
– cristae are usually directed perpendicularl to the long axis of the mitochondria

2 **Mitochondria with tubules (tubular type)**
– have longitudinally oriented tubular projections of inner membrane
– typical for cells producing steroid hormones, e.g., in adrenal cortex cells, in placental syncytiotrophoblast, or in the interstitial endcrine cells of Leydig of testis


Mitochondria with cristae


Mitochondria with tubules

The length of mitochondria is 0.75–3 µm, width 0.3–0.5 µm.

In the cytoplasm, mitochondria perform slow, oscillatory or circular movements, moving along the microtubules of the cytoskeleton to sites of higher energy needs.

There are several hundred to tens of thousands of mitochondria in one cell (depending on metabolic activity).

The term chondriome is generally used to designate all the mitochondria in a given cell.

Other types of mitochondria:
Mitochondria with vesicles contain small vesicles connected with the inner membrane using a short stem. Found in the cells of the adrenal cortex of rats and hedgehogs. Their presence in humans has not been confirmed.
Mitochondria with prisms have inner membrane protrusions of triangular cross section. Present in astrocytes of the brain in cats and hamsters. In humans, they have been described in astrocytes of the cerebral cortex (however, it is not clear whether it is an artifact caused by the processing of samples).

The discovery of mitochondria has a special history. In 1857, Albert von Kölliker observed granules in the cytoplasm of striated muscle fibers; in 1882, Walther Flemming observed filaments in the cytoplasm of cells; in 1886, Richard Altmann described granules that he called "bioblasts." All of them apparently observed mitochondria, which got their name in 1898 by Carl Benda.

Mitochondria are indispensable for cell life. They are absent only in mature red blood cells and in the keratinized keratinocytes of the epidermis.

A liver cell (hepatocyte) contains 500–4000 mitochondria, representing an average of 14% of the cell volume.

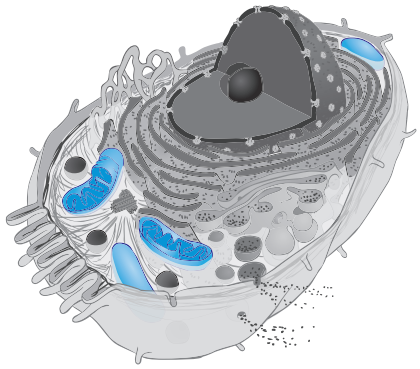
Mitochondria accounts for up to 40% of the volume of cardiac muscle cells.

In living cells, the mitochondria may be stained with Janus green or they are visible in phase contrast. In histological sections, they can be stained with iron hematoxylin.

Mitochondrial DNA encodes 13 enzymes involved in oxidative phosphorylation, 2 different ribosomal RNA molecules and 22 different transfer molecular RNAs.

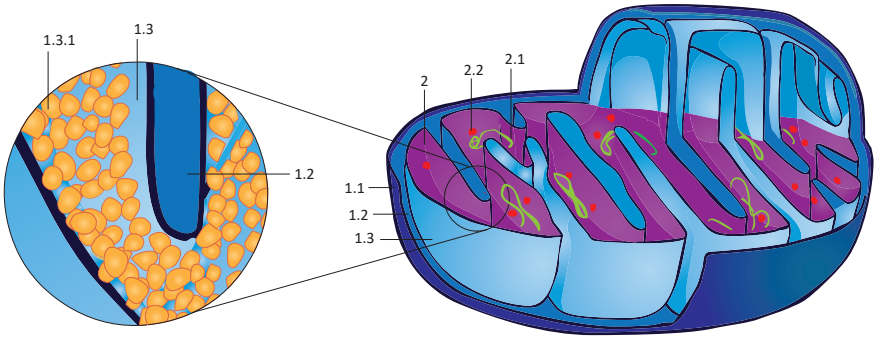
Structure

1 **Double-membrane mitochondrial envelope** (*tegumentum mitochondriale*)
- 1.1 **External mitochondrial membrane** (*membrana mitochondrialis externa*)
  - – smooth, highly permeable to ions and water
  - – contains numerous porins, transport canals permeable even for high-molecular substances
  - – lipid-protein ratio of 1: 1
- 1.2 **Intermembranous space** (*spatium intermembranosum*)
  - – between the outer and the inner membrane
  - – contains proteins that, after a damage of the outer membrane and their transfer to cytoplasm trigger cell apoptosis (e.g. cytochrome c and DIABLO protein, which binds to some apoptotic protein inhibitors)
- 1.3 **Internal mitochondrial membrane** (*membrana mitochondrialis interna*)
  - – membrane folding / invaginations, creating cristae or tubules
  - 1.3.1 **Cristae** (*cristae mitochondriales*) – folds
  - 1.3.2 **Tubules** (*Tubulus mitochondriales*) – tubular structures
  - – protein to lipid ratio 4: 1
  - – high cardiolipin-phospholipid content (up to 20%), which reduces the permeability of the membrane for the ions
  - 1.3.3 **Elementary particles** (*particulae elementares*)
    - – contain enzymes important for oxidative phosphorylation (ATP-ozomas)
    - – shape of a tennis racket under the electron microscope (diameter 10 nm)



Mitochondria in the cytoplasm

- 2 **Mitochondrial matrix** (*matrix mitochondrialis*)
  - – semi-liquid mass delimited by the internal mitochondrial membrane
  - – contains enzymes active in the Krebs cycle and beta-oxidation of fatty acids
  - 2.1 **Mitochondrial DNA filament / mitochondrial chromosome**
    - – circular double stranded DNA molecule
    - – usually not bound to proteins (histones)
    - – carrier of extra-nuclear (extrachromosomal) hereditability
    - – comes only from the mother (maternal inheritance)
    - – allows auto reproduction of mitochondria
  - 2.2 **Mitochondrial ribosomes / mitoribosomes**
    - – similar to prokaryotic ribosomes
  - 2.3 **Mitochondrial granules** (*granulae mitochondriales*) – storage of calcium ions

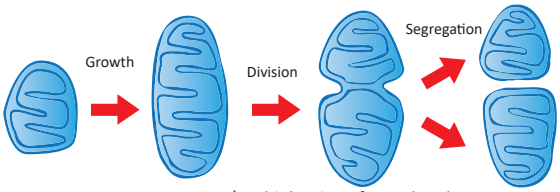


Detail on the internal mitochondrial membrane (mitochondrial matrix not depicted)

Structure of mitochondria

Division / multiplication of mitochondria

– the life cycle of the mitochondria is short
– transversal dividing, partition dividing the organelle is formed by the invagination of the internal membrane
– before the division, the size of the mitochondria increases
– conversely, in some cases mitochondria may mutually fuse



Division / multiplication of mitochondria

Ribosomes are **made of protein complexes and RNAs**. They are about 20 nanometers. They are **synthesized in the nucleolus** and get through the nuclear pores into the cytoplasm. They are either **loosely present in the cytoplasm** (synthesize peptides and proteins to be used by the cell itself) or **attached to a membrane of the rough endoplasmic reticulum** (synthesize proteins intended for exportation, the cell membrane, lysosomal enzymes). In the cytoplasm, they may be present as **individual structures or bound** together by an mRNA fiber to form **polyribosomes**. **Polyribosomes produce proteins intended to be used by the cell itself**.

Structure and content

Structure

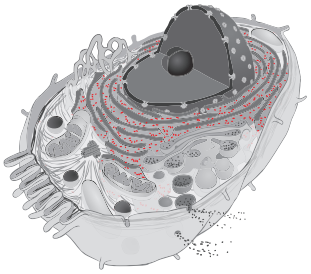
– consist of two subunits

- 1 **Large subunit** (*pars magna*)
  – has a sedimentation constant of 60S
- 2 **Small subunit** (*pars parva*)
  – has a sedimentation constant of 40S

Content

– contain several types of RNA

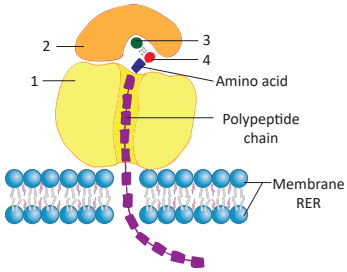
- 3 **Information / mediator RNA** (mRNA)
- 4 **Transfer RNA** (tRNA)
  5 **Ribosomal RNA** (rRNA)



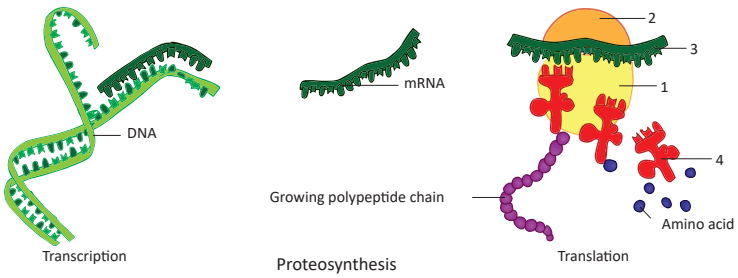
Ribosomes in the cytoplasm and on the surface of the RER

Proteosynthesis – protein synthesis

1. **The cell nucleus, genetic information**, stored in the order of purine and pyrimidine bases in DNA is transcribed to the molecule of messenger RNA (mRNA)
2. **during the transfer from the nucleus, mRNA is amended** and bound to the small ribosomal subunit
3. **Ribosomes will "read" the sequence of the mRNA bases and mediate the base pairing of the corresponding transfer RNA** (tRNA) to each triplet of bases (codon). On one end, tRNA have a complementary triplet of bases (anticodon); on the other end, they transfer an amino acid, which corresponds to the actual mRNA codon according to the genetic code
4. **The sequence of mRNA bases is gradually translated to form a polypeptide chain**, which is then processed inside an endoplasmic reticulum



Structure of a ribosome attached to the membrane of a rough endoplasmic reticulum



Cytology

Ribosomes were originally called Palade granules, according to their discoverer, American cytologist of Romanian origin George Emil Palade (1955).

Ribosomes deposited in the mitochondria are smaller, similar to the ribosomes of prokaryotic cells and are also called mitoribosomes.

Ergastoplasm is an outdated term for the basophilic regions of the cytoplasm with rough ER.

Neither ribosomes nor individual vesicles of endoplasmic reticulum are visible at a magnification level of the light microscope.

In 2016, Yoshinori Ohsumi was awarded a Nobel prize in Physiology or Medicine for the discovery of autophagy (merging of autophagosomes with lysosomes), which is used to decompose and recycle damaged and unnecessary organelles and molecules

Sarcoplasmic reticulum p. 144.

Clinical notes

Colchicine is a natural alkaloid with the effect of "mitotic poison". It comes from autumn crocus (*Colchicum autumnale*). It stops the polymerization and depolymerization of the microtubules of the mitotic spindle, thereby blocking the entire mitotic division before the start of anaphase. Colchicine is used in genetics to study karyotypes of dividing cells. After stopping mitosis, one can microscopically analyze the number and structure of chromosomes.

Inherited lack or defect in functions of some lysosomal enzymes causes congenital lysosomal storage diseases (lysosomopathy, thesaurismosis). Up to now, several dozens of these diseases have been reported, such as Tay-Sachs disease (imperfect decomposition of fat particles with the accumulation of gangliosides in brain neurons), Gaucher disease (fatty particles of glucocerebrosides deposited in spleen, bone marrow and liver) or Fabry disease (accumulation of glycolipids especially in the wall of small renal arteries, skin, heart and brain).

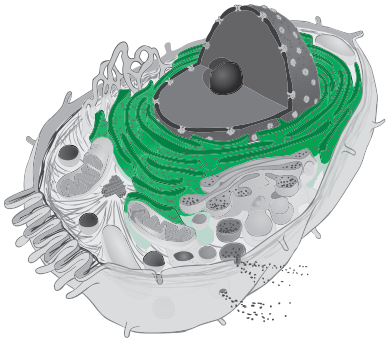
Zellweger's syndrome is a rare autosomal recessive disease caused by a disorder of the peroxisomal formation and function. It leads to a disruption of nerve system development and a postnatal defective myelination of nerve fibers. A typical diagnostic feature is the high level of very long carboxylic acids in blood plasma.

The endoplasmic reticulum is **a three-dimensional cavity system formed by one membrane**. Cavities are formed **by cisterns, pouches (vesicles) and ducts**. It is part of the so-called **membrane cell system** (together with the Golgi complex, lysosomes and secretory vesicles) involved in the **formation, modification, deposition and transfer of molecules in the cell** and on their uptake and excretion from the cell. It synthesizes substances that are transported out of the cell via **transport vesicles** or transported to the Golgi complex for further processing. The endoplasmic reticulum is interconnected with **the nucleus and the Golgi complex**. We distinguish the **rough (granular) endoplasmic reticulum**, which has ribosomes on its surface, and the **smooth (agranular) endoplasmic reticulum** without ribosomes. Rough and smooth ERs can continously merge into each other.

Rough endoplasmic reticulum (RER)

Structure
– a system of interconnected tubules and cisterns
– granular structure in electron microscope,
because ribosomes are bound on the surface of the membrane
– the large ribosomal subunit attaches to the reticulum membrane
with ribophorin I and II proteins

Function
– the emerging (nascent) protein chain
coming from the ribosome enters the RER and undergoes
additional modifications (post-translational modifications,
e.g. glycosylation, hydroxylation or other changes in the tertiary structure)
– newly formed proteins are transported to the Golgi apparatus via transport vesicles
– transport vesicles are covered with a membrane containing COP II proteins



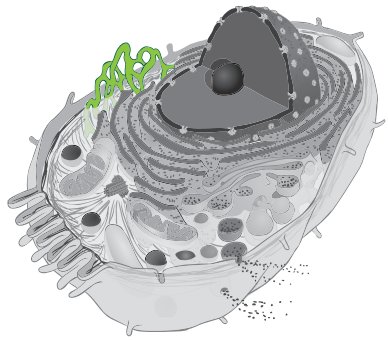
Rough endoplasmic reticulum
in the cytoplasm

Cells with high proteosynthetic activity
– the cytoplasm of the proteosynthetically active cells is more basophilic
(basic staining agents bind due to high RNA content in the cytoplasm)
1 **Hepatocytes (epithelial cells of liver)** - synthesize blood plasma proteins
2 **Fibroblasts** – synthesize both fibers and ground substance of the extracellular matrix
3 **Plasma cells** – synthesize antibodies (immunoglobulins)
4 **Nerve cells** – synthesize neurotransmitters and receptors
5 **Serous cells of exocrine glands** - form watery secretion
with high protein content (especially enzymes)

Smooth endoplasmic reticulum (SER)

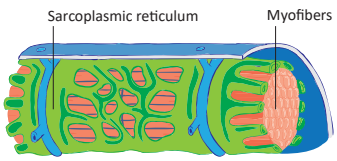
Structure
– a system of interconnected tubules and rarely flat cisterns as well
– no ribosomes on the surface

Function
1 **Synthesis of phospholipids of membranes, cholesterol, lipoproteins**
2 **Metabolism of glycogen** (contains the enzyme glucose-6-phosphatase)
3 **Synthesis of steroid hormones** (glucocorticoids, mineralocorticoids,
testosterone, estrogens and gestagens)
4 **Biotransformation and degradation of exogenous substances**,
e.g. medicinal products and poisons (cytochrome P450 monooxygenase
or conjugating enzyme glucuronyl transferase)
5 **Participate in contraction and relaxation of skeletal and cardiac muscle**
(release and uptake of Ca^{2+}), referred to as the sarcoplasmic reticulum
6 **Secretion of Cl^- ions during the production of HCl** in gastric parietal cells



Smooth endoplasmic reticulum
in the cytoplasm

Cells with relatively large amount of smooth endoplasmic reticulum
– the cytoplasm with an abundant smooth ERs stained eosinophilically
1 **Hepatocytes (epithelial cells of liver)** – in association with a glycogen conversion
and storage, with biotransformation and detoxification function,
cholesterol and lipoprotein synthesis
2 **Interstitial endocrine cells of Leydig in testis and adrenal cortex cells**
– synthesize steroid hormones
3 **Skeletal and cardiac muscle cells** - in association with the stored Ca^{2+}
– their smooth endoplasmic reticulum is called sarcoplasmic reticulum



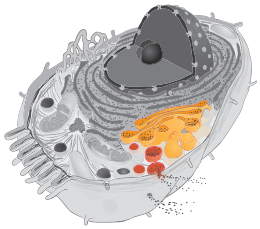
Sarcoplasmic reticulum
around the myofibril of muscle fibers

The Golgi apparatus is **a system of flat cisterns (vesicles)**, separated from the cytoplasm by **one membrane**. Cisterns are expanded at the end and **secretion vesicles** separated from them. **Dictyosome** is a unit made up of 3–7 cisterns. The Golgi complex is close to the **cellular nucleus and the rough endoplasmic reticulum**, which actively communicates with. **Post-translational modifications of proteins** to their final form (glycosylation, phosphorylation, partial proteolysis, etc.) are performed here.

Structure and function

Structure

1 **Dictyosome / Golgi stack** – has two poles/faces
- 1.1 **Cis face / Entry face** – serves for receiving vesicles in the direction of the rough endoplasmic reticulum
- 1.2 **Trans face / Exit face** – used for the separation of vesicles containing modified proteins



Golgi complex and vesicles in the cytoplasm

Function

1 **Post-translational modification of proteins**
– to their final form (glycosylation, phosphorylation, partial proteolysis, etc.)

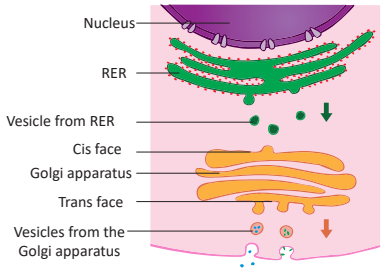
2 **Transfer function** – release of the vesicle, which remain in the cell (e.g. lysosomes) or are released from the cell by exocytosis

Vesicles

Significance of vesicles in the transport of substances in the cell

– most molecules, including proteins, are too large to be able to directly cross membranes
– these molecules acquire a membrane envelope and become part of vesicles

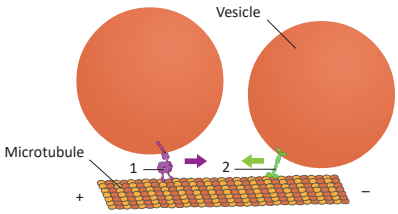
1. vesicles form in various parts of the cell, above all in the endoplasmic reticulum and the Golgi complex
2. vesicles transport their contents within the cell or out through its membrane
3. once they reach the destination, they merge with another membrane and release their content
   – the protein molecule itself passes the boundaries of membrane compartments, without having to go through the membrane itself



Formation and transport of vesicles

Vesicle movement

– vesicles travel along the routes set by microtubules and are driven by molecular motors, whose source of energy is ATP
- 1 **Dyneins** – direct the vesicles towards the centrosome
- 2 **Kinesins** – direct the vesicles away from the centrosome

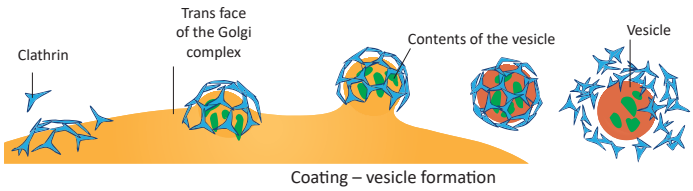


Vesicle movement

Coating

– the formation of vesicles is facilitated by proteins geometrically arranged on the surface of the membrane in a manner contributing to the formation of the vesicle

1 **COP I** – a protein encapsulating vesicles from the Golgi complex and directed back to the ER
2 **COP II** – a protein encapsulating ER vesicles directed to the Golgi complex
3 **Clathrins** – a protein encapsulating vesicles originating in the Golgi complex



Coating – vesicle formation

Golgi's complex was discovered with the use of impregnation methods in nerve cells, the Italian neurohistologist Camillo Golgi in 1898 originally called it "apparato reticolare interno" (internal reticular apparatus).

More than 200 different enzymes involved in the biosynthesis of glycolipids and glycoproteins have been described in the Golgi complex.

The Golgi apparatus can sort proteins coming from the endoplasmic reticulum to those intended to be part of lysosomes, those to become part of the cell membrane, and others intended to be released from the cell via the secretory vesicles.

Three scientists (James E. Rothman, Thomas C. Südhof and Randy W. Schekman) received a Nobel Prize in Physiology or Medicine for their discoveries of machinery regulating vesicle traffic, a major transport system in cells (intracellular transport of substances via vesicles).

During coating, the vesicles "wear a protein coat".

Some vesicles "travel" around the entire perimeter of the cell under the inner side of the cell membrane. This is ensured by the polymerization and depolymerization of actin.

SNARE proteins help to fuse membranes of individual vesicles or the membrane of one vesicle with the cell membrane. V-SNARE proteins on the vesicle are specifically recognized and bind to their counterparts on the target membrane (t-SNARE).

Peroxisomes were originally referred to as microbodies. This term is still often used in English literature. **Peroxisomes** resemble mitochondria due to the ability to beta-oxidize fatty acids .

Peroxisomes are very common in the cytoplasm of oligodendrocytes, where they are associated with the formation of myelin lipids necessary for the formation of myelin sheath around nerve fibers in the central nervous system.

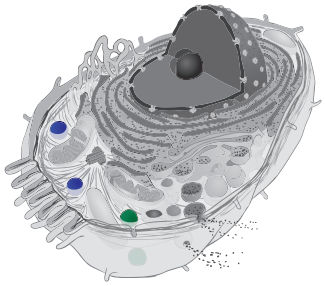
In stained blood smear, lysosomes in white blood cells appear as so-called non-specific azurophil granules, which are found in the cytoplasm of granulocytes and agranulocytes.

Siderosomes are iron-storage lysosomes in liver hepatocytes.

Lysosomes and peroxisomes are **organelles of spherical to ovoid shape**. Their size range from several dozen nanometers to 1 µm. They are delimited from the cytoplasm **by one membrane**. They have different origin and enzyme content.

Lysosomes

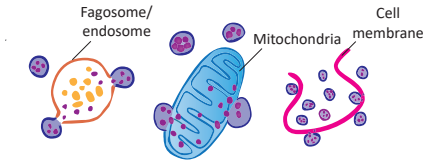
– small vesicles with uniform, granular or layered contents
– contain over 50 multiple enzymes with high concentration of protons (pH about 5), so-called acid hydrolases
– with their hydrolytic enzymes are responsible for intracellular digestion of endogenous and exogenous substances
– can serve as a storage of unnecessary substances or vice versa store the necessary substances (e.g. iron in hepatocytes)
– hydrolytic enzymes are synthesized in RER first in an inactive form
– subsequent modification of enzymes to their active form occurs together with the formation of primary lysosomal vesicles in the Golgi complex



Lysosomes and peroxisomes in the cytoplasm

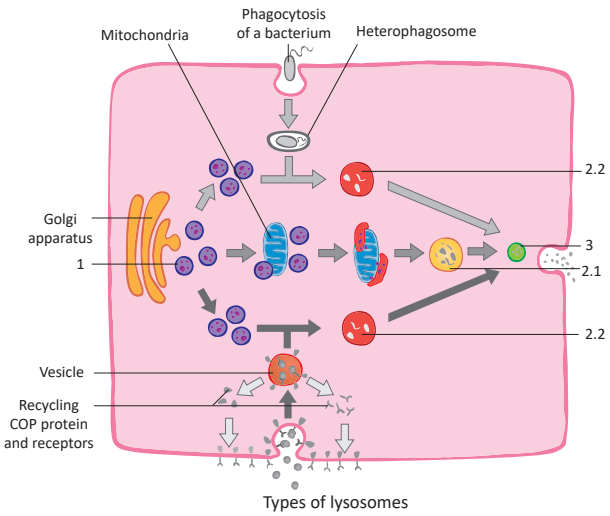
Function

1 **Intracellular digestion** – ensures the breakdown of substances received by the cell via pinocytosis and phagocytosis
2 **The destruction of various cell components** – decompose worn out, damaged and nonfunctional organelles
3 **Contribute to cell autolysis** in necrotic cell disintegration



Types

- 1 **Primary lysosome**
  – formed by budding at the trans face of the Golgi complex (nowdays are termed as Golgi vesicle transporting lysosomal enzymes)
  – contain enzymes, but do not yet contain a substrate, which is to be enzymatically metabolized
  2 **Secondary lysosome** – enzymatic degradation and digestion of the substrate, then fusion of the primary lysosome with another part of the cytoplasm
  - 2.1 **Autolysosome**
    – after merging with damaged or worn organelle
  - 2.2 **Heterolysome / phagolysosome** – after fusion with foreign material, that was previously received via pinocytosis or phagocytosis
- 3 **Tertiary lysosome** (telolysosomes, residual bodies)
  – formed when enzymatic activity is depleted, where lysozyme is no longer capable to process further substrate
  – can be excreted from the cell by exocytosis or is stored in the cytoplasm



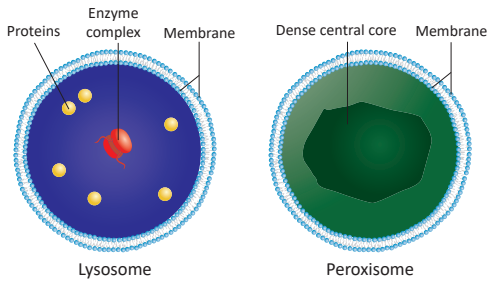
Types of lysosomes

Peroxisomes

– formed de novo by budding directly from the endoplasmic reticulum or by division of existing peroxisomes
– their half-life is only a few days (approximately two days)
– it can be shown histochemically that each peroxisome contains at least one oxidase and one catalase
– inside, there may be a crystalline core, consisting of a mixture of enzymes, substrates and cofactors, which is visible under electron microscope

Function of enzymes of peroxisomes

1 **Alpha- and beta-oxidation of carboxylic acids**
  – including long fatty and branched carboxylic acids
2 **Synthesis of cholesterol, bile acids and plasmalogens**
3 **Removal of toxic glyoxylate and reactive oxygen species** (hydrogen peroxide and superoxide)
4 **Decomposition of purines, polyamines and amino acids**



Cytoplasmic inclusions are non-living **components of cell cytoplasm** that can be delimited by a membrane. **They are accumulations of various metabolites** and can also have a storage function. Inclusions can store **lipid, saccharide or crystalloid substances of a proteinous nature. Color pigments and secretory granules** can be included in this group as well.

Fat droplets (*guttae adipis*)

– mostly accumulate fatty acid triacylglycerols
– energy storage
– may be delimited by a membrane, which may not be complete
– size range of 100 nm to more than 10 µm
– content of homogeneous appearance
– light to dark contrast by electron microscope

Lipid droplets
(lipoblast and univacuolar adipocyte)

under light microscope,

– in conventional histological processing (using alcohol to dehydratate the tissue) the fat dissolves leaving optically empty spaces in place of those droplets
– fat-soluble staining agents (Sudan III or oil red) are used to visualize these components
– white adipose connective tissue adipocytes contain one huge fat droplet, which fills almost all cytoplasm
– other cells (e.g. adipocytes of the brown fat tissue) contain numerous small fat droplets
– lipid droplets are abundant even in cells producing steroid hormones, e.g. adrenal cortex, interstitial endocrine cells of Leydig in testis

Glycogen granules (*granulum glycogeni*)

Glycogen granules
(decidual cell)

– not covered by a membrane
– saccharides are stored in the form of glycogen, which is the storage form of glucose
– glycogen is deposited particularly in hepatocytes, in skeletal and cardiac muscles or in decidual cells before and during the implantation of the embryo into the uterine mucosa
– in large quantities, it fills the cytoplasm of stratified squamous non-keratinizing vaginal epithelium in women of childbearing age; glycogen from desquamated epithelial cells serve as a source of energy for lactobacilli, which form the normal bacterial microflora of the vaginal mucosa and convert glycogen into lactic acid, leading to low pH inside the vagina
– histochemically, it is demonstrated by PAS reaction as a deep pink to purple reaction product
– under electron microscope, it has the appearance of an electron-dense granule of 15–30 nm (so-called beta-granules)
– beta-granules of glycogen form clumps (rosettes) with the size of 80–100 nm, called alpha-granules

Crystalloid inclusions (*granulum crystaloideum*)

Crystalloid granules
(interstitial endocrine cells of Leydig in testis)

– mainly composed of proteins

1 **Reinke's crystalloids** - function is unknown
  – in the cytoplasm of interstitial endocrine cells of Leydig in testis
  – length of up to 20 µm, width about 3 µm, not covered by a membrane
2 **Charcot-Böttcher's crystalloids** - function Unknown
  – in the cytoplasm of supportive / nurse cells of Sertoli in testis
  – 10-25 µm in length, not covered by a membrane
3 **Crystalloid core** (*corpus crystalloideum*)
  – antiparasitic effects (against unicellular parasites and nematodes)
  – in the lysosomes of eosinophilic granulocytes
  – covered with a membrane
  – consists of major basic protein with high content of the basic amino acid arginine, which is responsible for eosinophilia of the granules

Paraplasm is an obsolent term for cytoplasmic inclusion.

Glycogen is a storage form of glucose. Individual glucose molecules have high osmolar activity and it is not possible to store them in this form.

Pigmentation is the process of depositing pigments into tissues, causing their discoloration.

Darkness (skin color) is not dependent on the number of melanocytes, but on the number of present melanosomes.

Dark blue to black tattoo is created by the administration of ink into the dermis, where it is phagocyted by macrophages. If pure carbon is used as ink, it produces only a limited or no immune response at all.

Clinical notes

Steatosis is a pathological accumulation of lipid droplets in the liver.

In diabetes, glycogen accumulates in the cytoplasm, but also in the cell nucleus.

Exogenous pigments form after the pigment enters the body from the outside:
1. **Skin or mucous membrane injury:**
Tattooing – administration of colored particles to the skin via a needle or by rubbing them into wounded skin.
2. **Digestive system:**
Argyrosis – gray to grayish-colored skin due to silver deposits in the skin. **Chrysocyanosis** - bright coloration of the skin due to gold deposits in the skin.
3. **Respiratory tract:**
Pneumoconiosis – lung disease with fibrotization due to inhalation of silicon particles. **Anthracosis** – lung contamination with carbon particles found in industrial areas population. **Tabacosis** – lung pigmentation in chronic smokers.

Anthracosis - soot, smog and dust particles are deposited in pulmonary dust cells (alveolar macrophages that actively phagocyte the particles), pleura and lymph nodes in the area of the lung hilum. Macroscopically, it is a dark reticulation on the surface of the lungs

Albinism is a group of hereditary diseases characterized by little or no melanin pigment formation. It is caused by a disorder of tyrosinase function. Most people affected by albinism are sensitive to sunlight and are in an increased risk of skin cancer.

Pigment granules (*granulum pigmenti*)

– chemical substances of various composition and color
1 **Endogenous pigments** - form during metabolism
  1.1 **Melanin and neuromelanin**
  1.2 **Lipofuscin, lipochrome and ceroid** – pigments of a fatty nature
2 **Hematogenic pigments**
  2.1 **Myoglobin** - in muscle tissue
  2.2 **Hemoglobin** - in red blood cells
    2.2.1 **Hemosiderin, biliverdin, bilirubin, hematin, hematoidin**
      – hemoglobin breakdown products

Melanin (in the pigment cell of the epidermis)

Hemosiderin (in a siderophage)

Melanin

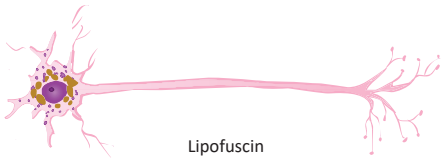
– formed in RER as a membrane covered melanosoma, which matures to form melanin granules
– biochemically, it is the product of tyrosine oxidation by tyrosinase enzyme (ultraviolet light increases the enzyme activity) and subsequent polymerization
– in the skin, it protects dividing cells exposed to sunlight from excessive exposure to harmful effects of ultraviolet light (especially UVB with the wavelength of 320-290 nm)
– melanin granules are produced in melanocytes of epidermis and hair follicles, they are released from melanocytes and permeate into the surrounding cells of the epidermis
– melanocytes are also present in the connective tissue of thw eyeball, in particular its middle vascular layer (*stratum vasculosum*), they determine the color of the iris
1 **Eumelanin** – causes brown skin color and black hair coloration
2 **Feomelanin** – causes rutilism (red, reddish, brown-red hair color)

Neuromelanin

– synthesized from L-3,4-dihydroxyphenylalanine, a dopamine neurotransmitter precursor
– probably involved in the protection of neurons from oxidative stress
– its amount in neurons decreases with age

Occurrence

– in the neurons of some regions of the brain (e.g. substantia nigra, area postrema, trigone of vagus nerve and locus caeruleus)
– pigmented layer of the retina of the eyeball
– some cells in the stria vascularis of the inner ear



Lipofuscin (multipolar neuron)

Lipofuscin

– a yellow-brown pigment, referred to as aging or "wear-and-tear" pigment
– its granules are residual bodies (residues after lysosome digestion of lipids and lipoproteins)
– lipofuscine granules typically accumulate around the cell nucleus
– occurs especially in long-living or highly metabolically active cells (neurons, cardiac muscle cells, hepatocytes, adrenal cells or supporting cells of the olfactory mucous membrane)
– the amount of pigment increases with age and its accumulation is also reflected macroscopically (e.g. senile brownish looking cardiac muscle)

Hemosiderin granules (*granulum haemosiderini*)

– rusty pigment containing iron in the form of ferritin
– the product of hemoglobin breakdown in the cytoplasm of macrophages
– most of the hemosiderin present macrophages of the spleen, liver and bone marrow (siderophages)
– hemosiderin is a part of secondary lysosomes, which are therefore referred to as siderosomes
– hemosiderin can be detected using Perls reaction, forming a blue precipitate (Berlin or Prussian Blue)

Hematoidin granules (*granulum haematoidini*)

– yellowish-brown pigment
– hemoglobin breakdown products after tissue bleeding also occur outside macrophages (in extracellular space)
– identical to bilirubin, which forms in macrophages after removing iron (via an intermediate called biliverdin)

Lipochrome granules (*granulum lipochromii*)

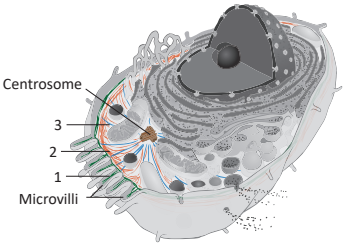
– orange pigment, occurs in adipose tissue
– higher amounts with increased intake of carotenoids in food (e.g. from carrots)

The cytoskeleton consists of three basic types of fibrous proteins that form three dimensional mesh structures: **microtubules**, **microfilaments** and intermediate filaments**. These** complex meshes are constructed from filamentary and **tubular** structural elements and together form a **dynamic cellular framework**.

Structure

Parts of the cytoskeleton

- 1 **Microfilament**
- 2 **Intermediate filament**
- 3 **Microtubules**



Cytoskeleton in cytoplasm

Fiber bundles

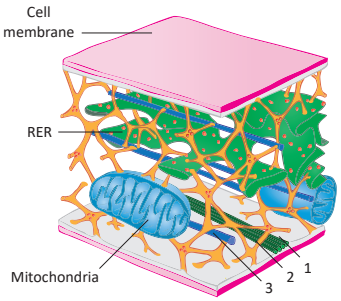
– fibers can be combined to stronger bundles, which can be visible by light microscope

1 **Tonofibrils** – intermediate filament bundles in the cytoplasm of epithelial cells
– very well developed in cells of epidermis

2 **Myofibrils** – contractile fibers in muscle cells and fibers
– consist of actin microfilaments and associated myosin fibers

3 **Neurofibrils** – intermediate filament bundles (neurofilaments) and microtubules (neurotubules) in the cytoplasm of nerve cells

4 **Glial fibrils** – intermediate filament bundles in the cytoplasm of astrocytes from the central nervous system



Cytoskeleton in cytoplasm (detail)

Microfilaments (*microfilamenta*)

– about 8 nm thick, consist of actin (protein)

1 **G-actin** – basic globular form of actin

2 **F-actin** – twisted fibrillar chain of actin, formed by the polymerization of G-actin

3 **Actin microfilament** – F-actin double helix
– the length of one thread is 37 nm, in most cells its total length exceeds the length of the microtubule system

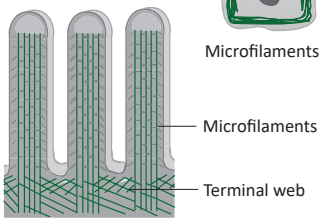
– dynamic arrangement, i.e. they grow and shorten over time

– gripping to the plates of zonulae adherentes

Microfilaments

Function

1 **They form the cytoplasmic projections** of some cells allowing amoeboid movement
1.1 **Pseudopodia** – stronger projections
1.2 **Lamellipodia** – flattened projections
1.3 **Filopodia** – very thin projections
1.4 **Microvilli** – multiple projections increasing the surface area of the cell
1.5 **Stereocilia** – branched and considerably longer than microvilli
– the microvillus and stereocilium contain approximately 20–30 microfilaments, which continue from the base of the projection to anchor the terminal web beneath the cell membrane



Longitudinal section of microvilli

2 **They facilitate anchoring and mobility of the cell membrane proteins**

3 **They maintain the shape of the cell and allow it to change**
– in the cytoplasm, they form a spatial network
– **Cortical cytoskeleton** – a terminal network of microfilaments just below the cell membrane

4 **They ensure the uptake and delivery of larger molecules through the membrane**, including phagocytosis

5 **They control the distribution of organelles** and cytoplasmic flow

6 **They detect the tension and movement in muscle cells and fibers**
– together with myosin fibers, they form the so-called contractile apparatus

7 **They participate in the growth of the terminal parts of neuron projections (axons and dendrites)**

G-actin F-actin Actin microfilament (F-actin double helix)

The fibrous structures of the cytoskeleton are 8–25 nm thick, therefore they are not visible under light microscope.

Neurofibrils are well-visible after gold and silver impregnation.

Ectoplasm is the peripheral cytoplasm in the cortical cytoskeleton.

There are also cells without intermediate filaments, e.g. germ cells, blastomeres during cleavage, or cells of embryoblast during the development of blastocyst.

Intermediate **filaments** first appear in the ectoderm of the germinal disc during embryonic development.

Microtubule-organizing centers (MTOCs) control the growth of microtubules. MTOCs contain also the third form of tubulin (gamma-tubulin), that probably controls microtubule dynamics.

In animals, the role of MTOC is filled by the centrosome, i.e. the structure anchoring microtubules and controlling their prolongation and shortening.

Ciliogenesis is the development of cilia from the basal body. The stimulation of ciliogenesis is the contact of the centriole with the cell membrane. Ciliary axoneme is formed by prolonging the microtubules A and B of the basal body.

Some sources also state other types of cytoskeletal fibers, so-called micro-trabecula. They are considered to be proteins forming transverse bridges between the other cytoskeleton fibers. Other sources regard them as an electron microscopic artefacts.

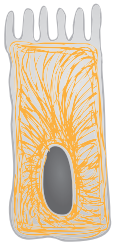
Clinical notes

Damage to microtubules or the inhibition of their polymerization lead to ceasing of the cell division and disintegration of the organelle positioning in the cytoplasm. It is the principle of the effect of some anti-cancer drugs (e.g. colchicine and vinblastine), which are targeted on rapidly dividing cells, where they induce apoptosis.

In clinical practice, immunohistochemical antibodies are used to distinguish various types of intermediate filaments. In pathology, we can detect the origin of a tumor cells, whose morphology can be otherwise significantly altered, but often retain their original intermediate filaments revealing their origin.

Intermediate filaments (*filamenta intermedia*)

– relatively rigid and flexible; therefore, they provide a tensile and compressive strength of the cells, thickness of approximately 10-12 nm
– do not undergo rapid dynamic reconstruction, making them different from microtubules and microfilaments
– interconnect organelles with membrane proteins
– anchoring to strong intercellular connections called desmosomes, thereby contributing to the cohesion between adjacent cells

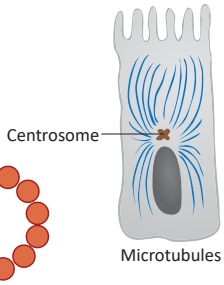

Intermediate filaments

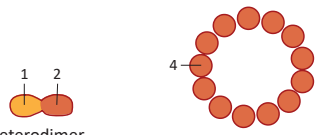
Types

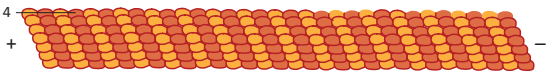
– based on the presence of individual proteins
1 **Desmin** – characteristic for muscle tissue
2 **Neurofilaments** – in nerve cells
3 **Cytokeratin (tonofilaments)** – in epithelial cells, more than 20 cytokeratin types are known
4 **Vimentin** – in cells of mesenchymal origin (connective tissue cells, endothelial cells, some smooth muscle cells)
5 **Glial fibrillary acidic protein (glial filaments)** – in glial cells of nerve tissue (in astrocytes and Schwann cells)
6 **Nestin** – in stem cells and undifferentiated cells, neuroepithelial cells
7 **Lamins** – reinforce the nuclear envelope from the inside, anchor chromatin and help restore the nuclear envelope after the division

Microtubules (*microtubuli*)

– are relatively long hollow tubes with a diameter of approximately 25 nm and a length up to several microns
– are rigid and do not grow, consist of tubulin subunits (small globular proteins)
1 **Alpha-subunit of tubulin**
2 **Beta-subunit of tubulin**
3 **Heterodimers** – formed by the junction of alpha and beta subunits
4 **Protofilaments** – elongated columns consisting of heterodimers
– parallel to the long axis of the microtubule
5 **Microtubule** – consists of 13 protofilaments
5.1 **+ (plus-end)** – region of microtubule growth
5.2 **- (minus-end)** – shortening region







Growth and shortening (dynamic instability) of microtubules

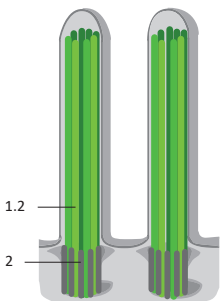
– microtubules are continually prolonged by polymerization of free cytoplasmic tubulin
– in other areas, they are simultaneously shortened by depolymerization

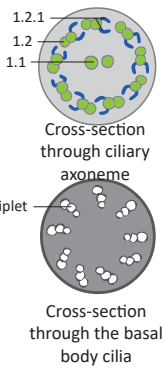
Function

1 **Their stiffness helps maintain cell shape and transfer organelles**
2 **They create the inner structure of the centriole**
3 **They create the mitotic spindle** during mitosis
4 **They control transportation of vesicles inside the cell**
5 **Neurotubules provide axonal transport** - cytoplasmic flow across the axons of neurons
6 **They are a component of the motile cytoplasmic projections** (cilia and flagella)

Structure of cilia and flagella

1 **Axoneme** – the inner skeleton of cilia, consists of (9 + 2) microtubules
1.1 **Central pair (doublet) of microtubules**
1.2 **Nine peripheral pairs of microtubules**
1.2.1 **Outer and inner dynein arms** - a diameter of 50 nm
– ensure the movement of adjacent microtubular pairs, and thus the bending and oscillation of the whole cilium/flagellum
2 **Basal body** (kinetosome) - the place the cilium grows from
– lies in the cytoplasm just below the base of the cilium
– consists of 9 peripheral triplets of microtubules
– the walls of adjacent microtubules forming doublets and triplets partly merge, so only the first microtubule consists of all 13 protofilaments, while adjacent ones of only 11 protofilaments



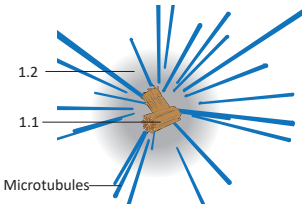


Cytoskeleton functions

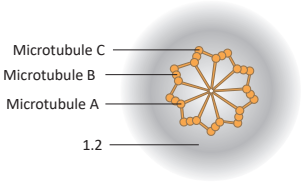
1 **Mechanical** – keeps the shape of the cell and is involved in its changes, attachment to tight and adhesive intercellular junctions
2 **Support** – determines the distribution and movement of organelles in the cytoplasm
3 **Transport** – moves vesicles and larger molecules (e.g. mRNA) in the cytoplasm
4 **Movement** – involved in cellular motion, is part of motile cilia and flagella
5 **In cell division** – pulls away daughter chromatids of chromosomes and participates in cell division (cytokinesis)

The centrosome consists of two short **hollow cylinders (centrioles)** formed by microtubules that are perpendicular to one another. It anchors microtubules and controls their dynamics, thus forming the microtubules organizing center. It is of a fundamental importance for the course of cell division; it is doubled before mitosis during the G2 phase.

1 **Centrosome** - during the interphase,
it is located near the cell nucleus
– the microtubules of the mitotic spindle grow out of it
– contains numerous proteins (e.g. gamma-tubulin) controlling microtubule growth
– consists of two perpendicular centrioles
- 1.1 **Centriole** - a short hollow cylinder whose wall is composed of 9 triplets of microtubules
  – they are referred to as A, B and C
  – the microtubule A is closest to the center
  – the walls of adjacent microtubules partly merge
    – centriole can be converted to the basal body of a cilium and flagellum
- 1.2 **Pericentriolar material**
  – an electron-dense layer around the centriole
  – visible by electron microscope



Centrosome



Centriole

6 Morphology of specialized cells

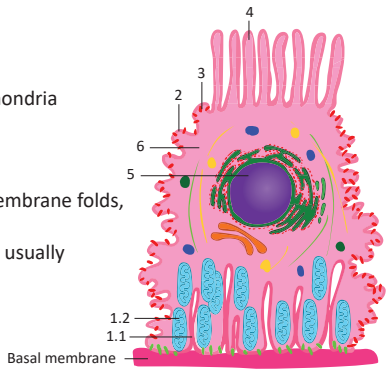
Some cells have adapted to their **specific functions** by changing their shape, surface or type and number of organelles **to an extent that they are** readily recognizable on the basis of this typical morphology. The appearance of **cells transporting electrolytes and cells producing proteins, steroids and mucus** is typical in both electron microscopy and light microscopy (using normal hematoxylin-eosin staining).

Electrolyte and water transporting cells

Examples: epithelial cells of striated ducts of salivary gland and proximal and distal tubules of nephron

Electron microscope image:

1 **Basal labyrinth** – cell membrane invaginations in the basal part of the cell with numerous mitochondria
- 1.1 **Cell membrane invaginations / folds**
  – enlarge the transport surface
  – contain ion pumps
- 1.2 **Mitochondria with cristae** – numerous in membrane folds, where they function as a source of energy
  – the longitudinal axis of the mitochondria is usually parallel to the longitudinal axis of the cell
- 2 **Lateral interdigitation**
  – numerous radial cytoplasmic projections between adjacent cells on the lateral side
- 3 **Lateral junctional complexes**
  – laterally just below the apical surface
  – prevent the transfer of substances through the intercellular space
- 4 **Apical microvilli** – in cells transporting also large amounts of water (e.g. a proximal tubule of nephron)



Electrolyte-transporting cell

Light microscope image:
- 5 **Large spherical dark nucleus located centrally**
- 6 **Eosinophilic cytoplasm (high intensity)** – due to the high number of mitochondria

7 **Fine basal striation** – the presence of mitochondria causes alternating darker and lighter rod-like structures perpendicular to the basal surface

The size of centrosome is about 1 µm. **Centriole** has a length of about 0.5 µm.

It is assumed that the centrosome of a fertilized egg (zygote) comes exclusively from the sperm, and therefore is of paternal origin.

The structure of the centriole and the basal body is identical. **Centrosome and microtubule organizational center** are synonyms.

Since centrosome duplicates before cell division, it has long been considered an organelle with its own DNA. However, this hypothesis was refuted; centrosome contains no DNA.

In the late 19th century, the zoologist František Vejdovský, a professor at Charles University in Prague, significantly contributed to the explanation of the role of the centrosome.

Many properties of centrosomes have not been explained, yet. Evolutionary, they probably come from the basal bodies of flagella in unicellular protozoa. The significance of their specific arrangement is not clear – they are formed by a pair of perpendicular centrioles.

The cells of proximal tubules in kidneys, which also transfer electrons, absorb large amounts of water and have high metabolic activity, have a very long brush border which is not clearly visible in histological slides. Long and numerous microvilli easily undergo autolysis, and are already damaged during the processing of tissue sample.

The lateral boundaries of adjacent cells transporting electrolytes are difficult to detect due to interdigitations.

Steroid hormones are synthesized from cholesterol.

Mucus is composed of glycoproteins. **Mucin** is the term for glycoproteins after hydration.

Alcian blue or muco-carmine staining may be used to detect mucus, eventually also histochemical PAS method (however, PAS reaction also stains glycogen and is not so specific. It can be elucidated by glycogen digestion via salivary enzymes, preserving only mucus.)
Mucin granules are not stained by hematoxylin-eosin, or a part of the mucin dissolves during the preparation of the slides, is released and creates optically empty spaces observable by a light microscope.

Cells producing proteins / proteosynthetically active cells

Production of proteins:

1 **For the needs of the cell itself** – permanent renewal of numerous receptors and cell membrane ion channels in nerve cells i.a.

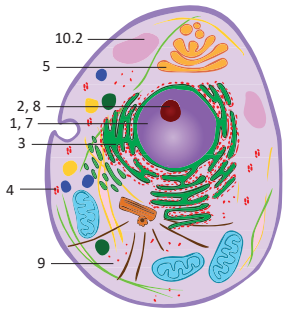
2 **For the direct release/export without the formation of granules** – production of antibody in the cytoplasm of plasma cells, blood plasma proteins produced by hepatocytes, fibers and the ground substance of connective tissue proper produced by fibroblasts i.a.

3 **For the release/export with the formation of secretory granules** – serous cells of the pancreas producing digestive enzymes, Paneth cells of the epithelium in the small intestine producing antimicrobial proteins, vesicles with transporters in the terminal part of nerve cell axons i.a.

Electron microscope image:

- 1 **Large spherical centrally located nucleus** – is pale with a predominance of euchromatin
- 2 **Nucleolus with nucleolonemas** (or compact nucleolus)
- 3 **Rough endoplasmic reticulum with ribosomes** – rich in the cytoplasm
  - – its cisterns can be widened and lie parallel to each other and above each other
  - – in polarized (glandular) cells, RER is mostly under the nucleus and the secretion product accumulates in the apical part
- 4 **Polyribosomes** – produce proteins intended to be used by the cell itself
- 5 **Golgi complex** – well-developed in cells producing secretory granules
  - – the secreted substance acquires here its final form before being released from the cell

6 **Electrondense (dark) secretory granules** – may have different densities



Proteosynthetically active cell

Light microscope image:

- 7 **Large spherical, relatively pale nucleus located centrally**
- 8 **Well-visible nucleolus** or more nucleoli
- 9 **Basophilic cytoplasm (medium to high intensity)** – due to the number of RNA-containing ribosomes
  - – connective tissue fibroblasts tend to have lighter spots in the basophilic cytoplasm (secretory vesicles for export)
  - – nerve cells have clusters of RER and ribosomes in the form of basophilic spots (Nissl bodies)

10 **Secretion granules** stained according to their content

- 10.1 **Basophilic granules** – acidic content e.g. serous cells of the pancreas
- 10.2 **Eosinophilic granules** – basic content e.g. Paneth cells of the epithelium of small intestine

Steroid-producing cells

Examples: interstitial endocrine cells of Leydig in testis, cells forming follicles and corpus luteum in the ovarian cortex and syncytiotrophoblast of placenta producing sex hormones

– cells of zona glomerulosa and zone fasciculata of the adrenal cortex producing glucocorticoids and mineralocorticoids

Electron microscope image:

- 1 **Tubular mitochondria** - their inner membrane forms tubules, not cristae
  - – their relevance for steroidogenesis is not clarified
- 2 **Smooth endoplasmic reticulum** - the main site of steroid hormone synthesis

3 **Lipid droplets** - cholesterol storage

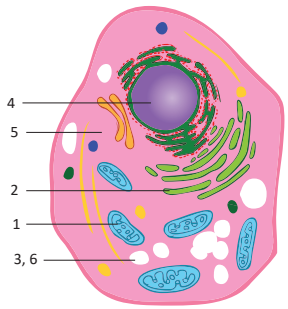
- 4 **Large, pale, spherical nucleus**

Light microscope image: cells cannot be uniquely identified

- 5 **Eosinophilic cytoplasm (high intensity)** - due to SER

6 **The area of lipid droplets** - creating a foamy appearance of optically empty spaces

- – lipids are dissolved during tissue processing



Steroid-producing cell

Mucus-producing cells/ mucinous cell

Examples: goblet cells (epithelium of small and large intestines and airways)

– mucous cells of salivary glands (sublingual and submandibular gland) and some small salivary glands (Weber's salivary glands of the root of the tongue)

– mucous cells of smaller glands in the wall of various organs (the submucosa of duodenum and esophagus, mucosa of stomach, urethra, trachea, etc.)

Electron microscope image:

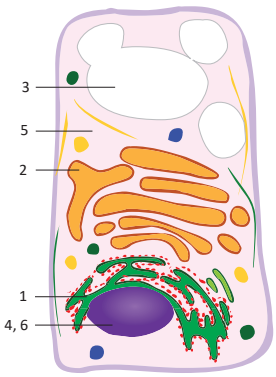
- 1 **Rough endoplasmic reticulum** – forms the proteinous part of the secretion
  - – when compared to serous cells, it is less developed, and its cisterns are not arranged collaterally
- 2 **Golgi apparatus** – very well developed, secretion condensation and glycosylation take place here

3 **Large light mucin granules (vesicles)** – fill a large part of the cell, often merging

- 4 **Flattened darker nucleus in the basal part of the cell** – compressed by large granules

Light microscope image:

- 5 **Pale to totally bright cytoplasm** – cells are very pale
- 6 **Flattened darker nucleus in the basal part of the cell** - often of half-moon shape



Mucous cell

The basic signs of life of cells include the **production of proteins and other organic substances, the exchange of substances and energy with the external environment, the storage and conversion of energy and substances** (metabolism), **growth and differentiation** and, in some cells, an **active movement**. One of the basic characteristics of the cell is also the **ability to divide** (auto reproduction). It is not only a simple increase in number, but also the **morphological and functional specialization of the cells**, which is a result of their differentiation. **Division and differentiation** are essential for tissue regeneration and repair. Gradual aging of cells leads to the loss of water, decrease in number of nuclear pores, increased number of genetic mutations, and with exception of stem cells, shortening of the terminal regions of chromosomes (telomeres) with rising number of divisions. The cell undergoes **programmed cell death**, apoptosis. **Apoptosis** is a physiological process that is **inevitable for the normal structure and function of all tissues**. The removal of undesirable, old and damaged cells is strictly controlled by genetically engineered mechanisms. Apoptosis disturbances are found in some pathological conditions.

7.1 Transfer of substances through membranes, endocytosis and exocytosis

The transfer of substances through the cell membrane is accomplished by two basic mechanisms. The first one is the **transport through the membrane**. In this process, smaller molecules directly **pass the double-layer of membrane phospholipids**, or utilize **protein carriers, channels or pumps** designated for this purpose. **Large molecules** that cannot cross the membrane enter the cell via **membrane cycle mechanism**. This process **creates vesicles formed by the received substance encapsulated by a cell membrane**. These vesicles **may merge with lysosomes or peroxisomes** in the cytoplasm. **Exocytosis** involves the process of delivering substances from the cell to the extracellular space.

Passive transfer/transport

– molecules move in the direction of the concentration gradient
– from the medium of the higher concentration to the medium of the lower concentration
– concentration on both sides of the membrane reaching equilibrium
– does not require energy facilitation
1 **Simple diffusion** - the permeation of substances across the lipid double-layer membrane (e.g. O_2, CO_2, N_2, steroid hormones)
2 **Osmosis** - transport of water across the lipid double-layer membrane
– from the medium of the lower osmotic pressure to the medium of the higher osmotic pressure
3 **Facilitated diffusion** - passive permeation of substances through transporters (integral membrane proteins) and ion channels
– transfer of amino acids and some ions
4 **Transfer via aquaporins**
– specialized protein water channels with a diameter of up to 0.2 nm
– capable of transferring selectively only water molecules in a large volume
5 **Specialized gap junctions**
- form hydrophilic channels with a diameter of 1.5 nm
– the channels can be opened and closed depending on the concentration of Ca^{2+}

Active transfer/transport

– molecules are transported against the concentration gradient
– energy-demanding process, energy is delivered by mitochondria in the form of ATP molecules
– based on cell membrane proteins that form:
1 **Ion channels/pumps** - with ATP-ase
2 **Transporters**

Nonpolar and lipophilic molecules permeate passively through biological membranes more readily than polar molecules.

Phagocytosis is used to ingest nutrients, especially in unicellular organisms (protozoa).

Caveolin-coated vesicles is the English term for caveosomes.

There are also vesicles not covered in either caveolin or clathrin. Their origin and significance are not known.
The apical surface of one duodenal enterocyte can hold up to 3000 microvilli.

The enterocyte brush border contains a glycoprotein and glycolipid layer, glycocalyx, that contains enzymes needed for final digestion of certain nutrients (e.g. disaccharidase).

The depth and segmentation of the intracellular secretory canaliculi of the gastric parietal cells vary with cell activity. Non-active cells, which do not produce HCl, do not have to contain these canaliculi.

The process of endocytosis and exocytosis facilitated by the cycling of the membranes. During endocytosis, a portion of the cell membrane is separated from the surface and envelops the received substance, and in exocytosis the membrane envelope reconnects with the cell membrane. Macromolecules rotate in the cytoplasm, including their membrane envelopes, and may merge with lysosomes or peroxisomes.

The process of phagocytosis was discovered by a Ukrainian scientist Ilja Ilyich Mechnikov, the Nobel Prize laureate in Physiology or Medicine in 1908.

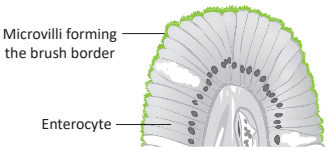
In Greek, fagein – eating (phagocytosis), **pinein** – drink (pinocytosis).

Emperipolesis comes from Greek words em – inside; peri – around; polemai – to roam.

Clinical notes

Hyperplasia of glandular compartments of the stomach due to various stimuli (hyperplasia of gastrin-producing cells, in pancreatic adenoma, etc.) leads to the overproduction of HCl due to the multiplication of parietal cells. The condition is called Zollinger-Ellison syndrome and clinically manifests as numerous ulcerative lesions due to self-digestion of the gastric mucosa.

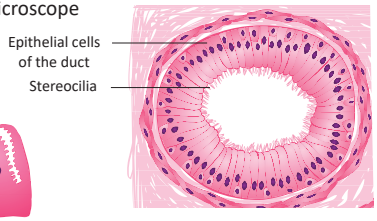
Adaptation and enlargement of the cell surface for substance transfer



Villus of the mucosa in the small intestine

1 **Microvilli** – numerous immotile projections of apical cell surface, reinforced with a mesh of 20–30 actin fibers
– **Brush (microvillous, striated) border** (*limbus microvillosus*) – the complex of microvilli
– size, shape, and number of microvilli depend on cell function
1.1 **Enterocytes** – absorptive cells in the epithelium of the small intestine
1.2 **Colonocytes** – absorptive epithelial cells of the colon
1.3 **Epithelial cells of the proximal tubules of nephron** - absorb about 90% of primary urine
2 **Stereocilia** – long and branched immotile hair-like protrusions, structurally similar to microvilli (but about 3–4 times longer)
2.1 **Epithelial cells of the duct of epididymis** – absorb testicular fluid flowing from the testis together with the sperm
3 **Basal labyrinth** – invaginations of the cell membrane of the basal domain of the cell, numerous mitochondria present in at those folds
– the number of mitochondria between the folds causes basal striation visible under the light microscope
3.1 **Epithelial cells of proximal and distal tubules of nephron**
– transfer ions and water from the processed primary urine to the blood vessels, or selectively excrete certain substances in the opposite direction as needed
3.2 **Intralobular ducts of large salivary glands (called striated ducts)**
– absorption of ions gives rise to hypotonic saliva
4 **Intracellular canaliculi** – numerous, deep and branched invaginations of the cell membrane
4.1 **Parietal cells of proper gastric glands** – the membrane includes ion pumps (H^+-K^+-ATPase) carrying protons into gastric juice (acid pH of 1.5–2)


Gastric parietal cell with intracellular secretory canaliculi

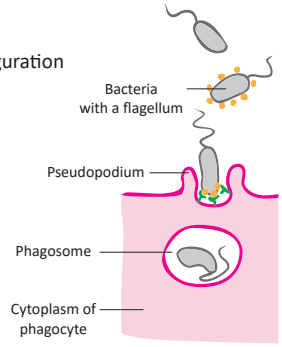


Duct of the epididymis

Endocytosis

– the mechanism of macromolecule and particle intake associated with changing the cell membrane configuration

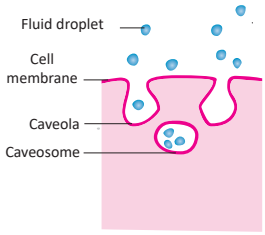
Types of endocytosis



Phagocytosis

1 **Phagocytosis** – intake of solid particles (above 0.5 µm)
– belongs to the powerful mechanisms of nonspecific immunity
1.1 **Pseudopodia** - the cytoplasmic projections of the cell surrounding a solid particle
1.2 **Phagosome** - absorbed particle enclosed in a cell membrane vesicle
2 **Pinocytosis** – fluid intake
2.1 **Cell membrane caveola** - depression on the surface of the cell
2.2 **Pinocytic vesicle** (*vesicula pinocytotica / pinosoma*)
– originates from the caveola separated from the cell envelope
– restructuralization of cytoskeleton is involved in the formation of pseudopodia and cell membrane invaginations, in particular microfilaments placed just below the cell membrane

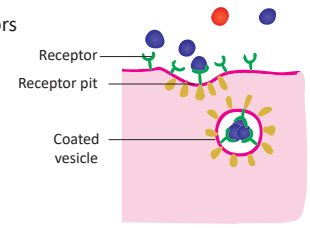
Types of endosomes



Simple pinocytosis

1 **Endosome** – a generic term for a membrane coated vesicle in the cytoplasm, whose content was received via endocytosis
2 **Early endosome** (*endosoma novum*) – coated vesicle just below the cell membrane
3 **Late endosome** (*endosoma tardum*) – coated vesicle found in close proximity to the cell nucleus
– the pH inside the endosomes decreases during maturation
– late endosomes may have heterogeneous contents
3.1 **Multivesicular bodies** (*corpusculum multivesiculare*)
- arise from late endosomes if their membrane is sunk in

Types of pinocytosis



Receptor mediated pinocytosis

1 **Simple, non-specific pinocytosis**
1.1 **Caveolae** – develop at any point in the cell membrane as invaginations, i.e. without specific receptors
– nonhomogeneous fluid content of water and molecules
– the formed caveola is covered by the protein caveolin at its cytoplasmic side
1.2 **Caveosomes** – caveolin-coated vesicles developed from the original caveola
2 **Receptor-mediated pinocytosis**
– receptors located on the outer surface of the cell membrane
– the cell selectively accepts vitamin B12, protein hormones, lipoprotein particles with cholesterol or transferrin
2.1 **Coated pit / foveola** – is coated by clathrins on the cytoplasm side
2.1.1 **Clathrins** – special proteins
2.2 **Coated vesicle** – occurs after the separation of the foveola with specific fluid content
– the vesicle is coated with a clathrin layer at its cytoplasmic side
2.2.1 **Clathrin triskelions** - trimers formed on the vesicle surface from clathrins, shaped like tripods

Phagocytosis as a mechanism of non-specific immunity

– in humans, it is the basic mechanism of non-specific, innate immunity
– in addition in foreign particles recognition (e.g. bacteria, dust particles in lung alveolas), phagocytosis also removes worn, damaged and old cells, e.g. blood cells in the spleen

Cells with phagocytic activity

– all phagocytes contain numerous lysosomes in the cytoplasm

1 **Microphages**
– neutrophilic granulocytes are referred to this way
– cells present in the first line of acute inflammation

Microphage (neutrophilic granulocyte)

2 **Macrophages**
– cells with pronounced phagocytic activity
– developing from monocytes (type of white blood cells), which migrate from blood vessels into the connective tissue (diapedesis)
– collectively referred to as the cells of the mononuclear-phagocyte system

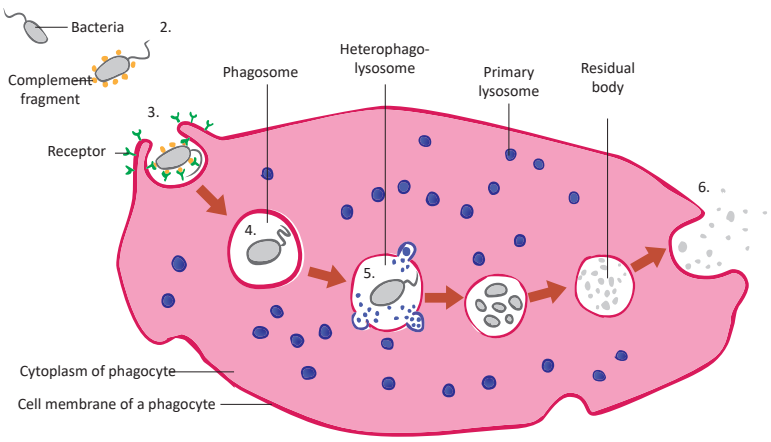
Macrophage

3 **Eosinophilic granulocytes**
– white blood cells with lower phagocytic activity
– phagocyte particles labelled with antibodies (so-called immunocomplexes)

Eosinophilic granulocyte

Phagocytosis process

1. **Chemotaxis** – in an inflammatory process
   – before the phagocytosis itself, phagocytes are attracted to the required site by chemicals called chemotaxins
2. **Opsonization** – labelling and "flavoring" of phagocyted particles by opsonin binding (antibodies, complement components etc.), which significantly facilitate and speed up the subsequent phagocytosis
3. **Mutual recognition and attachment**
   – with receptors on the surface of the membrane of the phagocyte
4. **Swallowing (ingestion)** – surrounding the particle with pseudopodia
   – restructuralization of the cell membrane and the cortical cytoskeleton (especially microfilaments)
   – it forms a temporary, membrane-coated organelle, phagosome
5. **Degradation** – the phagosome merges with the primary lysosome containing enzymes to form a secondary lysosome (heterophagolysosome)
   – the mechanism of decomposition is hydrolysis at a very low pH, oxidative damage to the absorbed particle and other antimicrobial enzymatic effects (e.g. lactoferrin, lysozyme, defensin)
6. **Exocytosis** – residual bodies may be removed from the cell after the completion of digestion



Phagocytosis process

Mononuclear-phagocyte system p. 226.

Skin melanocytes deliver melanin granules to surrounding cells via cytokrine secretion. The produced melanin granules are "injected" into the cytoplasm of the surrounding keratinocytes. Melanin protects the genetic material of the mitotically active cells of the basal and spinosum layers of the epidermis from the mutagenic effect of UV radiation.

Signal molecules secreted by exocytosis in the surroundings may act at various distances from the point where they are released. They can affect surrounding cells within the reach of diffusion or local microcirculation (paracrine secretion) or at greater distances, where they are transmitted via blood or lymphatic circulation (endocrine secretion). In autocrine secretion, the target cell is identical to the cell producing the signal molecules, e.g. a growth factor is produced in tumor cells, which have the ability to stimulate themselves to grow and divide.

Clinical notes

Not all microorganisms are destroyed after phagocytosis. The cause of tuberculosis, *Mycobacterium tuberculosis*, inhibits the fusion of phagosome with the primary lysosome and survives within the macrophages. The cause of fever Q, *Coxiella burnetti*, can survive within the phagosome, resisting low pH and lysozyme enzyme activity. *Lysteria monocytogenes*, a cause of meningitis, can use the enzyme hemolysin to decompose the membrane of the phagosome, survive and multiply within the cytoplasm of the cell it was phagocyted by.

Trogocytosis has also been confirmed even among hemato-oncological malignant disease cells, where it may correlate to cytostatic resistance.

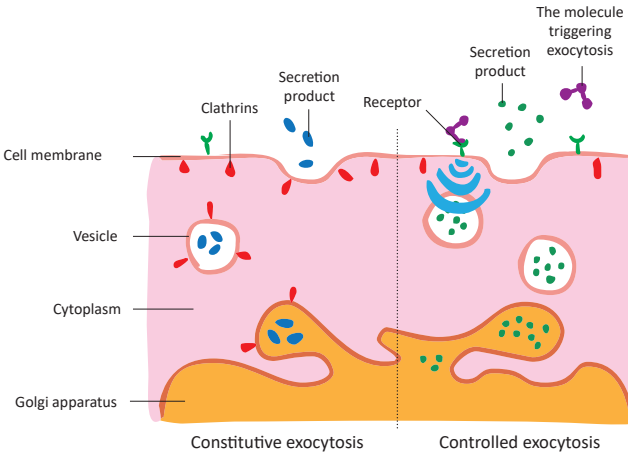
Emperipolesis occurs in some malignancies of hematopoietic and lymphatic system.

Exocytosis

– transfer of substances from the cell to the extracellular space
– to release enzymes, hormones, neurotransmitters, intercellular matter components, but also unnecessary content (e.g. residual bodies)

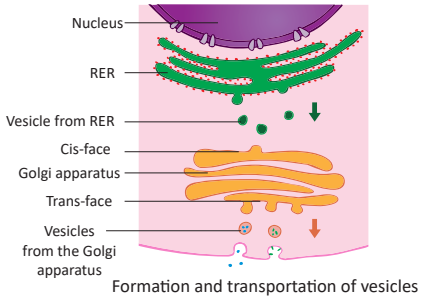
1 **Controlled / regulated exocytosis**
– controlled by the change in Ca^{2+} level
– secretion of matter into the outer environment stimulus captured by a receptor

2 **Constitutive exocytosis**
– not controlled by the change in Ca^{2+} level
– smooth movement of vesicles, where the vesicle membrane is simultaneously used to supplement the cell membrane



Steps of secretion

1. **Synthesis of the substance in the rough endoplasmic reticulum**
2. **Substance processing in the Golgi complex**
3. **Transfer of secretory vesicles and granules**
   – transmitted via microtubules and microfilaments using protein motors (kinesin, dynein, myosin) towards the cell membrane
4. **Merging of the vesicle membrane with cell membrane**
   – SNARE proteins involved



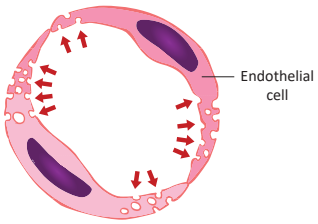
Formation and transportation of vesicles

Cells of glandular epithelium may use exocytosis to release

1 **Mucous (protein-polysaccharide) vesicles**
2 **Serous vesicles and granules**
3 **Seromucous vesicles**
4 **Endocrine vesicles containing hormones**

Transcytosis

– macromolecules received via endocytosis pass in the form of vesicles through the cytoplasm
– their content does not change during the transfer and is released on the opposite side of the cell via exocytosis



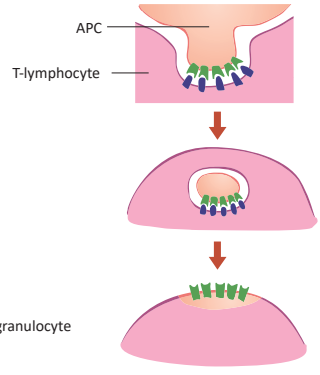
Transcytosis

Examples of cells

1 **Endothelial cells of the continuous capillaries (without pores and apertures)**
– transfer proteins from the blood to the surrounding tissue
2 **Mesothelial cells** - lining the pericardial, pleural and peritoneal cavity
3 **M-cells** – part of the epithelium of the small and large intestine
– transport foreign antigens from intestinal content to the cells of the immunity system (macrophages and lymphocytes) located in the subepithelial connective tissue (lamina propria)

Trogocytosis

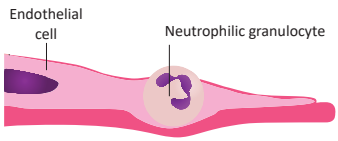
– transport of cell membrane proteins or whole sections of the cell membrane
– the cell actively "tears" a portion of the cell membrane of another cell
– used in communication between immune cells, e.g. lymphocytes obtain surface molecules and a part of the membrane from the antigen-presenting cell, thus altering the function of the lymphocytes
– **Immunological synapse** - molecular reorganization of membranes, which occurs in trogocytosis between lymphocytes and antigen-presenting cells (APCs)



Trogocytosis

Emperipolesis

– the presence of a whole and living cells within the cytoplasm of another cell (thus different from the phagocytosis)
– occurs in leukocyte transfer through the endothelial cells of capillaries

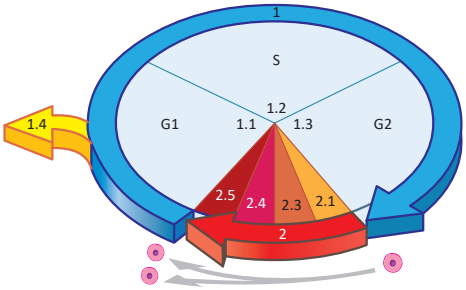


Emperipolesis

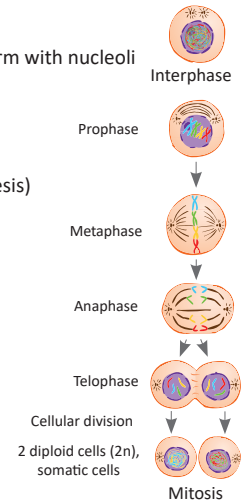
Reproduction belongs to the **basic signs of life of the cell**. It is based on **the division** of already existing cells. **The cell cycle** consists of two stages: **interphase and mitosis**. With the exception of some highly specialized cells (e.g. mature nerve cells and cardiac muscle cells), the cells retain their ability to **divide to form two daughter cells** (**mitosis**). **Both them** nucleus (karyokinesis) *and the* whole cell (cytokinesis) *divide. These* processes are sequential with a partial overlap. Meiosis **occurs only** during gametes formation**. In meiosis, the daughter cells have a** haploid number of chromosomes**, i.e. half of the genome.**

Cell cycle

- 1 **Interphase** – a period between two cell divisions, consists of three steps
  - 1.1 **G1 phase** – cell growth, intensive protein and RNA production
    - – the number of organelles multiplies
  - 1.2 **S phase (synthetic)** – duplication of nuclear DNA, histones are formed in the cytoplasm
  - 1.3 **G2 phase** – DNA testing and correction of possible errors
    - – preparation for mitosis, duplication of centrosome
    - – the production of proteins necessary for cell division (e.g. mitotic spindle)
  - 1.4 **G0 phase** – in terminally differentiated cells a state outside of the replicative cell cycle, which cease to divide and perform their specific functions
- 2 **Mitosis (M phase)** – division of the cell
  - 2.1 **Prophase** – chromosomes resemble fibrous, spiral-like structrue ("spirem")
    - – chromatin condensation, chromosomes become microscopically visible
    - – nucleolus disintegration; centrosomes move toward opposite poles of the cell
    - – microtubules begin to form the mitotic spindle
  - 2.2 **Prometaphase** – disintegration of the nucleus and fragmentation of the fibrous lamina of the nucleus
    - – some microtubules of the mitotic spindle are anchored to the area of chromosomal centromeres, referred to as kinetochores
  - 2.3 **Metaphase** – chromosomes are arranged in the equatorial plane
    - – chromosomes have the shape of curved sticks and their centromeres are directed against each other, resembling a star ("monaster") microscopic appearance
    - – the mitotic spindle formed by the microtubules occupies over 10% of the volume of the cytoplasm
  - 2.4 **Anaphase** – duplicated chromosomes separate from each other and move to opposite poles of the cell, each daughter chromosome now consists of one chromatid with a centromere
    - – this formation resembles two microscopically appearing stars close to each other ("diaster")
    - – chromosome motion is caused by prolongation and shortening of the mitotic spindle microtubules
    - – towards the end of the anaphase, the cell begins to strangle in the middle and cytokinesis starts
  - 2.5 **Telophase** – daughter chromosomes come close to the centrosomes at the opposite poles of the cell
    - – nucleus envelopes are renewed and a two new nuclei form with nucleoli
    - – chromosomes prolong and decondensate, and thus are no longer visible microscopically
    - – the microscope is transiently able to discern two fibrous, spiral-like structures ("dispirem")
    - – the division into two daughter cells is complete (cytokinesis)



Cell cycle



Mitosis

Regulatory genes of the cell cycle: Proteins encoded by tumor suppressor genes stop the cell cycle, facilitate cell differentiation and, in case of damage, trigger apoptosis. **Proteins-encoded by protooncogenes** support the continuation of cell cycle, suppress cell differentiation, suppress apoptosis.

The *TP53* gene is referred to as the "guardian of the genome" because the p53 protein can stop cell division until damaged DNA is repaired. If DNA damage is too extensive and irreparable, it will induce apoptosis.

The prometaphase was previously considered the final part of the prophase and not a separate phase of mitosis.

The entry into the G0 phase may be reversible. For example, lymphocytes can circulate between blood and tissues in the G0 phase for years. If they are stimulated by the appropriate antigen, they return to the cell cycle, divide and differentiate into powerful immune or memory cells.

Each phase of the cell cycle has its own checkpoint, which checks if all the steps necessary for the given phase were correct. If no damage is detected, the cycle advances to the next stage. The cell attempts to repair the detected errors and stop the cell cycle or begin apoptosis.

Relationship between karyokinesis and cytokinesis: Karyokinesis (the division of the nucleus) begins in the prophase and ends in the telophase. **Cytokinesis** (the division of the cell) begins at the end of the anaphase and ends in the telophase. A contractile ring of actin microfilaments and myosin forms under the cell membrane in the equatorial plane during cytokinesis. The contractile ring protrudes into the cytoplasm.

Clinical notes

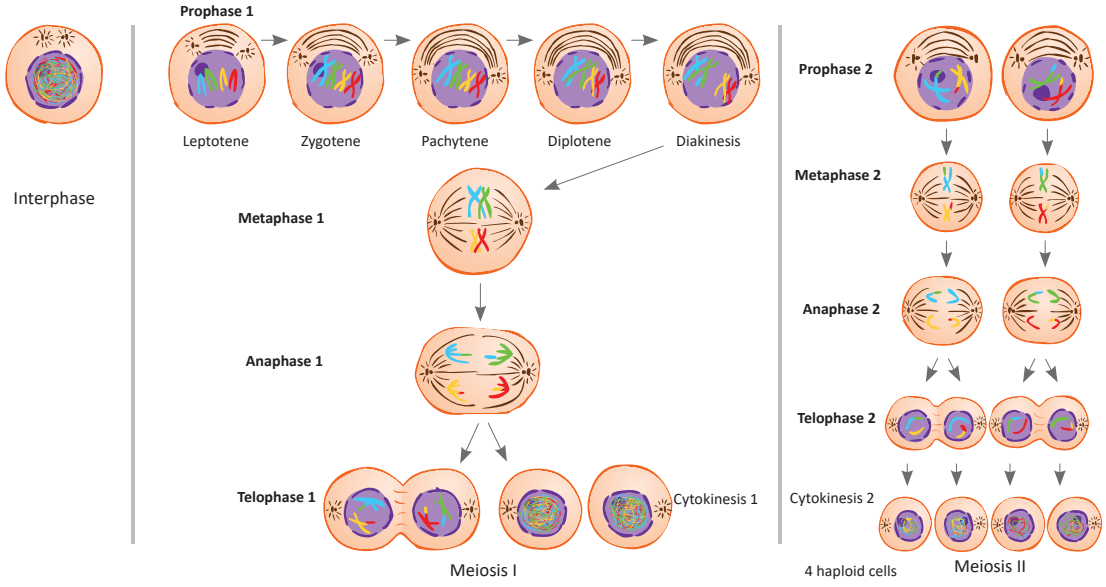
The dysfunction of cell cycle regulatory genes (e.g. mutations or viral infection) can result in cell cycle dysregulation and malignant transformation (malignant transformation) of the cell.

Tumor suppressor genes encode proteins that regulate cell division. Any changes to their structure or the inactivation of the encoded protein may result in malignant cell transformation. The most investigated genes are TP53 and RB1.

Meiosis

– specialized type of cell division which reduces the number of chromosomes by half
  – the daughter cells end up with a haploid number of chromosomes (1N = 23) from the original diploid number (2N = 46)
– occurs in the maturation of male and female sex cells (gametes), i.e. during spermiogenesis and oogenesis
- fertilization, when a male and female sex cells merge, does not give rise to a zygote with a double number
  the number of chromosomal sets (4N), which is an emergence of a two normal (diploid) chromosome count (2N)
– consists of two consecutive divisions, divided by an interphase (without DNA duplication)

1 **Meiosis I.** – first, reductional division
  – the number of chromosomes decreases by half; two haploid daughter cells are created from an original parental diploid cell
  – there is also an exchange of genetic segments as the paired chromosomes intersect (crossing over)
  1.1 **Prophase I.** – consists of several stages
    1.1.1 **Leptotene** – chromosome condensation begins
    1.1.2 **Zygotene** – homologous chromosomes (one originating from the father and the other from the mother) are arranged in pairs and are tightly aligned in proximation (2 conjugated chromosomes are referred to as bivalents)
      – **Bivalents** are shortened and amplified, they are bound by synaptonemic complexes; there are 23 bivalents in humans
    1.1.3 **Pachytene** – there are slits between the chromatids of each homologous chromosome and each bivalent is visibly made of 4 chromatids (tetrades = 4 chromatids in 2 conjugated chromosomes)
      – **Crossing over** – parts of homologous chromosomes are recombined (mutual exchange of a part of the genetic material between non-sister chromatids of homologous chromosomes)
    1.1.4 **Diplotene** – breakdown of synaptonemic complexes, homologous chromosomes remain linked in the areas, where genetic material was exchanged (chiasms, crossing).
      – **Chiasms** are a visible sign of crossing-over and confirm intense recombination of the paternal and maternal genetic material in the creation of gametes (thus maintaining the genetic variability of the sex cells)
    1.1.5 **Diakinesis** – transition to metaphase I, strong chromatid condensation takes place and the nucleus envelope disintegrates
      – sister chromatids are linked in centromeres of both original homologous chromosomes
  1.2 **Metaphase I.** – chromosome condensation peaking, chromosomes are arranged in the equatorial plane, centromeres oriented toward the opposite poles of the cell
  1.3 **Anaphase I.** – chromosome chiasmata separate, double homologous chromosomes move in opposite directions to opposite poles of the cell (no chromatid isolation occurs; complete double chromosomes move to the opposite poles of the cells, which is the basic difference over the mitotic anaphase)
  1.4 **Telophase I** – a group of chromosomes get to the opposite poles of the cell
    – after the end of telophase the cell enters a very short interphase; meiosis I forms 23 double chromosomes
2 **Meiosis II.** – second, equational division
  – sister chromatids are divided into two daughter cells
  – is similar to normal mitotic division, consists of prophase II, prometaphase, metaphase II, anaphase II and telophase II.
  – in anaphase II, the chromosomes in the centromere site are divided into two chromatids and move to the opposite poles of the cell
  – at the end of the meiosis, daughter cells contain a quarter of the nuclear DNA content and half the number of chromosomes of the original cells



Starting from **early embryonic development,** uninterrupted **cell proliferation takes place in the organism.** Some tissues and organs have a **high mitotic activity** throughout the life – e.g. epithelia. In addition to the proliferation, the opposing process occurs – the **apoptosis**, **programmed cell death**. It is **genetically encoded**, **requires a supply of energy in the form of an ATP** and the apoptosis of one cell **does not interfere with the surrounding cells** and **does not induce an inflammatory response**. In contrast, **cell necrosis** affects most surrounding cells and is accompanied by an inflammatory reaction.

Apoptosis

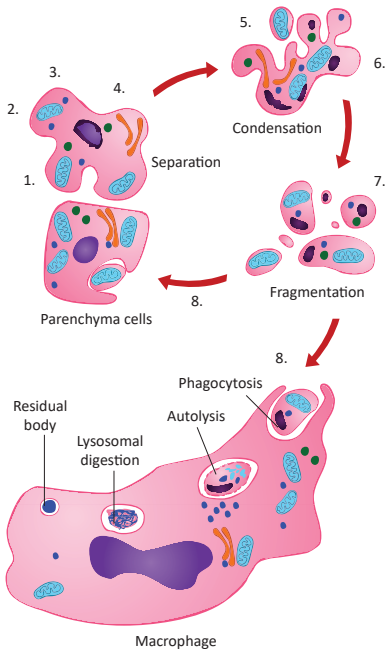
– referres to programmed, natural or physiological cell death, silent cell death or organized collapse of a cell

Main proteins important for apoptosis

1 **Caspases** – a family of proteolytic enzymes cleaving proteins at the site of cysteine and aspartic acid
– initially, present in the cell cytoplasm in the form of an inactive pro-caspases, which are activated by autocatalytic cleavage or other proteases
2 **Initiator caspases** – important at the start of the activation cascade leading to apoptosis (e.g. caspases 2, 8, 9 and 10)
3 **Executioner caspases** – irreversibly activate the mechanism of apoptosis (e.g. caspases 3, 6 and 7), the mechanism of their effect is:
– inactivation of enzymes responsible for repairing damaged DNA
– activation of endonuclease that cleaves nuclear DNA into shorter fragments
– organelle membrane damage, cell protein hydrolysis
– disruption of cytoskeleton components
4 **Bcl2** – the major antiapoptotic factor, a proto-oncogene product
5 **Apaf-1** – mediates apoptosis after mitochondrial damage
6 **Bax** – cell death protein
7 **Protein p53** – a tumor suppressor gene product
– plays a key role in regulating cell counts, suppressing abnormal cell proliferation and in the detection of severe DNA defects stops the cell cycle and can trigger apoptosis

Cell changes during apoptosis

1. **The cell volume decreases** and it acquires a rounder shape due to the collapse of the cytoskeleton
2. **Cytoplasm appears more dense**. organelles fill less space
3. **Degraded chromatin aggregates** under the nuclear envelope, the so-called nuclear pycnosis
4. **Synthetic processes in the cell gradually stop**
5. **The nuclear membrane tears**, nuclear DNA is split (fragmented), the nucleus disintegrates to several discontinuous portions, the so-called nucleus karyorrhexis
6. **Irregular protrusions (blebs) develop on the surface of the cell membrane** ("blebbing")
7. **Apoptotic bodies are formed** (*corpuscula apoptotica*), which are the residues of the cell membrane; therefore, their content does not spill to the surrounding environment
8. **Apoptotic bodies are absorbed by surrounding specialized phagocytes** and adjacent cells and are spread in heterophagolysosomes
9. **Apoptosis does not lead to an inflammatory reaction around the cell**



Cell apoptosis followed by phagocytosis by macrophages

Cytology

In ancient times, Hippocrates and Galen used the term apoptosis for hair loss and bone thinning. The original Greek term apoptosis meant the falling-off leaves from trees.

In adults, an average of 50–70 billion cells die by apoptosis each day.

In 2002, Sydney Brenner, H. Robert Horvitz and John E. Sulston were awarded a Nobel Prize for Medicine or Physiology for their discoveries concerning genetic regulation of organ development and programmed cell death.

Caspases are a family of proteolytic enzymes cleaving proteins at the site of cysteine and aspartic acid. Hence their English name caspase = cysteine-aspartic protease.

English protein names:
Bcl2: B-cell lymphoma 2 protein
Apaf-1: apoptosis protease activating factor 1
Bax: Bcl2-associated X protein

The germinal cell layer in various organs was previously referred to as a cambium layer. Nowdays this term is used only in botany.

Clinical notes

Syndactyly is a congenital developmental disorder characterized by a fusion of finger buds or a failure of their separation. Some types are caused by insufficient apoptosis of cells which forms tissue between the developing fingers and toes during embryonic development.

Polydactyly is a congenital anomaly, which generates supernumerary fingers or toes. Some types are associated with excessive apoptosis between developing fingers and toes.

Metastatic tumor cells are resistant to anoikis. This mechanism is still unknown.

Stem cells have many properties similar to tumor cells, e.g. high proliferative activity. Therefore, stem cell research must consider the safety of their use in clinical practice.

First experimentation of stem cell administration into damaged organs and tissues was disappointing – stem cells did not persist at the site of damage for a long time or differentiated in undesired pattern. However, even short-term effects of stem cells in the affected tissue have been found to stimulate self-repairing mechanisms, probably through parakrine secretion of growth factors by the stem cells.

Apoptosis

Mechanisms of apoptosis induction

1 **External activation pathway** - via the "death receptors" on the cell membrane
(the best known one is Fas receptor) and the activation of caspase 8 and 10
– can be triggered by cells of the immune system (activated T lymphocytes or NK cells)
2 **Internal activation pathway** - mitochondria and their intermembrane space release cytochrome c
(signal to initiate programmed cell death) and caspase 9 activates
– another option is the stress path leading through the endoplasmic reticulum
to an activation of the caspase 12 or genome damage leading through TP53 gene products

Significance of apoptosis

1 **Maintaining the body homeostasis** – regulates the balance between dividing cells and dying cells
2 **Shortening of telomeres at the terminal parts of chromosomes** – at the end of cell "life-time"
3 **Cell selection** – e.g. gametes and immunologically active cells
4 **Protection of the organism from high-risk cells** – e.g. malignant or virus-infected cells
5 **Protection of the organism from foreign cells** – e.g. parasites and transplants
6 **Physiological destruction of uterine mucosa (endometrium)** – during embryo implantation, i.e. early embryonic development
7 **Selection of bad and "unwanted" cells and organ remodeling** – during embryonic and fetal development

Examples of apoptosis during prenatal development

1 **Separation of developing fingers and toes** by the abolishing of the in between connective tissue (the future interdigital spaces)
2 **The disappearance of Müller ducts** in male embryos
3 **The disappearance of Wolffian ducts** in female embryos
4 **Apoptosis of ectodermal cells** in the fusion of branchial arches with other bases
during the development of the face, jaw, lips and hard palate
5 **Correcting mechanism in brain development**
– eliminates neurons that have not established functional connection with other neurons in time

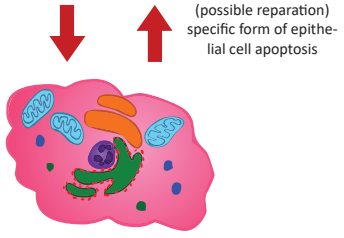
Examples of apoptosis in the postnatal period

1 **Elimination of over 97% of future T lymphocytes** which do not complete their maturation in the thymus
– These are lymphocytes that do not recognize self and non-self antigens and could
trigger a reaction against the antigens of the body itself as well as against foreign antigens
2 **The involution of the follicles** - from several million primordial ovarian follicles, only about 400
mature eventually; the others are subjected to apoptotic involution called follicular atresia
3 **Destruction of keratincytes** in the surface layers of the epidermis
4 **Destruction of glandular cells** of the mammary gland after breastfeeding ceasing

Anoikis

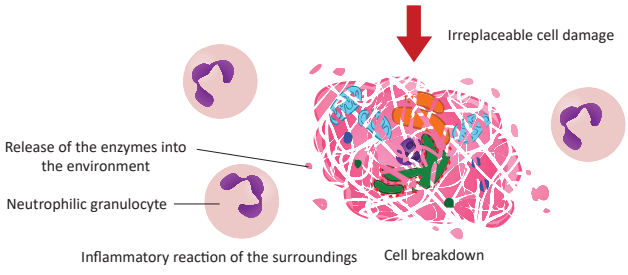
Reversible cell damage

– induced by the separation of the cells from their environment, that occurs in
anchorage-dependent cells when they detach from the surrounding extracellular matrix



Necrosis

– the result of irreversible damage to the cell or group of cells
(after ischemia, physical or chemical damage)
– a pathological process known as sudden (acute) cell death
– cells first increase their volume due to oncotic pressure
swelling (oncosis), the cytoplasm is more eosinophilic
– breakdown of cell membrane and organelle membranes leads
to the release of enzymes and other substances into the cell's surroundings,
causing an inflammatory reaction of the environment
– the first inflammatory cells at the site of acute inflammation
are neutrophilic granulocytes



Reversible and irreversible damage to cells
leading to repair processes or necrosis

Human cells can be divided into three groups. In one group, **the cells permanently live in the inactive (G0) phase of the cell cycle and**; they are not replaced in the event of destruction. Examples are cardiac muscle cells or the vast majority of neurons. The second group contains **cells with very long G1 phases**, which **form equally differentiated populations** and which are able to divide even in the stage of full differentiation. Examples include endothelial cells of blood vessels or neuroglial cells of the nervous tissue. The third group contains **cells, which are supplemented from little-differentiated reserve cells named** as stem cells. The **stem cells do not have a limited number of cell divisions** and this division results in **asymmetrical pair of daughter cells** that are used **both for stem cell restoration and for differentiation**. They can be the basis for some medical fields – **regenerative medicine** and **cell-based therapy**.

Stem cell definition

1 **They remain at a low degree of differentiation**, but have the ability to differentiate into other cell types (plasticity)
2 **They are the source of new cell generations** – they enable the body to maintain and repair damaged and worn tissue and organs
3 **They have a lasting ability to self-renew** (self-replication) – their number does not change significantly
4 **The length of their cell cycle varies** – different populations divide often differently
5 **Their mitosis creates two different daughter cells** (asymmetric mitosis) – one retains the stem cell function, the other one differentiates

Microscopic signs

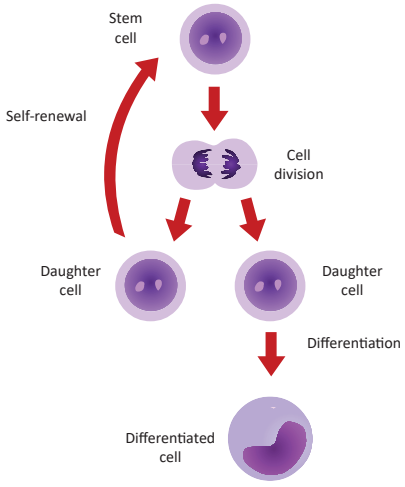
1 **A pale nucleus predominantly euchromatin**, **a prominent large nucleolus** (or more nuclei)
2 **Electron microscope can reveal folds in the nucleus** increasing contact surface between the cytoplasm and the nucleoplasm
3 **Free ribosomes and polyribosomes** predominate in the cytoplasm - because they form proteins especially for their own use
4 **Other organelles are scarcely developed**

Differentiation of stem cells based on their plasticity

1 **Omnipotent/totipotent** – they can form all the cells of the organism, both cells of the whole embryo and extraembryonal structures (umbilical cord, yolk sac, amniotic sac, fetal part of the placenta, allantois)
– truly omnipotent cells are a fertilized egg (zygote) and morula cells up to the stage-8 blastomere
2 **Pluripotent** – they originate from omnipotent cells, they can differentiate in almost all cell lines
– e.g. layers of the embryonal trilaminar germ disc, the ectoderm, mesoderm and endoderm
3 **Multipotent** – progenitor cells capable of differentiating into multiple cell lines with specific common features (e.g. hematopoietic stem cells or mesenchymal stem cells)
– the terms pluripotent vs. multipotent, similar to progenitor and precursor cells, are not defined exactly and are interchanged in some sources
4 **Oligopotent** – have the potential to differentiate into several cellular lines; precursor cells of the lymphoid or myeloid line during hematopoiesis or undifferentiated small intestinal epithelial cells lying on the bottom of the crypts of Lieberkühn (capable of differentiation into absorptive enterocytes, mucus-forming goblet cells, Paneth cells or endocrine cells)
5 **Unipotent** – able to differentiate into another type, e.g. satellite cells allowing the regeneration of skeletal muscle fibers

Types of stem cells

1 **Embryonic** – obtained from the body of the embryo in the morula stage or later from the blastocyst (approximately day 5 after fertilization)
– **Advantage:** able to differentiate into all types of human cells
– **Limitations:** moral, ethical and legislative aspects of their acquisition (possible damage or death of the embryo in the pre-implantation stage), only used in animal experiments
2 **Somatic** – obtained from different tissues of adult individuals
– **Advantages:** available in larger quantities (e.g. during liposuction of the adipose tissue, from bone marrow), moral, ethical and religious reasons no longer limit their collection and use
– **Disadvantage:** limited ability to differentiate into various cell lines
3 **Induced stem cells** – obtained by reprogramming (causing by overexpression of some genes and growth factor production) of normal somatic cells to pluripotent ones
– **Advantages:** may be collected and used in the same patient, there is no risk of rejection of the administered cells, no moral, no ethical and religious reasons to limit their collection and use
– **Risks:** insufficiently explored area, yet only at the stage of laboratory experiments
– the number of stem cells obtained using this method is relatively low, the risk of their potential malignant transformation is not completely accounted for



Differentiation process in the self-renewal of stem cells

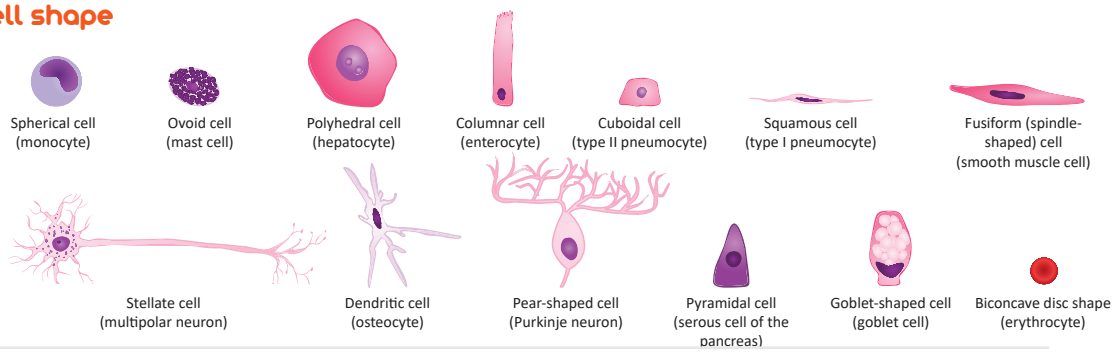
Differences between heterochromatin and euchromatin	
Heterochromatin	**Euchromatin**
Transcriptionally inactive	Transcriptionally active
Highly condensed	Poorly condensed
Most interphase cells have only 10% of chromatin in the form of heterochromatin	Most interphase cells have up to 90% of chromatin in the form of euchromatin
DNA is replicated only in the late part of the S-phase	DNA is replicated at the beginning of the S-phase

Differences between spermiogenesis and oogenesis	
Spermiogenesis	**Oogenesis**
It begins in puberty, continues for the rest of the life; one wave takes about 2 months	It begins prenatally, but stops in the prophase of meiosis I until the puberty or later reproduction age of a woman (up to decades), continues only shortly before ovulation; meiosis II completes in case of fertilization
4 full and equivalent gametes are created	There will be one full oocyte, and two to three incomplete polar bodies (*polocytes*)
Spermatogonia can also undergo mitosis postnatally	Each woman is born with a given number of oogonia, which are stopped in the prophase I.
Continues up to high age in the man, to death or the disappearance of sex hormones effect	Continues until climacterium, which starts on average at the age of 51

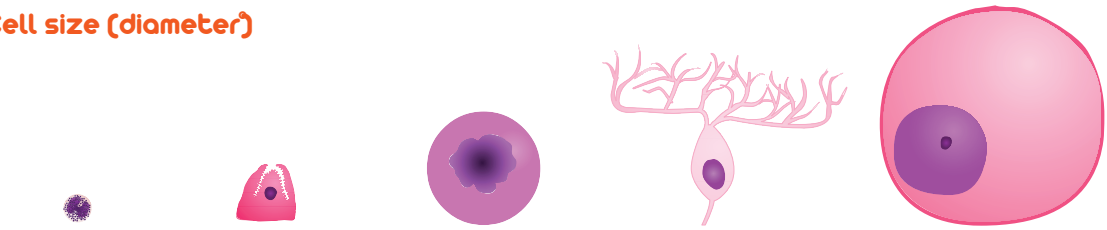
Differences between apoptosis and necrosis		
Specific characteristics of the process	**Apoptosis**	**Necrosis**
Cell membrane	Integrity not disturbed, formation of membrane protrusions (blebbing)	Integrity disturbed, the content of the cytoplasm is released into the intercellular space
Cell size	Decreased, therefore free space around the cell is microscopically visible	Increased
Chromatin	Condensation, marginalization and chromatin fragmentation	First preserved, later fragmented
Cell organelles	Preserved until later stage	Edematous, enlarged
Energy needs	Active process dependent on energy	Passive process, lack or total exhaustion of energy
Gene activity	Increased	No observed changes
Restriction of DNA	Specific	Random
Ion pump activity	Preserved	Lost
Distribution	Affects individual cells	Affects a single cell or bigger tissue areas
Induction	Slow (hours)	Quick (seconds)
Further course	Formation of small apoptotic bodies	Complete disintegration of the cells and their membranes
Inflammatory reaction of the surroundings	Missing	Present

Microscopy and description of individual cells focus on various properties such as **cell shape and size, cell membrane specialization, relation to the surroundings of the cell** (context). We also notice the **volume of nucleus and cytoplasm, stainability, structure and granularity of the cytoplasm**. **We describe the number, shape, chromatin density, location of the nucleus and the presence of nucleoli in the nucleus**.
In schematic pictures, the cells are not displayed accurately in relative proportions.

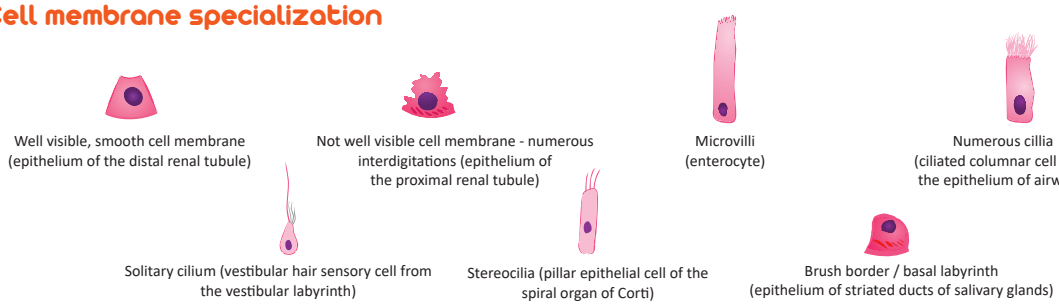
1 Cell shape



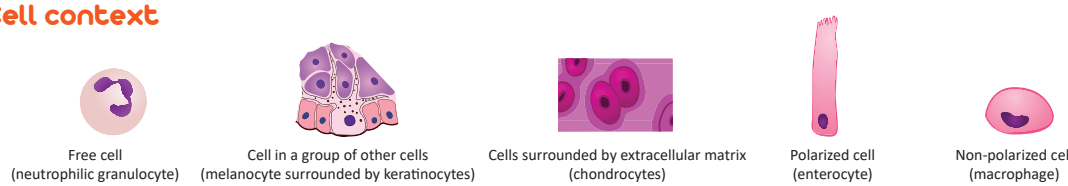
2 Cell size (diameter)



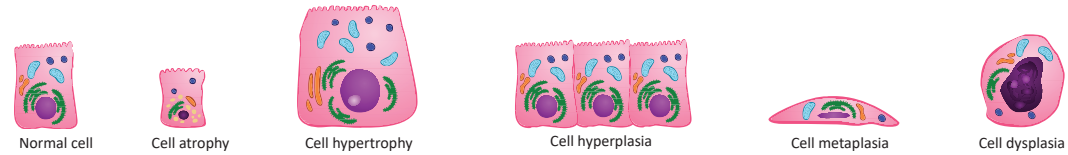
3 Cell membrane specialization



4 Cell context



5 Changes in size, shape, function, and cell number



6 Nuclear – cytoplasmic ratio

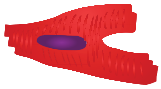

Nuclear – cytoplasmic ratio of 4:1 (precursor cell - proerythroblast)


Nuclear – cytoplasmic ratio of 4:1 (lymphocyte)


Nuclear – cytoplasmic ratio of 1:2 (hepatocyte)


Nuclear – cytoplasmic ratio of 1:1 (osteoblast)

7 Staining of the cytoplasm and its intensity


Eosinophilic staining – high intensity (cardiac muscle cell)


Eosinophilic staining – medium intensity (enterocyte)


Eosinophilic staining – low intensity (gastric surface mucous cell)


Basophilic staining – high intensity (plasma cell)


Basophilic staining – medium intensity (granular cell in the follicle in the ovarian cortex)


Basophilic staining – low intensity (enteroendocrine cell)

8 Cytoplasm structure


Homogeneous cytoplasm (smooth muscle cell)


Granular cytoplasm (with granules) (eosinophilic granulocyte)


Vacuolized cytoplasm (lipoblast)


Striated cytoplasm (epithelium of striated ducts of salivary glands)


Cytoplasmic translucency ("halo") (plasma cell)

9 Localization and size of visible non-homogeneities / nucleus in the cytoplasm


Diffuse localization (granules of a basophilic granulocyte)


Perinuclear localization (lipofuscin granules in neuron)


Apical localization (granules of the gastric chief cell)


Basal localization (nucleus of a goblet cell)


Peripheral localization (univacuolar adipocyte with a peripherally compressed nucleus)


Eccentric localization (nucleus of a plasma cell)

10 Nucleus shape

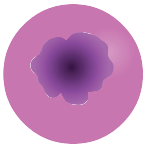

Flat nucleus (type I pneumocyte)


Fusiform nucleus (fibrocyte)


Bacilliform/elongated nucleus (smooth muscle cell)


Spherical nucleus (lymphocyte)


Spherical nucleus with an indentation (centrocyte)


Irregular nucleus (megakaryocyte)


Ovoid nucleus (ciliated cell)

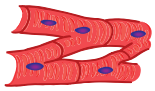

Kidney-shaped nucleus (monocyte)


Curved but not lobular (band) nucleus (young neutrophilic granulocyte)


Segmented nucleus (neutrophilic granulocyte)

11 Number of nuclei


Mononucleate cell (fibroblast)


Binucleate cell (cardiac muscle cell) – above


Multinucleate cell (osteoclast)


Multinucleate fiber (skeletal muscle fiber)


Anucleate cell – without nucleus (erythrocyte)

12 Chromatin density / staining of nucleus


Optically clear nucleus (bright type A spermatogonium)


Vesicular nucleus (neuron)


Nucleus of medium density (chondrocyte)


Granular nucleus (urothelial basal cell)

"Clock-face" nucleus (plasma cell)

Dense nucleus (cardiac muscle cell)

Pyknotic nucleus (sperm cell)

13 Peculiarities of nucleus

Pyknosis

Karyorrhexis

Karyolysis

Apoptosis of the nucleus

14 Mitotic figures of nucleus

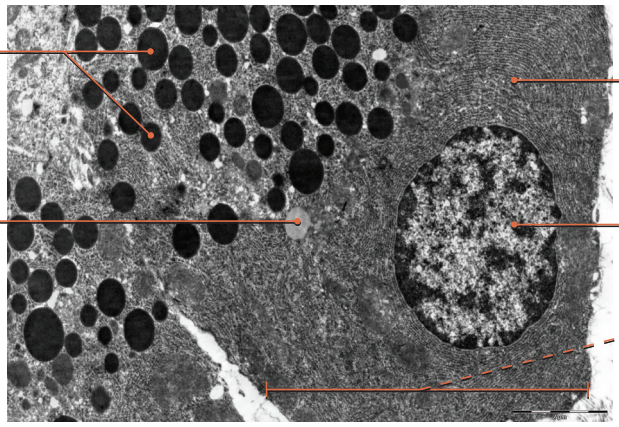
Prophase (spirem)

Metaphase (monaster)

Anaphase (diaster)

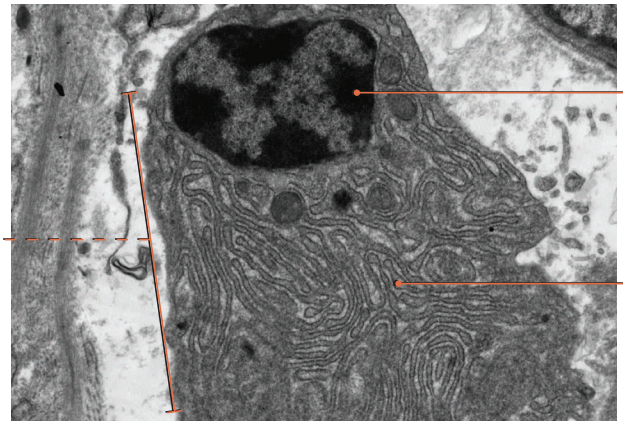
Telophase (disperem)

Serous cell of the pancreas



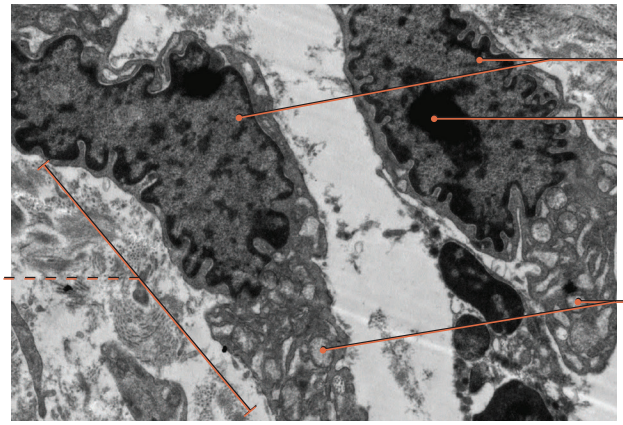
Electron micrograph, Original magnification: 7,100×

Plasma cell from lose connective tissue



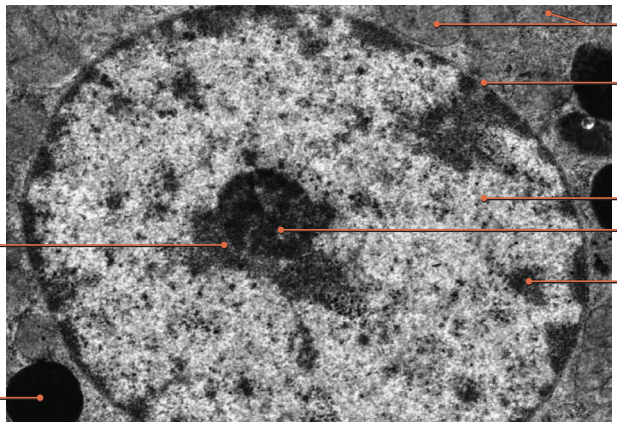
Electron micrograph, Original magnification: 8,900×

Fibroblasts from loose connective tissue



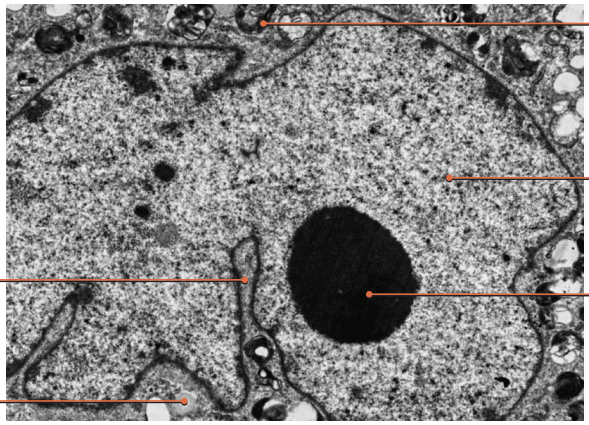
Electron micrograph, Original magnification: 7,100×

Cell nucleus of an epithelial cell the proximal tubule of kidney



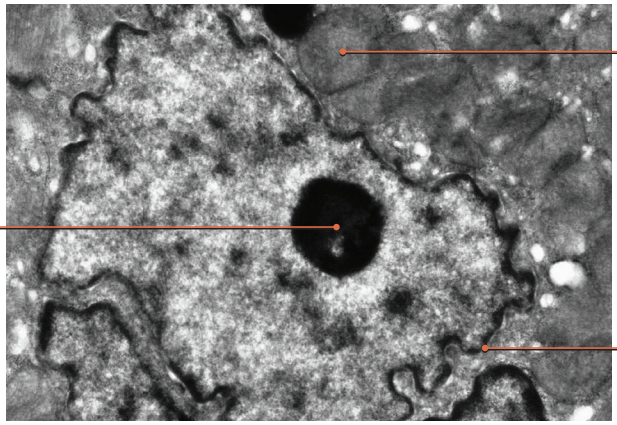
Electron micrograph, Original magnification: 11,000×

Nucleus of preadipocyte from a white adipose tissue



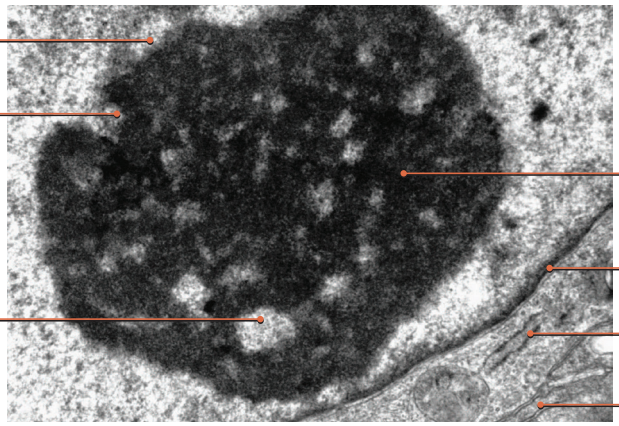
Electron micrograph, cell from *in vitro* cultivation, original magnification: 7,100×

Nucleus of a cardiac muscle cell



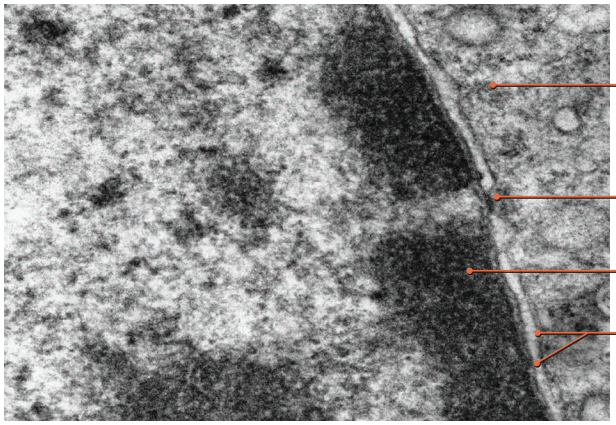
Electron micrograph, Original magnification: 14,000×

Nucleolus of preadipocyte from white adipose tissue



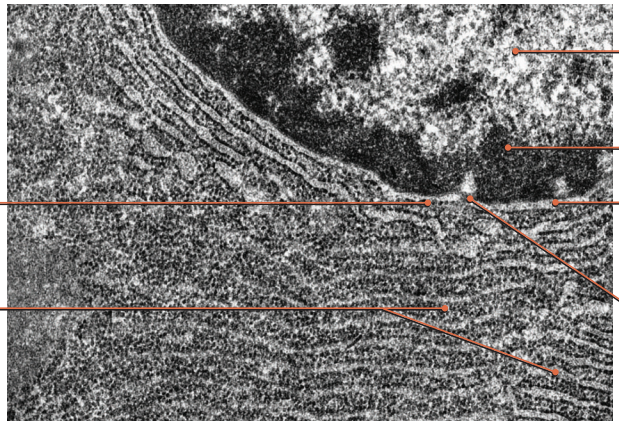
Electron micrograph, Original magnification: 22,000×

Cell nucleus of an epithelium cells of proximal tubule from kidney



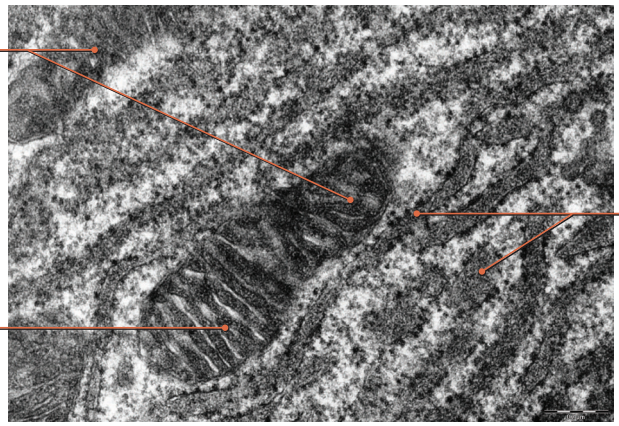
Electron micrograph, Original magnification: 56,000×

Part of the serous cell of the pancreas



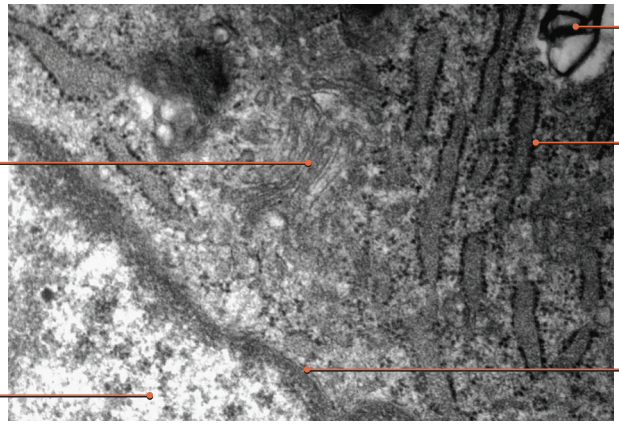
Electron micrograph, Original magnification: 28,000×

Cytoplasm of a plasma cell



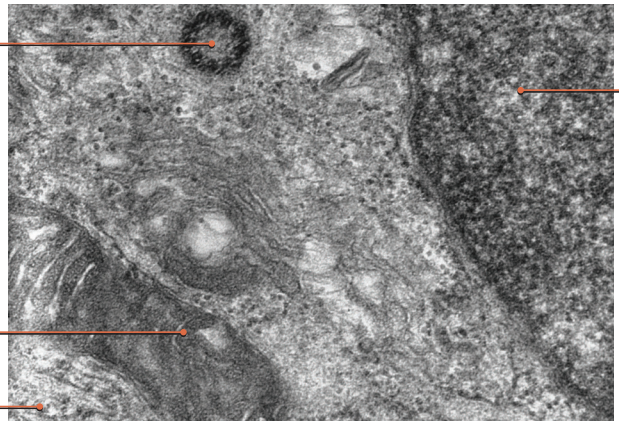
Electron micrograph, Original magnification: 44,000×

Detail of the cytoplasm close to the fibroblast nucleus



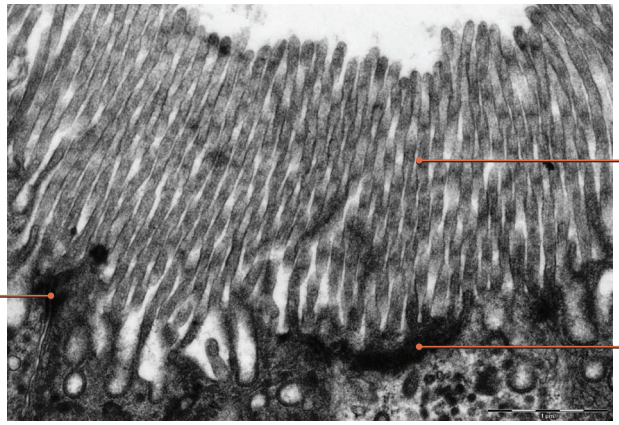
Electron micrograph, Original magnification: 36,000×

Centriole in fibroblast cytoplasm



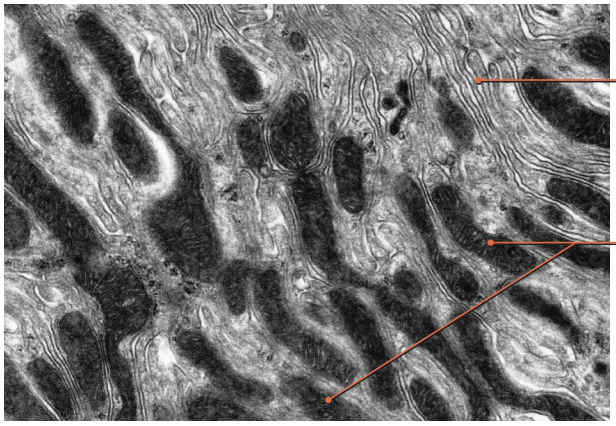
Electron micrograph, Original magnification: 44,000×

Microvilli of the epithelial cell of proximal tubule from kidney



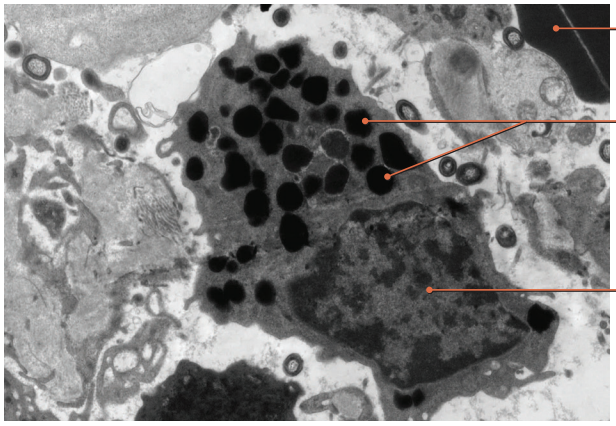
Electron micrograph, Original magnification: 18,000×

Basal labyrinth of the epithelial cell of proximal proximal tubule from kidney



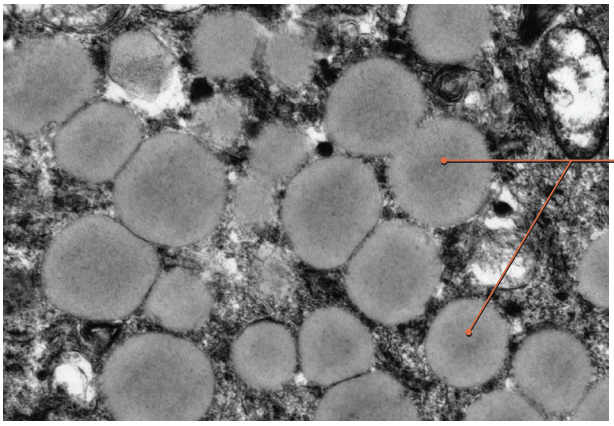
Electron micrograph, Original magnification: 18,000×

Macrophage from the splenic red pulp



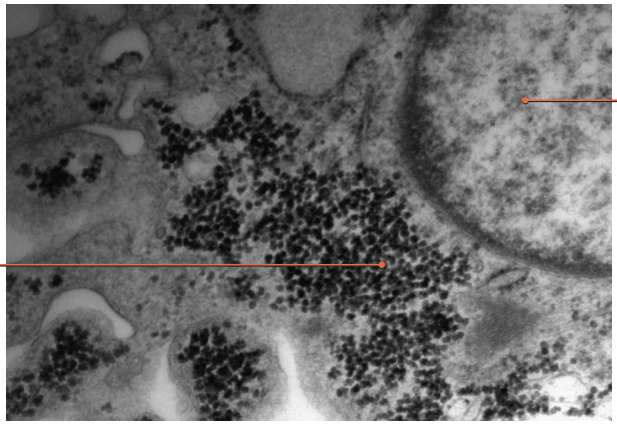
Electron micrograph, Original magnification: 7,100×

Lipoblast of white adipose connective tissue



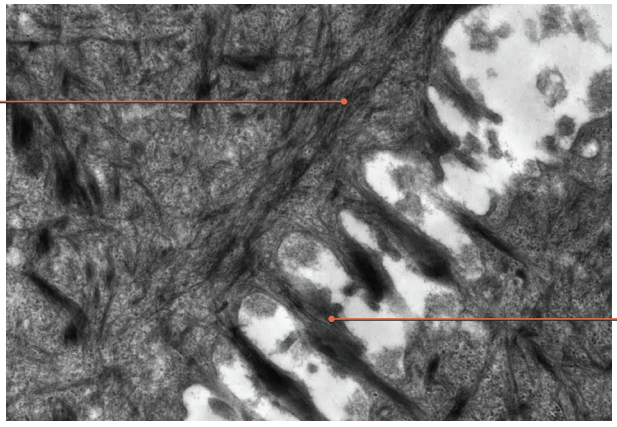
Electron micrograph, Original magnification: 18,000×

Precursor of skeletal muscle fibers



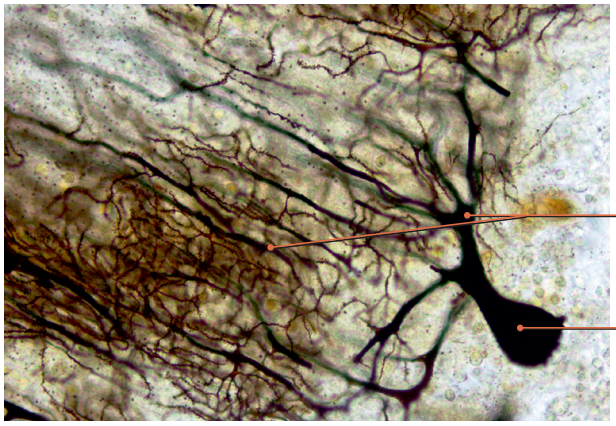
Electron micrograph, Original magnification: 36,000×

Cytoskeleton in the gingival stratified epithelium



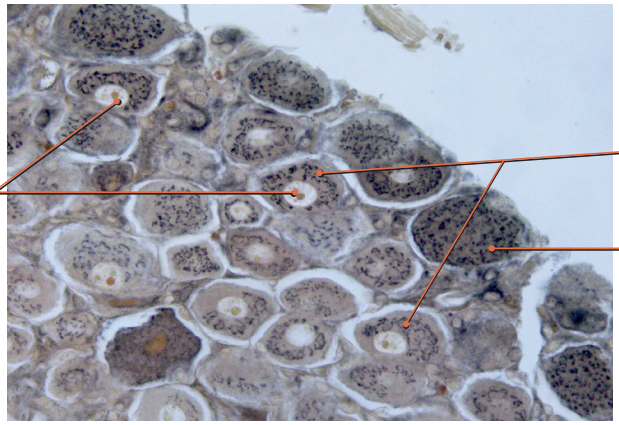
Electron micrograph, Original magnification: 14,000×

An example of a large cell: Purkinje cell in the cerebellar cortex



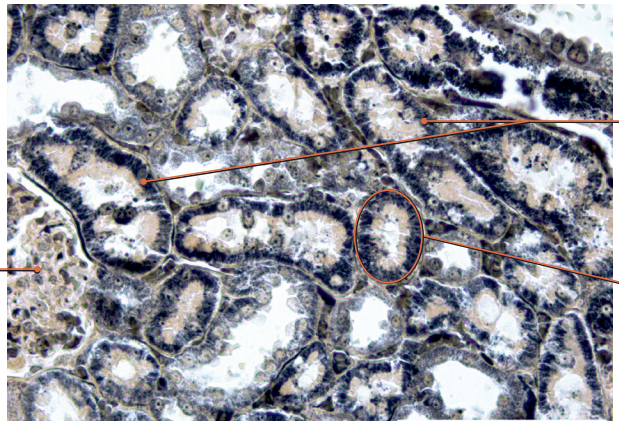
Golgi impregnation method, Lens: 40×

Golgi complex and nucleolus of spinal ganglion neurons



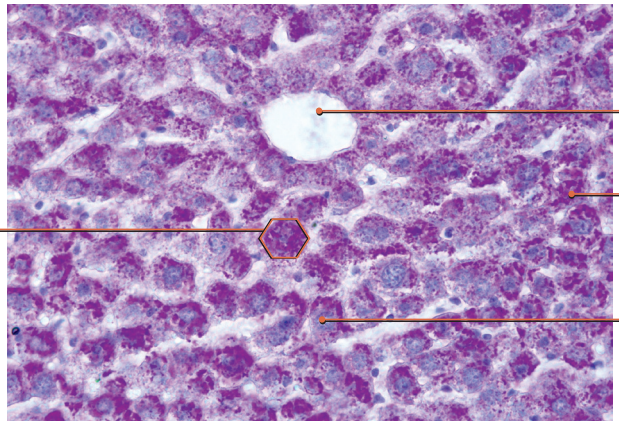
Staining: Golgi method, Lens: 40×

Mitochondrial group in epithelial cells of renal proximal tubules



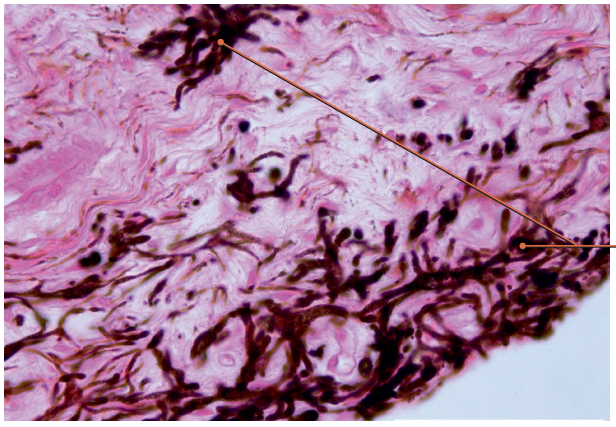
Staining: iron hematoxylin, Lens: 40×

Glycogen granules in the cytoplasm of liver cells (hepatocytes)



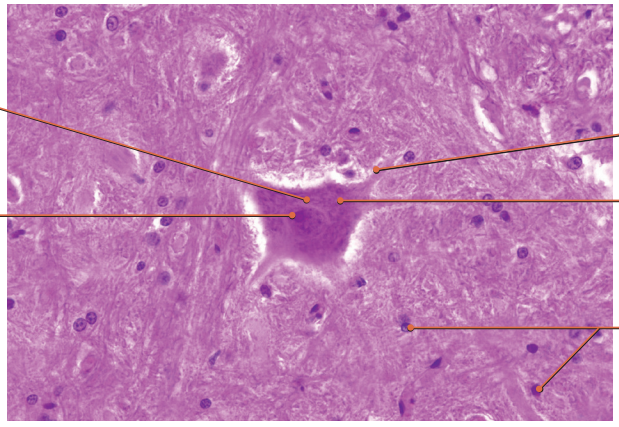
Staining: PAS reaction and hematoxylin, Lens 40x

Endogenous pigment granules in the melanocytes of the middle layer of the eye ball



Staining: eosin, Lens: 40×

A cell with a high proteosynthetic activity - neuron from spinal cord



Staining: HE, Lens 40×

I. Discovery of cells and the cell theory

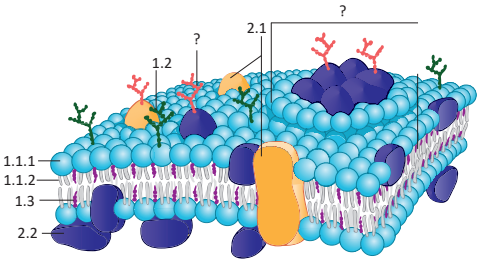
1. What are the basic cornerstones of the "cell theory" and which scientists are considered its authors? (p. 19)
2. Name the basic differences between prokaryotic and eukaryotic cells (p. 19)

II. Functional characteristics of animal cells

3. By which mechanisms cells communicate with each other? (p. 20)

III. Morphology of human cells

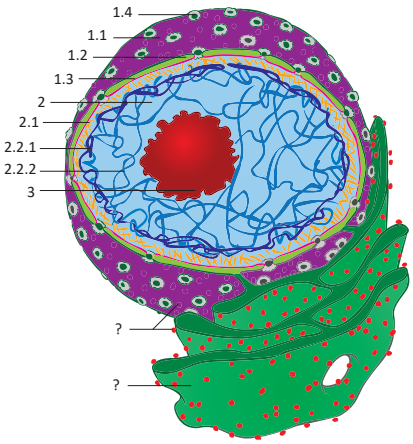
4. Name the basic shapes of human cells. (p. 21)
5. Give examples of the smallest and largest cells of the human body. (p. 22)
6. Hypertrophy and hyperplasia of uterine smooth muscle cells occur concomitantly during pregnancy. Explain these two terms. (p. 22)



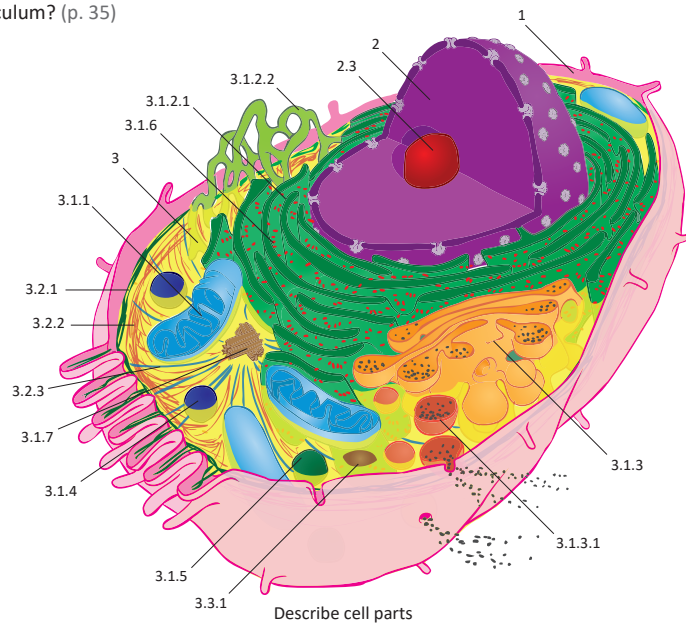
Describe the molecular structure of the cell membrane

IV. Basic cell characteristic

7. Explain what is the "fluid mosaic model". (p. 25)
8. What is glycocalyx and what is its significance for a cell? (p. 25)
9. Give examples of a multinucleated human cells and explain the term "syncytium". (p. 26)
10. Name the main components of the nucleus in an interphase. (p. 27)
11. What is a 3D network of intermediate filaments inside the nucleus called and which function does it have? (p. 28)
12. What is the difference between euchromatin and heterochromatin? (p. 29)
13. How does the nucleus of a cell, which produces a large amount of protein, look like under the microscope? (p. 30)
14. What are the functions of the nucleolus? (p. 30)
15. Name the organelles with one and two membranes. (p. 31)
16. The endosymbiotic theory (symbiogenesis) describes the evolutionary origin of mitochondria. Explain this theory. (p. 32)
17. Which cells are characterized by the presence of mitochondria with tubules (tubular type)? (p. 32)
18. Describe the basic structure of mitochondria. (p. 33)
19. How does the stainability of the cytoplasm change in the high occurrence of rough endoplasmic reticulum and ribosomes? (p. 34)
20. How are polyribosomes bound together in the cytoplasm and with what? What holds them together? (p. 34)
21. What are the basic steps of protein production? (p. 34)
22. What are the differences in structure and function of the rough and smooth type of endoplasmic reticulum? (p. 35)

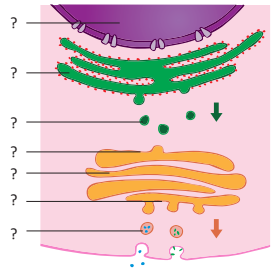


Describe the parts of an interphase nucleus



Describe cell parts

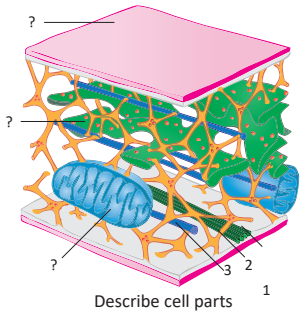
23. What is the function of sarcoplasmic reticulum and in which cells does it occur? (p. 35)
24. What is the functional difference between the cis-face and the trans-face of the Golgi complex? (p. 36)
25. What is the difference between primary, secondary and tertiary lysosomes? (p. 37)
26. Which cell organelle is responsible for creating new lysosomes? (p. 37)
27. What is the function of peroxisomes in the cell? (p. 37)
28. Name at least one staining method to visualize fat (lipid) droplets. (p. 38)
29. Name examples of cells that form glycogen storage in the form of granules. (p. 38)
30. Give examples of exogenous pigments. (p. 38)
31. Why is lipofuscin called as a wear and tear pigment? (p. 39)
32. Name the components of the cytoskeleton and describe their basic functions. (p. 40 and 41)
33. What does "dynamic instability of microtubules" mean? (p. 41)
34. Describe the typical arrangement of microtubules in the core of a cilium or a flagellum. (p. 41)
35. Intermediate filaments of cytokeratins, desmin and vimentin are typical for which tissues? (p. 41)
36. Describe the structure of the centriole. (p. 42)



Describe the formation and transportation of vesicles

V. Morphology of specialized cells

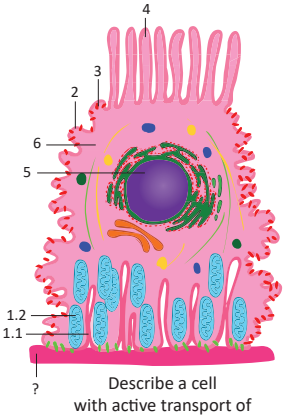
37. Define the basal labyrinth and list examples of cells where it is well-developed. (p. 42)
38. What are the clusters of rough endoplasmic reticulum and ribosomes in the cytoplasm of nerve cells called? (p. 43)
39. Which organelles and cytoplasmic inclusions are typical for steroid-producing cells? (p. 43)



Describe cell parts

VI. Transfer of substances through membranes, endocytosis and exocytosis

40. Describe the structure of microvilli. What is the function of brush border? (p. 44)
41. Name the individual phases of phagocytosis. (p. 46)
42. Give examples of cells with phagocytic activity. (p. 46)
43. Explain the term transcytosis and give an example, where it occurs in the organism. (p. 47)



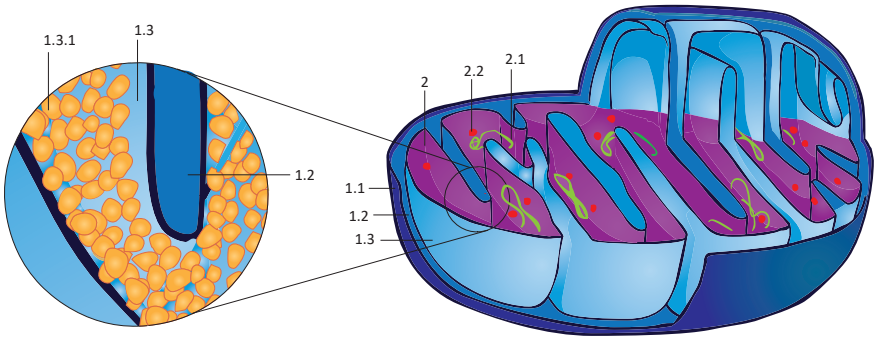
Describe a cell with active transport of electrons and water

VII. Cell cycle (p. mitosis and meiosis)

44. What is the difference between tumor suppressor genes and protooncogenes? (p. 48)
45. Name and describe the cell cycle phases. (p. 48)
46. Which phases of mitosis do the following morphological formations appear in: monaster, diaster, spirem and dispirem? (p. 48)
47. What does "crossing over" during meiosis I mean? (p. 49)

VIII. Cell death and cell regeneration

48. Apoptosis is precisely defined morphologically. Describe the microscopic changes of a cell undergoing apoptosis. (p. 50)
49. What is the significance of apoptosis in homeostasis of the body? (p. 51)
50. What are the basic properties of stem cells? (p. 52)



Describe the structure and content of the mitochondria

We thank the following **experts** for their valuable advice and comments that have made a significant contribution to improving the chapter **Cytology**.

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