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UNIVERZITY KARLOVY

OUTLINES OF HISTOLOGY

Jaroslav Slípka
Zbyněk Tonar

KAROLINUM

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Reviewed by:
Sarah Leupen, Department of Biological Sciences, University of Maryland Baltimore County, USA
Ivan Varga, Institute of Histology and Embryology, Faculty of Medicine, Comenius University, Bratislava, Slovakia

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PREFACE

Histology is a science of the tissues which are formed by conglomeration of cells and extracellular matrix. We are always interested in understanding the origin, microscopic structure and function of these tissues.

Contemporary general histology deals – in addition to the description of the fundamental unit of the tissue, the cell – with four kinds of basic tissues, presented in this textbook. These tissues participate in construction of various organs and organ systems.

This textbook outlines the courses in general histology, given to the international students of general and dental medicine in the first year of their pregraduate studies at the Charles University, Faculty of Medicine in Pilsen. The first edition was prepared in 1994 and revised in 2004 by Prof. Dr. Jaroslav Slípka, DSc (1926–2013), who was an enthusiastic and inspiring researcher and teacher at the Department of Histology and Embryology. The second edition was updated in 2017 to reflect some of the advances in teaching of histology. Nevertheless, the illustrations and the concise concept of the book designed originally by prof. Slípka were kept. We recommend using this textbook for revising and summarizing the essential knowledge. For full color textbooks and atlases that are necessary for understanding the histological slides, see the literature recommended at the end.

We wish all our students might enjoy the insight into the universe of cells and tissues the human body is made of. Welcome to the world of Histology!

Zbyněk Tonar
Pilsen, 2017

PART I: THE CELL

The cell is a basic integrated entity of all living organisms. It is a fundamental morphologic and physiologic unit, capable of multiplication, metabolism, growth, excitability and other specialized functions. The microscopic analysis of the fine structure and function of cells is referred to as *cytology*.

There are two different structural types of cells:

Prokaryotic cells with no nuclear membrane and no membranous organelles like in bacteria.

Eukaryotic cells with a nuclear membrane and various membranous organelles. These cells can form assemblies, classified into four basic tissues in multicellular animals *(Metazoa)*. The science of the morphologic and functional features of cells and tissues constitutes histology, the topic of this textbook.

Shapes and dimensions of cells: Although the primary form of cells is rounded or spherical, during development of tissues cells become, depending on their function, squamous, cuboidal, columnar, pyramidal, spindle

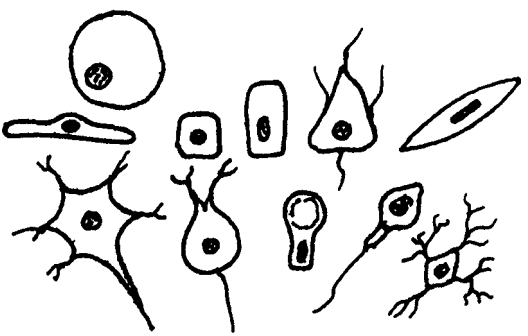

Fig. 1 Shapes of cells

shaped, star shaped, goblet shaped etc. The shape of cells is organized by an internal scaffolding of proteins known as the cytoskeleton. Those cells which have remained free, e.g. blood cells, retain their spherical form. Most of the cells of the human body range from 4–30 micrometers in diameter; the largest are the oocytes (150 μm in human). The red blood cell, which ranges around 7.5 μm in diameter, can be used as a rough measure of the size of the tissue cells seen in the same field.

Composition of cells: The cell is formed by *protoplasm* which is composed of *cytoplasm* (or *cytosol*), the fluid matrix of the cell, and *nucleoplasm*, the matrix of the nucleus. Cytoplasm is composed of a colloid solution, contained by a cell (or plasma) membrane – *plasmalemma*. The cytoplasm contains many smaller elements – subcellular structures – called *organelles* which provide the framework for cellular activities. It contains also many of the essential enzymes and metabolites. In the nucleoplasm is the genetic material in the form of chromosomes. Chemical composition of cells: in addition to water and inorganic substances, cells contain four main classes of organic constituents: proteins, carbohydrates, fats (lipids) and

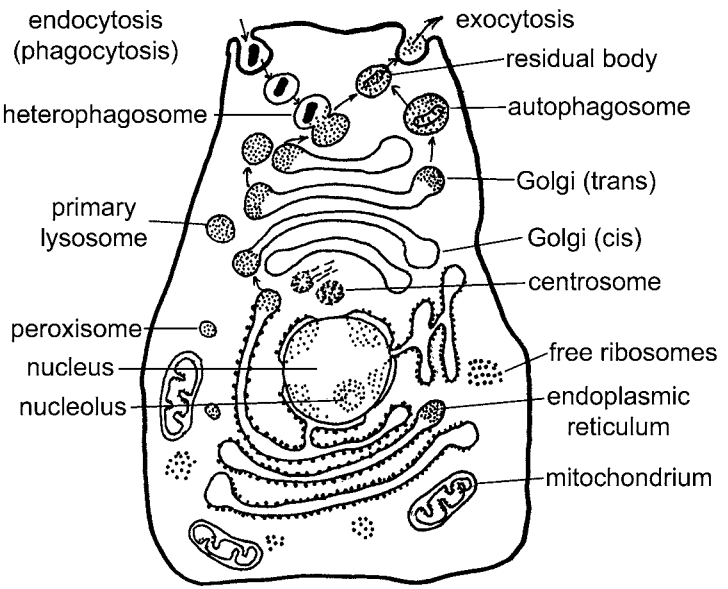

Fig. 2 The cell

nucleic acids. The pH of the cytoplasm ranges between 7.0–7.4. However, in most histological staining methods, the cytoplasm of most cells appears as slightly acidophilic (e.g., stained pink to reddish by an acidic dye named eosin using the routine hematoxylin-eosin staining).

Cell membranes

The term comprises not only the outer membrane surrounding each cell, i.e. **plasmalemma**, but also the membranes surrounding cellular organelles. The basic structure consists of a **lipid bilayer** containing specialized proteins in association with surface carbohydrates.

The membrane *lipids* are of three types: *phospholipids*, *cholesterol* and *glycolipids*. The phospholipids are organized into a double layer of molecules, in which each molecule has an outer hydrophilic head and an inner hydrophobic chain. Cholesterol is inserted into the phospholipid bilayer and is present in about the same amounts as are phospholipids, and is responsible for the mechanical stability of the otherwise fluid membrane. Glycolipids with their associated sugars are exposed to the extracellular surface and are involved together with glycoproteins in intercellular communication as mediators of cellular interactions like adhesion and recognition.

Membrane protein molecules can be classified according to their spatial relations to the membrane: *Integral (intrinsic) membrane proteins* of-

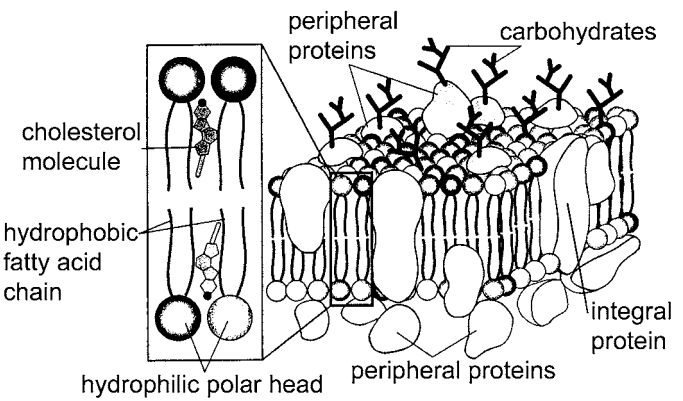

Fig. 3 Cell membrane

ten span the whole lipid bilayer from one surface to another, and form a transmembrane channel for passing the ions through the membrane. Some integral membrane proteins are confined to the inner or outer part of the membrane only. The *peripheral (extrinsic) membrane proteins* are not fully embedded within the lipid bilayer and are more loosely attached to a membrane surface.

Some membrane proteins are receptors, which allow cells to respond to external signals when binding a variety of *signaling molecules* (or *ligands*). Binding of signaling molecules (released by a signaling cell) to their receptors activates in the target cell an intracellular *second messenger* system, initiating a cascade of reactions that result in the required response. For example, a hormone (the first messenger) activates through a receptor a transmembrane protein – *adenylate cyclase*, which in cytoplasmic region catalysates the transformation of ATP to *cyclic adenosine monophosphate* (*cAMP*), i.e. the second messenger.

Numerous membrane proteins bear polysaccharide chains and represent the *glycoprotein molecules*. The membrane carbohydrates cover the extracellular surface of the cell membrane like a sugar coating – the *glycocalyx*. The polysaccharide chains confer a certain surface specificity on every type

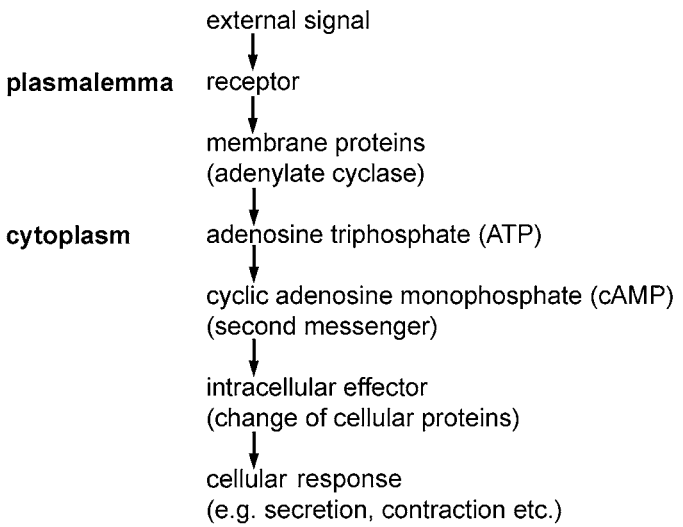

Fig. 4 Cellular processing of external signals

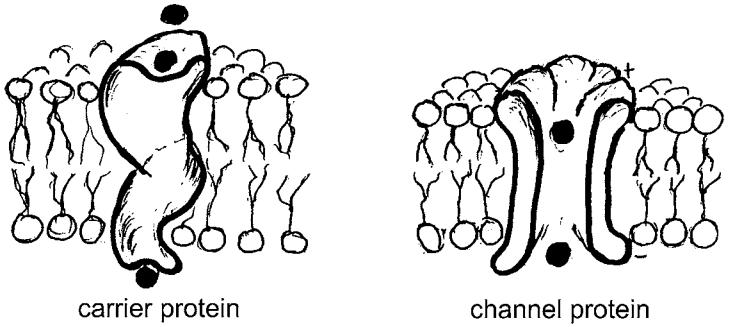

Fig. 5 Membrane transport

of cell. The glycocalyx is directly involved in the recognition and adhesion of different cell types, particularly during morphogenesis. The carbohydrate chains can be demonstrated by staining with lectins (proteins extracted mostly from some plants).

The role of the cell membrane lies not only in preserving the integrity of the cell, but also in cell-cell recognition and selective transport of molecules. Whereas the cell membrane is impermeable to most large molecules, it is permeable to some smaller molecules and ions, and so important for bringing needed material into the cell and releasing waste products. The membrane is equipped with *active transport mechanisms* to transfer various substances (e.g., glucose, amino acids) in the required direction. Small molecules are bound to an integral carrier protein which undergoes series of conformational (shape) changes to release the molecule on the cytoplasmic side. Some ions can be transported according to the ion gradient through the plasmalemma by ion selective channel proteins via a mechanism called *facilitated diffusion*. Another example is a *sodium-potassium pump* which utilizes energy from mitochondria to release the sodium ions from the cell and to pump potassium into the cell (see, e.g., nerve tissue).

The cell can also ingest macromolecules from the extracellular space by invagination of the cell surface, termed **endocytosis**. The invaginated cell membrane encloses the incorporated material for further processing in an *endocytotic vesicle (endosome)*. In the case of very small molecules, we specify the endocytotic process as *pinocytosis (i.e. cell drinking)* with the formation of *pinocytotic vesicles*. For ingestion of large particles (e.g. bacteria) the term *phagocytosis (cell eating)* is used. In such cases the cell

extends cytoplasmic processes which engulf the material and ingest it in endosomes, called *phagosomes*.

The reverse process is called **exocytosis**, in which the products produced in cells can be released. The membrane bound vesicles fuse with cell surface and discharge their content into the extracellular space.

The invaginated cell membrane forms a so called *coated pit*, which bears surface receptors that bind specific extracellular ligands. The pit is covered on the cytosolic side by a coat protein – *clathrin* – in form of a lattice. The invaginated membrane then fuses to form an endocytic vesicle – *endosome*

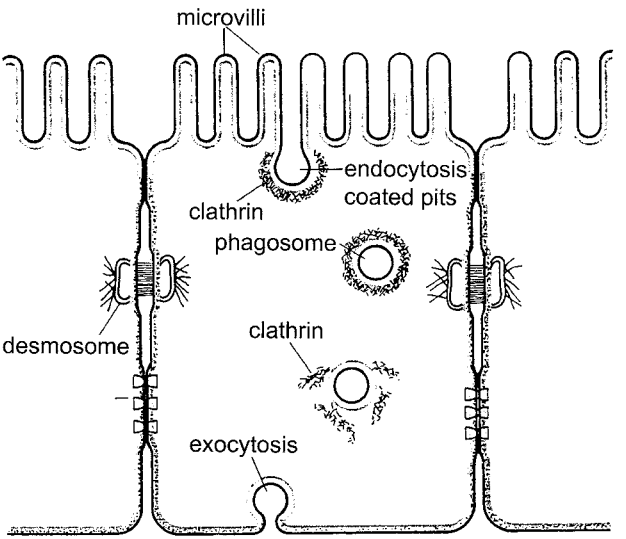

Fig. 6 Exocytosis and endocytosis

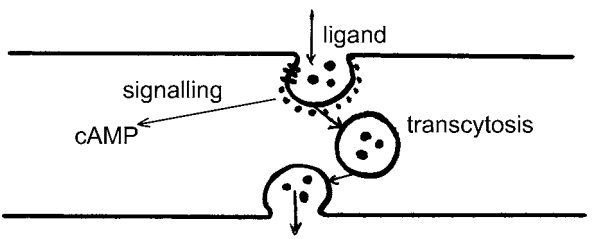

Fig. 7 Transcytosis

(phagosome). During the process of internalization the clathrin is shed and returns to the surface.

Similar membrane invaginations, coated with another protein – *caveolin* – have been termed the *caveoli*. They are responsible for the transport of the substances in vesicles from one side of a flat cell (e.g., endothelium lining the blood and lymph vessels) to the opposite one. This process is called **transcytosis**. Their receptors can also play a role in intracellular signaling by triggering the intercellular messenger system (e.g., in smooth muscle).

Nucleus

The nucleus is the largest membrane-limited, spherical or ovoid organelle, situated usually in the center of the cell (missing only in mature mammalian RBCs). Its diameter usually varies between 5–10 μm. It is composed of *nucleoplasm,* which contains chromatin, and the nucleolus. The nucleus is separated from the cytoplasm by the nuclear membrane (*nucleolemma*).

The **nuclear membrane** is built by two concentric membranes, separated by a narrow space – the *perinuclear space*, which can be continuous with the rough endoplasmic reticulum. On the inner membrane are anchored some filamentous proteins – *lamins*, which form a sort of scaffolding of the nucleoplasm. The outer nuclear membrane can be associated with ribosomes. Both membranes fuse in numerous circular *nuclear pores*, which are not open, but bridged by a thin protein diaphragm, permeable to some molecules, e.g., to mRNA.

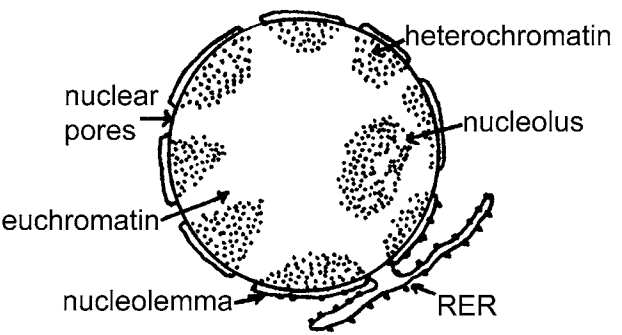

Fig. 8 Nucleus

The **nucleolus** is a dense nonmembranous structure within the nucleus, seen during interphase only. It measures 1–3 μm. Active cells (embryonic, tumorous etc.) have usually larger or even multiple nucleoli. It stains basophilic, being rich in rRNA and proteins, and it disappears during cell division, but reappears in the telophase stage of mitosis.

The nucleolus is rich in rRNA and protein, accumulated into ribosomal subunits, which are then transferred to cytosol through the nuclear pores. It consists of three distinct regions. The pale area – *fibrillar center* – surrounds the so called *nucleolar organizer DNA regions*. There the tips of 5 chromosomes are located and their genes (nucleolar organizers) code for rRNA. The dark thread-like structure, the dense fibrillar component, consists of primary transcripts of rRNA molecules beginning to form ribosomes. The granular regions – *granular components* – consist of maturing ribosomal subunits.

Chromatin

There are two forms of chromatin: *Heterochromatin* is seen as condensed basophilic clusters of coarse granules, often adjacent to the nuclear membrane. It represents an inactive form of chromatin. *Euchromatin* represents actively transcribed DNA and appears as lightly stained areas of nucleoplasm. Its structure is seen in the electron microscope only.

A molecule of **deoxyribonucleic acid (DNA)** is made up of two polynucleotide strands wound together in the form of a double helix. Each strand consists of alternating phosphate and deoxyribose sugar groups, and it has a nitrogenous base extending as a side chain from each sugar group into the double helix. There are two types of bases: **purines** (adenine and guanine), and the **pyrimidines** (cytosine and thymine).

There is an obligatory pairing of the bases on one strand by hydrogen bonds with the bases on the other. Such complementary base pairing exists between *adenine (A)* and *thymine (T)*, and between *guanine (G)* and *cytosine (C)*. The building blocks of nucleic acids are the *nucleotides*, composed of bases linked to sugar and phosphate groups.

DNA is the repository of genetic information. The information transfer from the nucleotide sequence of DNA to the amino acid sequence of a protein involves **three forms of RNA** – *ribosomal (rRNA), transfer (tRNA)* and *messenger (mRNA)*. The molecule of *ribonucleic acid (RNA)* is single stranded and is not self-replicating, so that all forms of RNA are tran-

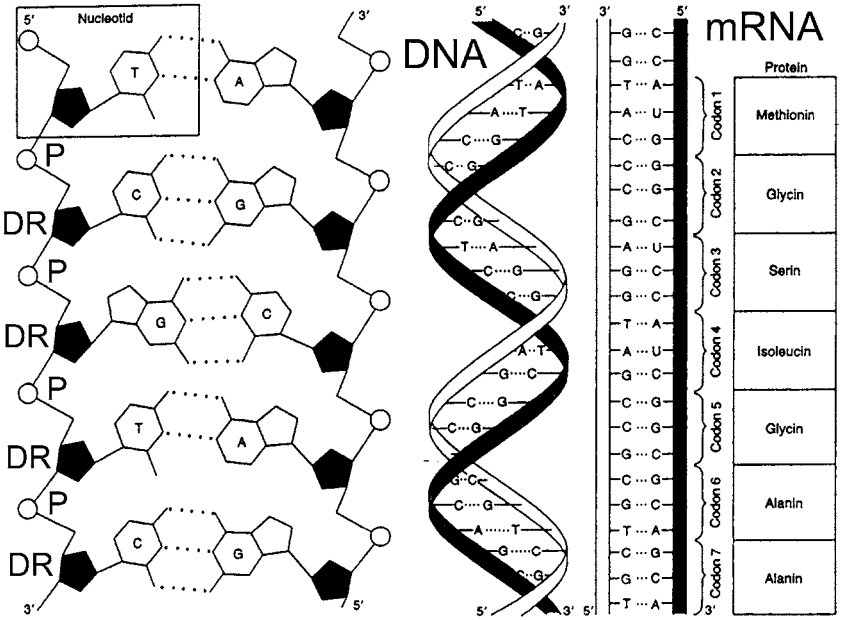

Fig. 9 Molecule of DNA

scribed from DNA. DNA serves as a template for a complementary strand of RNA during a process of *transcription*. RNA differs from DNA. The sugar ribose is present instead of deoxyribose and the base *uracil (U)* replaces *thymine (T)*.

Chromatin is formed mainly by coiled strands of DNA, wound around proteins – **histones**. The basic unit of chromatin is the *nucleosome*. Nucleosomes are regularly repeated globular structures, like beads on a string. The nucleosomes form a *chromatin fiber* of 30 nm in diameter. Coiled chromatin fibers surround the chromosome protein core during cell replication and are extensively condensed to form distinct **chromosomes**, structures that are visible with the light microscope.

The mitotic chromosome possesses two arms, extending from its *centromere*. The adenine-thymine-rich regions of chromosomes produce a pattern of *G bands* (stained with Giemsa stain), unique for each chromosome and characteristic for each species. The units of heredity are located at specific regions on the DNA molecule and are called *genes*. Each gene repre-

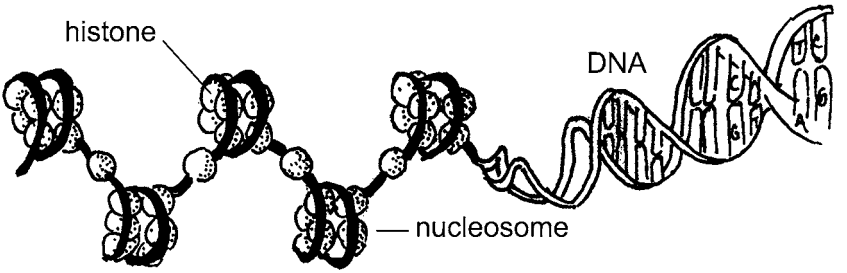

Fig. 10 Chromatin fiber

sents a specific segment of the DNA molecule that codes for the synthesis of a particular protein.

The **number of chromosomes** is specific for each species of living organism. The number and type of chromosomes in an individual is known as his or her *karyotype*. The human genome is made up of 46 chromosomes. This diploid number represents 23 homologous pairs of chromosomes. Of these 22 pairs are *autosomes*, and one pair represents *sex chromosomes (heterochromosomes, allosomes)*. The germ cell has only 23 chromosomes

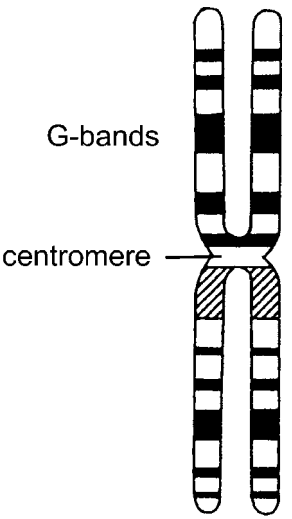

Fig. 11 Condensed chromosome visible and stained during mitosis

(haploid number), from which are 22 autosomes, and one sex chromosome, which differs in female and in male germ cells. In females, each ovum always contains an X chromosome, while in males the spermatozoa are of two kinds – one carrying sex chromosome X and the other Y. The resulting sex of a newborn depends on the kind of sperm which fertilizes the ovum. A male somatic cell then possesses 44 autosomes and XY combination of sex chromosomes, whereas a female has also 44 autosomes, but XX sex chromosomes.

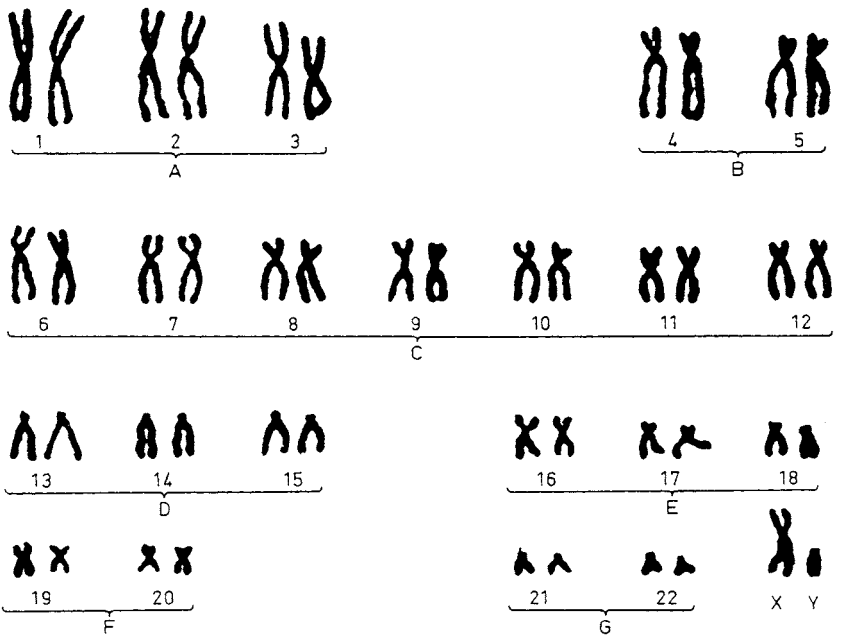

Fig. 12 Human male karyotype

Only one of the two XX sex chromosomes of the female somatic cell is activated during interphase. The other one is inactive and appears condensed as a clump of heterochromatin attached to the nuclear membrane in form of a *Barr body*. It can be observed in 20–40% of epithelial cells in smears taken from the oral mucosa or in form of a small drumstick attached to the nucleus of the neutrophilic granulocytes.

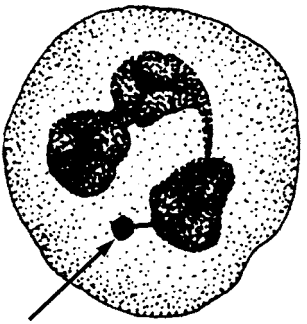

Fig. 13 Barr body in a neutrophilic granulocyte of a female

Cell cycle

The somatic cells exist in the states of division *(mitosis)* and nondivision *(interphase)*. Interphase represents a longer period between mitotic division that begins immediately following telophase of the mitosis. It cannot be considered as a resting stage, because during this period of time the cell increases its size and *replicates* its genetic material.

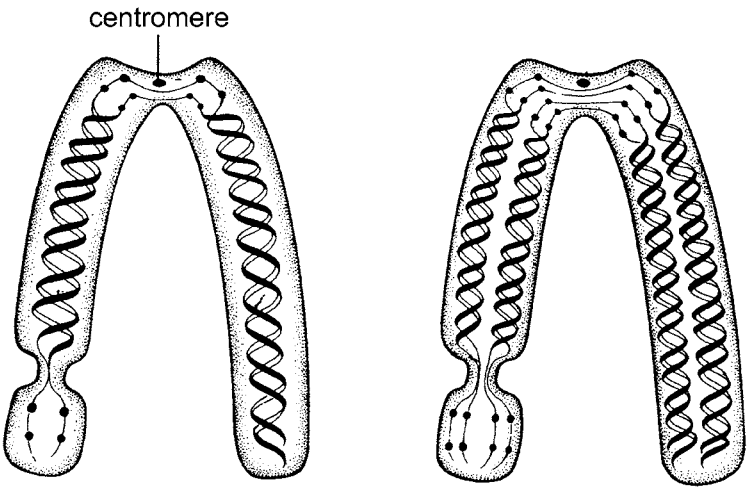

Fig. 14 DNA replication and doubling of chromatids

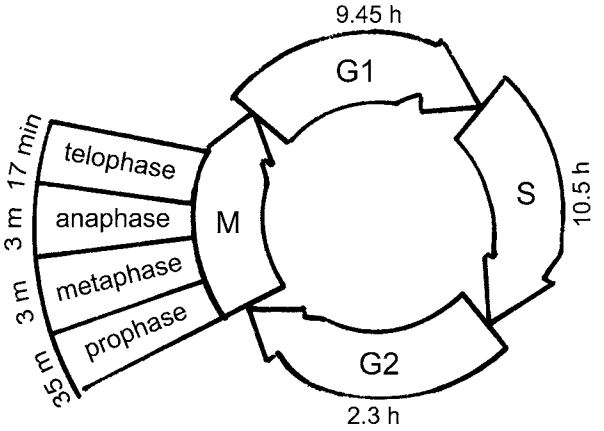

Fig. 15 Cell cycle and average duration of its phases

The two DNA strands unwind and separate and each strand serves as a template for the synthesis of new strand alongside it. Complementary base pairing occurs determined according the base sequence of preexisting strand. Two identical double-stranded DNA molecules are formed – one half persisting from the original one and the second half being synthesized anew.

Interphase can be subdivided into three phases: During the *G1 (gap) phase* when the synthesis of material essential for DNA duplication begins, the nucleolus reappears and the centrioles begin their duplication. The next stage is represented by *S phase (synthetic)*, when the genome is duplicated and the cell contains twice its usual complement of DNA in preparation for the mitosis. During the last stage of the interphase, the *G2 phase*, the RNA and proteins essential to cell division are synthesized, and energy is stored so that the cell is prepared for mitosis.

Mitosis

Mitosis represents a short period in which the cell divides its nucleus and cytoplasm into two identical daughter cells. During mitosis the 46 chromosomes become highly condensed. In the cytoplasm spindle fibers appear and the centrioles split and migrate to opposite ends of the cell, where they act as organizing centers for the spindles.